The Scientific Approach to Getting Healthier as You Get Older

HOW NOT TO AGE

MICHAEL GREGER, M.D., FACLM

NEW YORK TIMES BESTSELLING AUTHOR OF *HOW NOT TO DIE* AND *HOW NOT TO DIET*

FEATURING DR. GREGER'S ANTI-AGING EIGHT FOR LONGEVITY AND VITALITY

HOW NOT TO AGE

THE SCIENTIFIC APPROACH TO GETTING HEALTHIER AS YOU GET OLDER

MICHAEL GREGER, M.D.

FLATIRON
BOOKS
NEW YORK

Begin Reading

Table of Contents

About the Author

Copyright Page

For my great-aunt Pearl
(1911–2015)

Preface

I turned fifty in the process of writing this book, so the subject has a certain salience lacking from my last nutrition book, *How Not to Diet*, which covered weight loss. There is, however, a clear parallel between the two topics: Both are tainted with the same corrupting influence of commercial interests. The diet[1] and anti-aging[2] industries are both multibillion-dollar behemoths. With so much money in the mix, the temptation to promote products purporting all sorts of preposterous claims is apparently irresistible.

Even an educated layperson seeking basic, practical advice in either arena, living lighter or longer, is faced with an inscrutable barrage of pills and potions. Even as a physician with the luxury of wading neck deep through the peer-reviewed medical literature, it's been a challenge to tease out the naked truth from the emperor's clothing. But that makes the endeavor all the more important. If it took me three years to sift through all the science on aging, I'm afraid the casual observer would have little hope in separating facts from farce. A former president of the Gerontological Society of America wrote that "few subjects … have been more misleading to the uncritical and more profitable to the unscrupulous."[3]

The anti-aging field is said to be a "fertile ground for cons, scams and get-rich-quick schemes,"[4] with the popular literature on the subject harboring a "huge amount of misinformation."[5] Marketers often target older people with quack remedies for aging.[6] Their wares are hawked pervasively on the internet as well as brick-and-mortar "anti-aging" clinics.[7] These schemes have been the subject of multiple Senate and congressional inquiries with names like "Swindlers, Hucksters and Snake Oil Salesmen"[8] and "Quackery: A $10 Billion Scandal."[9] These days, the anti-aging

industry in America may be worth more like $88 billion,[10] with the global industry valued at $292 billion.[11] This encompasses everything from wrinkle creams to televangelist Pat Robertson offering "Pat's Age-Defying Protein Pancakes." Aging may not be good for health, one economics editorial put it, "but it certainly is good for business."[12]

BLINDED BY SCIENCE

According to one industry group, 60 percent of Americans sixty-five and older are pursuing anti-aging interventions,[13] yet, according to the director of the Institute for Biomedical Aging Research, in almost all instances, these interventions are not supported by science.[14] They sound like they are, though. Scientific breakthroughs exploited by the sensationalist press have long been opportunistically repackaged by profiteers.

Nineteenth-century advances in magnetism led to ads asserting, "[t]here need not be a sick person in America … if our Magneto-Conservative Underwear would become a part of the wardrobe of every lady and gentleman, as also of infants and children." Less comically, more tragically, public interest in Marie Curie's work led to a range of radioactive products said to "revitalize" and "energize."[15] As one *Wall Street Journal* headline read, "The Radium Water Worked Fine Until His Jaw Came Off."[16]

Today, this so-called scienceploitation is evident in hundreds of rogue "stem cell" clinics concentrated in California and Florida,[17] using the language of science to give a veneer of legitimacy to their unproven therapies.[18] In their *Scientific American* feature "No Truth to the Fountain of Youth," three noted aging researchers concluded that the "public is bombarded by hype and lies."[19]

One of those researchers was sued for more than $200 million by the cofounders of the American Academy of Anti-Aging Medicine[20] for presenting the organization with a Silver Fleece Award, a mock prize shaming "the most ridiculous, outrageous, scientifically unsupported or exaggerated assertions about intervening in ageing or age-related diseases."[21] The American Academy of Anti-Aging Medicine countered that it "does not promote or endorse any specific treatment nor does it sell or endorse any commercial product."[22] However, looking back at its website, it has actively solicited and displayed a whole catalog of advertisements in its

"Find an Anti-Aging Product or Service" directory whose development, it justifies, was "prompted by the numerous inquiries received each day."[23,24]

The "gerontological establishment" has been accused of trying to wantonly sabotage upstarts like the American Academy of Anti-Aging Medicine,[25] whose cofounder claims to be fighting the "old-line philosophy" that "aging is inevitable, nothing can be done, get used to it, grow old and die."[26] I see merit on both sides of this culture clash, with the field of gerontology (the study of old age) struggling to retain hard-fought gains in public funding for basic aging research versus the more ambitious anti-aging crusaders who appear to more fundamentally question underlying assumptions. "Simply put," the American Academy of Anti-Aging Medicine's official response to the criticism read, "the death cult of gerontology desperately labors to sustain an arcane, outmoded stance that aging is natural and inevitable."[27]

The anti-aging medicine movement would have more credibility had it been started by those steeped in the research rather than "entrepreneurial businessmen responding to market opportunities,"[28] but the backlash against the anti-aging new wave may have pushed the pendulum too far in the other direction. Yes, as noted by the founding editor in chief of *Biogerontology*, the history of anti-aging research is undoubtedly "replete with fraud, pseudoscience, quackery and charlatanism,"[29] but the (admirable!) crusade against any whiff of impropriety seems to have led to a knee-jerk "all hype, no hope" position that belies the genuine scientific advances that have been made in the feasibility of intervening in the aging process.[30]

I know in some circles today, "science" is a dirty word. After years of COVID craziness, colleagues I once respected for their intellect seemed to have abandoned their critical thinking skills. If you have been similarly sucked down some rabbit hole of cabalistic conspiracies, this may not be the book for you. It is true that the pandemic revealed glaring institutional flaws that even encroached on the scholarly literature. Two of the most prestigious medical journals were forced to retract papers over concerns of data integrity.[31,32] But scientific journals remain the gold standard for establishing the best approximation of truth about our shared reality. To paraphrase Winston Churchill's quote about democracy as a form of governance, the peer-reviewed medical literature is the worst way to establish facts about our health—except for all the others.

SHOWING MY WORK

An editor in chief of a leading gerontology journal claims that most anti-aging scientists "widely known to the public are unscrupulous purveyors of useless nostrums."[33] It is easy to be swayed by charismatic gurus, but when it comes to something as life-and-death important as the health and well-being of ourselves and our families, we should rely not on anecdote but on evidence. That's why I cite everything to the teeth. *How Not to Die* had about 2,000 citations. *How Not to Diet*, 5,000. This book ended up with more than 13,000, which turned out to be a problem.

I promised the publisher a book with no more than about 600 pages, but when all was said and done, my manuscript was closer to 2,150 pages. Yikes. I didn't want to lose any content, so my first stab at trimming was to put the 995 pages of citations online. here, there's a web address (see.nf/citations) and QR code for the full list of searchable citations referenced throughout this book.

Over the last three years, my team and I read more than 20,000 papers on aging so you don't have to—but you're certainly welcome to! The advantage of presenting the citations online is that it allows me to hyperlink each one to take you directly to the source. That way, you can download the PDFs and access the original research yourself.

Nevertheless, that still left me with a manuscript with a quadruple-digit page count. I needed to figure out how to essentially halve the book to meet the publisher's printing specifications. The problem is there wasn't any chaff to chop. Too many popular physician authors recycle rehashed content from their prior works to cash in on another publication. I try to do the opposite, featuring all-new material, which is why, throughout the text, I refer you to sections in my previous books where I covered relevant concepts. (Search worldcat.org to find print copies, e-books, or audiobooks of all my works at your local public library.) So, the only way I could think of to meet the target page count was to turn *How Not to Age* into a full audiovisual experience.

You'll see I've sprinkled video links throughout the book. My team and I produced hundreds of bite-sized videos, each about five minutes long, to cover the hundreds of thousands of words of additional information I had to cut from this manuscript. Don't worry, all the actionable takeaways are self-

contained within this text. I just never want anyone to take my word for anything. I always strive to justify exactly how I arrive at each recommendation. Unfortunately, space limitations didn't always allow me to do that in this book, so even though I still relay the bottom-line conclusions, you may want to follow the links to take a deeper dive into the supporting evidence.

AGING IS THE ACTUAL LEADING CAUSE

There may be no such thing as dying from old age. From a study of more than 42,000 consecutive autopsies, centenarians—those who lived at least to one hundred—were found to have succumbed to diseases in 100 percent of the cases examined. Though most were perceived, even by their physicians, to have been healthy just prior to death, not one "died of old age." They died from disease, most commonly heart attacks.[34] Similar results were found from other autopsy series of centenarians[35] and those over eighty-five, an age bracket referred to in the medical literature as the "oldest old."[36,37,38]

If aging kills via diseases,[39] why wasn't my *How Not to Die* the only longevity book anyone needs? In it, I ran through what we can do to prevent, arrest, and reverse each of our fifteen leading causes of death, starting with heart disease, not only the number one killer of centenarians but of people in general.[40] In the United States, heart disease has been the leading cause of death every year since 1900, with the exception of 1918 when pandemic flu ruled the roost.[41] (In contrast, as I detail in *How to Survive a Pandemic*, COVID only made it to number three.[42]) Heart disease has been the leading cause of death and disability around the world for most of this century[43] and is projected to remain that way in the decades to come.[44] But is it *really*?

Because old age is the greatest risk factor for most of our killer diseases,[45] one could argue that the leading cause of death is actually aging.[46] The rate of death increases exponentially for age-related diseases, such as heart disease, cancer, stroke, and dementia.[47] So, yes, in the same age bracket, having high cholesterol can increase your risk of heart disease as much as twentyfold,[48] but an eighty-year-old may have *five hundred* times the risk of having a heart attack[49] compared to someone in their

twenties.[50] Eating a plant-based diet may reduce the risk of dementia as much as threefold,[51] but the difference in dementia rates between those older than eighty-five compared to younger than sixty-five is *three hundredfold*.[52] The reason we focus on things like cholesterol is that it is a *modifiable* risk factor, but what if the rate of aging was modifiable, too?

Instead of our current, piecemeal approach of focusing on individual degenerative diseases, what about slowing down the aging process itself? I remember as a nerdy kid I wanted to cure cancer when I grew up. Even if all forms of cancer were eliminated, the average life expectancy in the United States would only go up about three years.[53] Why? Because dodging cancer would just mean delaying death from something like a heart attack or stroke. If one age-related ailment doesn't get us, another will. Rather than playing "whack-a-mole" by tackling each disease separately, progress in decelerating aging could address all these issues simultaneously.[54]

Imagine if there was an intervention that didn't just reduce your risk of the leading killers but also arthritis, dementia, osteoporosis, Parkinson's disease, and sensory impairments. Because such risks tend to double every seven years, even just slowing aging, such that the average sixty-five-year-old, for example, would have the health profile and disease risk of today's fifty-eight-year-old, would be expected to cut *in half* everyone's risk of death, frailty, and disability.[55]

This is why I wrote *How Not to Age*.

Is Aging Itself a Disease?

For decades, one of the most contested questions in gerontology has been whether or not aging itself should be considered a disease.[56] Aging is natural, yes, but so is getting an infection and we call that a disease. Aging is universal. Yes, but everybody gets the common cold, too.[57] If you're interested, I dive deeper into the discussion in my video see.nf/agingdisease. What does it matter what we call it? A rose by any other name wilts just as fast. The hope is that disease classification would lead to greater resource

allocation for aging research, just as the recent declaration of obesity as a disease did for obesity research.[58]

You'd think Big Pharma would invest in what would certainly be a blockbuster drug. But why spend the money on research when it can be spent on marketing all the unproven anti-aging products they already sell? Many of the leading lines of dietary supplements are owned by drug companies.[59,60] They're the ones selling "cosmeceuticals"[61] and "age reverse" skin creams.[62] Drug maker Sanofi even partnered with Coca-Cola to come up with a "beauty drink."[63] They're already making money hand over fist preying on the public's gullibility and desperation for anti-aging products.[64] Why waste money on proving anything actually works?

ALIVE AND WELL

When asked, *How long do you wish to live?* and offered the choice of 85, 120, or 150 years, or indefinitely, about two-thirds said they'd prefer to live to be eighty-five. But, when the question was reframed as *How long do you wish to live in guaranteed mental and physical health?*, the most popular answer switched to an unlimited lifespan.[65] It's not just how long we live, but how well, embodied in the Greek myth of Tithonus, to whom Zeus granted eternal life, but not eternal youth, so he shriveled with age and began to babble continuously (before eventually transforming into a cicada).[66]

Longevity is indeed a Pyrrhic victory if those additional years are characterized by inexorable decline.[67] Only about 18 percent of people can be described as undergoing "successful aging."[68] Studies have found the prevalence of multimorbidity, the coexistence of multiple chronic diseases, ranges between 55 percent and 98 percent among older individuals.[69] By age eighty-five, more than 90 percent may have at least one disease and, on average, about four diseases.[70] And just like 85 percent of cancer patients tend to overestimate their survival,[71] so, too, do those with other chronic diseases. Those suffering from heart failure or chronic obstructive lung

diseases like emphysema are about three times more likely to die within the subsequent year than they predicted. Ninety-six percent of outpatient dialysis patients thought the odds were in their favor that they'd be alive five years later, but nearly half were dead in fewer than two years.[72]

This raises the concept of healthspan, the period of life spent in good health, free from chronic disease and disability.[73] No wonder people are skeptical about longevity interventions as we see our lifespans expand but our healthspans contract. "Everyone wants to live forever," to paraphrase Jonathan Swift, "but no one wants to grow old."

In the United States, for example, we're living longer in sickness, not in health. A twenty-year-old in 1998 could expect to live about fifty-eight more years, while a twenty-year-old in 2006 could look forward to fifty-nine more years. However, the twenty-year-old from the 1990s might live ten of those years with chronic disease, whereas now it's more like thirteen years. So it feels like one step forward, three steps back. The researchers also noted that we're living two fewer *functional* years—that is, years we're no longer able to perform basic life activities, such as walking a quarter of a mile, standing or sitting for two hours without having to lie down, or standing without special equipment.[74] In other words, we're living longer, but we're living *sicker*.

That is why this book addresses both lifespan and healthspan. What's the point of living longer if you can't enjoy it vibrantly? It is my sincere hope this book adds not just years to your life but life to your years.

Introduction

My earlier book, *How Not to Die*, was not about living forever. It was not *How to* Not *Die*. Instead, it was how not to die prematurely, in pain after a long, chronic, disabling illness. The good news I shared is that we have tremendous power over our health destiny, in that the vast majority of premature death and disability is preventable with a healthy enough diet and lifestyle. *How Not to Age* has a similar premise. This book is not about immortality but rather how to age with grace and vitality rather than suffering from the ravages of infirmity and decrepitude. But why can't we stop aging and go on forever?

"MAN WILL NEVER BE CONTENTED UNTIL HE CONQUERS DEATH." —BERNARD STREHLER

From the Epic of Gilgamesh more than 4,000 years ago[75] to the recent quincentennial of Ponce de León's pursuit for the fountain of youth, humankind has yearned for the mythical elixir of life that would remedy the scourges of aging.[76] And why not? It's not like aging is some immutable constant in nature. Evolution has produced lifespans in animals that vary more than a millionfold, from mayflies whose adult lives may last only a few minutes to clams clocking in at over five hundred years.[77] Just like the Wright brothers may have taken inspiration from birds, we can take inspiration from animals that age slowly, if at all.[78]

Why can't we live forever? Some animals do, and I'm not talking about a two-hundred-year-old whale or even a thousand-year-old tree. There are actually species (with names like the immortal jellyfish) who apparently do not age and could technically go on forever.[79] In a sense, humans are

immortal, in that a few of our cells live on—the sperm or egg cells lucky enough to find each other. Each of our kids grows out of one of our cells, and that alone—I mean, the fact that a single cell can grow into a person—should make, in comparison, the notion of keeping our body going indefinitely seem biologically trivial. One little fertilized microscopic blob can turn into perhaps the most complex object in the known universe, the human brain, with its 100,000 miles[80] of 86 billion neurons[81] making 150 trillion connections.[82] If that's possible in biology, then what isn't?

Still, there is much skepticism in the scientific community, where many believe aging is an irreversible process.[83] "Anti-aging" is compared to "anti-gravity."[84] Vocal critics in the gerontology community have accused those suggesting the possibility of greatly extended human lifespans as being "contemptible … for duping the public" and claim that "anything past 130 [years of age] is ridiculous."[85] Such doubts are reliably countered by proponents who quote preeminent scientists of yore making similarly absolutist claims that did not age well.[86] Nobel Prize–winning physicists spoke of the prospect of nuclear power as "talking moonshine," a "completely unscientific Utopian dream, a childish bug-a-boo."[87] Lord Kelvin, considered one of the greatest scientists of his time, notoriously asserted, "Heavier-than-air flying machines are impossible,"[88] doubling down on their impracticality in 1902, just one year before the first flight at Kitty Hawk.[89]

Already in the laboratory, genetic mutations can affect a tenfold increase in lifespan, at least in a species of tiny worm.[90] In mice, dietary and genetic manipulation yields more like a 70 percent increase.[91] Single tweaks, such as methionine restriction, incorporated into one of my Anti-Aging Eight (see here), can extend the average and maximum lifespans of rats by about 40 percent,[92] which could translate to boosting human lifespan to an average of about 110, with the rare "centenarian" hitting 140 years of age.[93] These results have yet to be replicated in people, but if we discovered interventions not only to slow aging but to actively repair the accumulated damage, the sky could be the limit.

Starry-eyed scientists in the field imagine that time could be effectively melted away, like that surrealist painting of drooping clocks,[94] a "rejuvenation of your body leading ultimately to an endless summer of literally perpetual youth."[95] A "longevity escape velocity" is envisaged in

which we would just have to live long enough for innovations to add more time than is passing, the tipping point at which each year we can add at least one extra year of life expectancy.[96] This could theoretically enable humanity to have an essentially unlimited lifespan. Imagine dying the year before the critical juncture! I remain agnostic as to whether such a breakthrough is possible, but I hope this book will help regardless, whether you're striving to live long enough to live forever[97] or just trying to die young as old as possible.

FOUR BOOKS IN ONE

When I sat down to write (or rather stood up and started walking, typing at my treadmill desk), I needed to make a decision. What should I focus on? The more superficial signs of aging that everybody wants to know about, like wrinkles and graying hair, or the clinical aspects, like declining cognition? Or should I address how we might slow the aging process itself? I decided, as you can probably guess by the heft if you're reading a printed copy old-school style, all of the above.

My inspiration for writing *How Not to Age* was a consensus document titled "Interventions to Slow Aging in Humans" that was compiled by the top researchers in anti-aging medicine, the likes of Drs. Fontana, Longo, Sinclair, and dozens of others—nearly everyone who's anyone in the field. Brought together to identify the most promising strategies for developing drugs to combat aging, they identified a list of "essential pathways," for example, the pharmacological inhibition of the hormone IGF-1 or drugs to block the enzyme mTOR. As I looked through the list, I realized: *Every single one of these pathways could be regulated through diet.* That became the opening section of this book.

PART I: SLOWING ELEVEN PATHWAYS OF AGING

The science of aging has been called "the most dynamic and provocative in modern biology."[98] An attempt to classify the theories of aging published more than thirty years ago identified more than three hundred such theories, and the number has only grown since then.[99] In Part I, I identify the eleven most promising pathways for slowing the sands of time, ending each with

practical proposals for targeting them naturally with diet and lifestyle changes. Part I is the nerdy section, and it contains critical concepts and terms that will be used throughout the book.

PART II: THE OPTIMAL ANTI-AGING REGIMEN

The odds of living to age one hundred have risen from approximately one in twenty million to as high as one in fifty.[100] Why do some make it to their hundredth birthday but others don't? It's not just a matter of picking better parents. Studies following identical twins suggest that no more than 20 to 30 percent of the variance in lifespan is explained by gene inheritance.[101] The media loves stories about hard-living centenarians who attribute their longevity to some combination of lard, vodka, and their favorite brand of cigarette, but how do centenarians and supercentenarians (those older than 110) really eat and live?

In Part II, I delve deep into the behaviors that those in the five longevity hot spot "blue zones" around the world share in common. In constructing the optimal anti-aging regimen, I explore the best and worst foods and beverages. Is red wine deserving of its symbolic status for longevity? What about coffee? I cover the "longevity vitamin" ergothioneine, the vegetarian's Achilles' heel, and the best exercise and sleep routine for the longest, healthiest life.

PART III: PRESERVING FUNCTION

Then, in Part III, I get to the nitty-gritty. What can you do to preserve your bones, bowels, and circulation? Your hair, hearing, and hormone balance? Your immune function and joint health? Your mind and your muscles? Your sex life and skin? Your teeth, your vision, and, finally, your dignity in death? There are chapters on each. Sneak peeks can be had at see.nf/trailer.

PART IV: DR. GREGER'S ANTI-AGING EIGHT

My Anti-Aging Eight is the final section of the book, an actionable checklist to complement the Daily Dozen I established in my earlier book *How Not to Die*. In addition to the wealth of recommendations throughout *How Not to Age*, this last part highlights specific foods, supplements, or

behaviors that have the potential to offer some of the best opportunities to slow aging or improve longevity. My aim is to cover every possible angle for developing the optimal diet and lifestyle for the longest, healthiest lifespan based on the best available balance of evidence.

I. Slowing Eleven Pathways of Aging

INTRODUCTION

It has long been said that the best hope for a long life is to choose your parents wisely.[102] Doesn't longevity just run in the family? Siblings of centenarians, people who live to be at least one hundred, are certainly more likely to become centenarians themselves, and their parents are more likely to have lived to be at least ninety.[103] On the other hand, the lifespans of spouses sometimes correlate as much as—or even more than—those of genetic relatives.[104] Your partner may have as much of an impact as your parent. After all, we don't only pass down genes. Perhaps Grandma's healthy recipes or even a lifelong love of running runs in the family, too.

HOW IMPORTANT ARE YOUR GENES?

To tease out the role of genetics, researchers often turn to twin studies, comparing differences between identical twins and fraternal twins.[105] Check out see.nf/genes to understand exactly how this ingenious method works to estimate heritability and what this and other methods have found. In short, only about 15 to 30 percent[106] or less[107] of our lifespan appears determined by our genes, which means *how* we live our lives may determine the bulk of our destiny.

To leverage the lifespan leeway we have beyond the relatively small genetic component, we must first understand the various aging pathways. The term "anti-aging" has been much abused in popular culture, attached to all manner of unproven products and procedures. The term should probably be reserved for things that can delay or reverse aging through the targeting

of one or more of the established aging mechanisms.[108] In a landmark paper cited more than 7,000 times in the biomedical literature,[109] "The Hallmarks of Aging" identified nine common denominators of the aging process. I expound on them in see.nf/genes and address each one in this book.

There's a Fly in My Aging Research!

There are numerous ways to try to unlock the mysteries of aging. You could study long-lived individuals like centenarians and supercentenarians (people who reached the age of 110), for instance, or particularly long-lived smokers to uncover the secrets to their resilience.[110] Or, you could strike out in the opposite direction and study short-lived people, investigating tragic accelerated aging syndromes like progeria, where children age at eight to ten times the normal rate,[111] wrinkling, balding, and then typically dying around age thirteen of a heart attack or stroke.[112] Or, you could study long-lived animals. There's a clam called the ocean quahog, whose heart can beat more than a billion times over its five-century lifespan.[113]

In my video see.nf/models, I talk about both the opportunities and difficulties of extrapolating from the "model organisms" used in aging research, such as yeast, worms, flies, and mice,[114] as well as citizen science initiatives in which family dogs are enrolled in noninvasive studies to investigate why some "Methuselah dogs" reach ages of twenty-five or more, but 99.9 percent of other dogs do not.[115] Aged pooches suffer many of the same ravages of aging that we do, such as arthritis, cancer, cataracts, kidney problems, and muscle loss.[116] Advances made in canine longevity might not only be applicable to human aging but have the intrinsic value of enhancing the quality and quantity of life for the more than seventy million canine

companions with whom we share our homes in the United States alone.[117]

AMPK

In my book on everything evidence-based in weight loss, *How Not to Diet*, there is a section titled Amping AMPK. AMPK (AMP-activated protein kinase) is an enzyme that acts as a sensor for plants and animals, similar to a fuel gauge in a car. It revs up when it detects a depletion of the universal fuel, just as a light may blink on your dashboard when you're almost out of gas. AMPK flips the switch in your body from storing fat to burning it to restore energy balance. That's why AMPK is known not only as the *master energy sensor*[118] in our body but also the *fat controller*.[119] That's why it played a starring role in *How Not to Diet*. But it doesn't affect only weight control. It can also control aging.[120]

In times of plenty, our cells can plow full steam ahead. However, when times are lean—when there isn't enough food for an animal or enough light for a plant (darkness is essentially plant starvation)[121]—AMPK kicks in to reorient the cell into conservation mode and start tapping into energy stores, like burning off body fat. Our cells can also institute a recycling program called autophagy.

Autophagy is a housekeeping process by which defective cellular components, such as misfolded proteins that had been allowed to build up wastefully in times of surplus, are broken down and scrapped for spare parts. As I discuss in detail in the Autophagy chapter, autophagy doubles as both salvage operation and garbage disposal unit, scavenging raw materials in scarce supply while clearing away some of the built-up damaged debris that is implicated in the aging process. This is one of the reasons AMPK is increasingly recognized as a pro-longevity factor.[122] AMPK induces autophagy, which cleans house, sweeps away accumulated waste, and effectively institutes a sort of cellular reset.[123]

There are three main ways longevity researchers establish an aging pathway: Does the factor worsen with age? If you amplify it, does it accelerate aging? And, if you dampen it, does it slow aging and thereby

extend lifespan?[124] The loss of AMPK activity as we age fits all three criteria. As we grow older, AMPK levels drop and it gets harder to activate, harder to flip the switch to recharge our batteries.[125] When this decline is exacerbated, aging is hastened (at least in mice),[126] but when this process is reversed and AMPK activation is boosted, lifespan is extended in model organisms[127]—by as much as 38 percent in *C. elegans*,[128] a roundworm I profile in see.nf/models.

Up and down the evolutionary tree of life, the most reliable way to extend lifespan may be long-term food restriction.[129] AMPK activation is thought to be one of the mechanisms for this longevity boost. What was remarkable about the AMPK-boosting experiments, though, is that the animals' lives were extended even though they were allowed to eat as much as they wanted.[130] AMPK activators can effectively fool the body into thinking it is starving, switching it into protective housecleaning mode without causing any pangs of deprivation. In this way, AMPK activators can be considered dietary restriction *mimetics*, or imitators. That's why AMPK is considered a "druggable" target for longevity, with pharmaceutical companies producing a variety of AMPK activators.[131]

EXERCISE IN A PILL

Is there a way we can naturally boost AMPK activation to slow aging without starving ourselves? Since AMPK is activated by a fuel shortage, if we don't want to limit the amount of energy going in through our mouths, then we have to ramp up the amount of energy going out through our muscles. If you put people on bikes and take muscle biopsies while they cycle, a near tripling of AMPK activity can be detected within twenty minutes.[132] That's one way exercise can result in weight loss.

AMPK activation also leads to mitochondrial biogenesis, the formation of extra mitochondria, the power plants where fat is burned.[133] So, AMPK doesn't just shovel more fat into the furnace—it also builds more furnaces to burn that fat. This helps explain why endurance training enables us to run faster and farther over time. So, might an AMPK activator be "exercise in a pill"? Indeed, when sedentary mice were given an AMPK-activator drug for a month, it boosted their running endurance by 44 percent.[134] After one such

drug was discovered at the famed Tour de France,[135] AMPK activators were banned by the World Anti-Doping Agency.[136]

So, are we talking about not only fasting in a pill but an exercise mimetic, too? A way to trick our body into thinking it's starving without suffering from hunger, while also amping up our physical prowess? Obese individuals are often "unwilling to perform even a minimum of physical activity," wrote a group of pharmacologists, "thus, indicating that drugs mimicking endurance exercise are highly desirable."[137] The "mass appeal" of such a pill may tempt Big Pharma to "view physical inactivity as a market to be medicalized for profit,"[138] but that pales in comparison to the *universal* market for an anti-aging remedy.

POWER PLANT MAINTENANCE

In his book *On Youth and Old Age*, the Greek philosopher Aristotle described death as the loss of inner heat.[139] Well, the progressive loss of function of the estimated ten million billion mitochondria spread throughout our body[140] is considered a core tenet of the biology of aging,[141] one of the nine established hallmarks.[142] Mitochondrial dysfunction isn't just a consequence of aging, though, but also one of its causes. Dysfunctional mitochondria are thought to actively contribute to the aging process,[143] an insight illustrated by a pioneering experiment published in the early 1990s.[144]

If you inject mitochondria from a young rat into a human cell, nothing happens. The cell doesn't appear to notice. Each human skin cell averages about three hundred mitochondria, and adding ten to fifteen extra mitochondria from a rat pup doesn't appear to have any effect. But if you add the same number of mitochondria from an old rat—a centenarian in human years[145]—the human cells start to show signs of degeneration within just a few days.[146] Even just having a few percent of those old mitochondria was enough to drive the human cells to an early grave. So, age-impaired mitochondria don't just become less efficient—they may become actively harmful. That's where AMPK comes in.

With age, our mitochondrial function declines,[147] but building new cellular power plants, expanding existing ones, and decommissioning old ones (so-called *mitophagy*) are ways in which AMPK could promote

survival.[148] AMPK is said to serve as a "mitochondrial guardian" and in that role may help protect against the ravages of age-related disease.[149]

If an AMPK-activating drug really could help us reap the fat-burning and health-promoting benefits of fasting and exercise without the hunger and sweat, one could imagine how it would become one of the best-selling drugs on the planet.

And it is.

METFORMIN

Sold originally as Glucophage (meaning "sugar eater"), metformin is now prescribed more than eighty-five million times a year in the United States alone.[150] Despite all the strides in biotechnology, Big Pharma has yet to come up with a safer, more effective, first-line treatment for type 2 diabetes than an AMPK-boosting drug that retails at pennies per pill.[151] In see.nf/metformin, I talk about its interesting origin story and all the other upsides, including the mind-blowing revelation that diabetics placed on metformin may live longer lives than those who never got diabetes in the first place.[152] From a longevity standpoint, it's as if their diabetes diagnoses were beneficial, because they then had access to this lifespan-enhancing drug. If metformin is so powerful as to more than offset such a dreaded diagnosis as diabetes, should everyone be taking it?

In see.nf/metformindownsides, I cover its common but mild symptoms and the rare but potentially fatal one.[153] Another adverse consequence of metformin is less side effect than main effect. The way metformin boosts AMPK is by impairing our body's ability to produce energy by acting as a mild mitochondrial poison, so, not surprisingly, it may undercut physical fitness achievements from exercise, including aerobic capacity[154] and muscle gains.[155]

The only way to determine if metformin's benefits outweigh its risks for expanding the healthspan and lifespan of nondiabetics is to put it to the test. Enter the upcoming TAME trial, Targeting Aging with Metformin, which I profile in see.nf/tame. The bottom line is that there may be reason to temper our expectations. Though it can increase the average lifespan of certain mice by 5 percent, at a higher dose, metformin actually shortens lifespan.[156] Further reservations about its panacean prospects arise from the landmark

Diabetes Prevention Program study in which the drug only appeared to benefit those at highest risk.[157] One small study even found that despite metformin alleviating the insulin resistance of diabetics, the drug actually made things worse for nondiabetic obese individuals without the family history of diabetes.[158] So, healthier individuals may not reap the benefits of metformin that we try to extrapolate from longevity studies on diabetics.

FOODS THAT MAY IMPAIR AMPK

There's a type of saturated fat called palmitic acid that suppresses AMPK.[159] Although originally discovered in palm oil, palmitic acid is most concentrated in meat and dairy fat.[160] Of all saturated fats, palmitic acid appears particularly pathogenic when it comes to metabolic disease, cardiovascular disease, cancer, neurodegenerative diseases, and inflammation,[161] which is at least partly attributable to AMPK inhibition. This may be why saturated fat can be so toxic to the liver.[162]

SATURATING YOUR LIVER

Nonalcoholic fatty liver disease has become the leading cause of chronic liver disease in the world.[163] Studies now estimate seventy-five to one hundred million people in the United States already have it—about one in three American adults.[164] The overaccumulation of fat in the liver is caused by the overconsumption of calories,[165] but not all calories are equally liver-fattening. Excess sugar is often framed as the main culprit, but saturated fat is even worse. See my video see.nf/liver for details, but basically, overfeeding sugary foods, like candy and soda, can increase liver fat by 33 percent, whereas overfeeding the same amount of saturated fat (butter and cheese) increased liver fat by 55 percent.[166] Overfeeding unsaturated fats, like pecans and olive oil, only caused a 15 percent increase in liver fat,[167] presumably because unsaturated fats don't impair AMPK as potently as do saturated fats.[168]

What makes saturated fat particularly insidious is that it can increase liver fat even without enforced overeating. *Excess* sugar calories can foie gras your liver with fat, but even if you have people swap twenty-five spoonsful of sugar in the form of candy and soda into their diets each day, liver fat remains unchanged as long as they keep overall calorie intake

steady. But, if you do that with a fraction of the amount of saturated fat in the form of meat and dairy, even without being made to overeat, study subjects marbled their livers with 39 percent more fat within four weeks.[169]

FOODS THAT MAY BOOST AMPK

We know of more than a hundred plant products that can activate AMPK,[170] but many of them are toxic, to defend against noshing nibblers. Take nicotine, for example. Fat biopsies show that, compared to nonsmokers, those who light up have more than five times the AMPK activation.[171] Unsurprisingly, smokers often gain weight when they quit,[172] and nicotine gum can blunt that phenomenon.[173] Although smoking cigarettes may be one of the worst things you can do to yourself, it's one of the most reliable ways to lose weight, thanks to AMPK.[174] Is there any way to get the AMPK-boosting benefits without the risks of dying a gruesome death from lung cancer?

BARBERRIES

Because AMPK activation leads to weight loss, I cover a number of natural AMPK activators in my book on the subject, including berberine, found in barberries. Rather than reiterate it here, allow me to refer you to the Raising the Barberries section of my Amping AMPK chapter in *How Not to Diet.*

In short, barberries, which can be found inexpensively priced at Middle Eastern groceries in dried form, have been shown to successfully lower LDL cholesterol levels an average of fourteen points (mg/dL),[175] as well as improve acne,[176] artery function,[177] triglycerides, blood sugars, and insulin resistance.[178] One could achieve the dose of berberine used widely in China for diabetes management,[179] which is presumably AMPK-enhancing, by eating as few as two teaspoons of barberries three times a day or a single tablespoon twice a day.[180] Eating the whole food is preferable, especially since an analysis of berberine supplements on the market found that 60 percent failed to match what was claimed on their labels.[181]

A word of caution: Barberries are classified as unsafe to eat during pregnancy and are not recommended for consumption while breastfeeding.[182] The reason so many different plants produce compounds that activate AMPK may be for self-preservation; they may be trying to

fend off herbivores by producing compounds that impair animal metabolism. These functions can be harnessed for our benefit but could potentially be harmful for developing fetuses and infants. Cyanide is another AMPK activator and can kill by completely blocking energy production, whereas compounds like berberine and metformin are thought to just impair our mitochondrial function, making energy production less efficient.[183]

BLACK CUMIN

Black cumin is another plant traditionally used in Middle Eastern cuisines that can boost AMPK.[184] Please see the Black Cumin section in my Appetite Suppression chapter in *How Not to Diet*. In summary, from the more than one thousand papers published in the medical literature about the spice, daily black cumin consumption has been found in systematic reviews and meta-analyses of randomized controlled trials to significantly improve weight loss,[185] cholesterol, triglycerides,[186] blood pressure,[187] and blood sugar control.[188] Typical doses used in studies are just 1 or 2 g of black cumin a day, which is about a quarter teaspoon.[189] Using such small amounts allows researchers to conduct randomized, double-blind, placebo-controlled trials by putting the whole-food spice into capsules rather than extracting out just a few components.

The spice also lowers markers of inflammation, such as C-reactive protein,[190] and has favorable effects on inflammatory conditions, such as asthma,[191] rheumatoid arthritis,[192] and a common cause of hypothyroidism called Hashimoto's thyroiditis.[193] Black cumin also appears to help get rid of kidney stones[194] and help with the symptoms of menopause.[195] The dose used in most of these studies would cost about three cents a day.

HIBISCUS AND LEMON VERBENA TEA

Another AMPK-boosting zinger is hibiscus,[196] which delivers the tart cranberry-like flavor and bright red color of Red Zinger tea. Also known as *roselle* or *jamaica*, hibiscus tea has been enjoyed around the world for millennia as both a delicious hot or cold drink and an ancient medicinal remedy.[197] In *How Not to Die*, I covered its blood pressure benefits, working as well as,[198] or even beating out, some antihypertensive medications in

head-to-head clinical trials.[199] In *How Not to Diet*, in the Flower Power section of my Fat Blockers chapter, I describe its role in AMPK activation[200] and in improving blood sugars, LDL cholesterol,[201] artery function,[202] and weight loss,[203] with or without another herbal tea, lemon verbena. See here for my note about tooth enamel and sour beverages, though.

VINEGAR

Hibiscus[204] and black cumin[205] bump up AMPK the same way barberry's berberine and metformin do—by interfering with cellular energy production. Can we activate AMPK without mucking with our mitochondria?

Alcohol is yet another plant product that activates AMPK, but it does so by a totally different mechanism. Our body detoxifies alcohol into acetic acid but has to use energy to then metabolize it.[206] So AMPK is activated naturally in response to this fuel expenditure.[207] Before alcohol gets fully converted into acetic acid, though, there is a toxic intermediate called *acetaldehyde*, which is a known carcinogen. That may be why alcohol consumption has been found to increase the risks of at least half a dozen cancers,[208] including breast cancer, even among light drinkers.[209] Is there any way to skip over the toxic step and take in acetic acid directly?

Upon reviewing AMPK's role in burning off excess body fat, a researcher determined that "it is crucial that oral compounds with high bioavailability are developed to safely induce chronic AMPK activation … [for] long-term weight loss and maintenance."[210] Why develop such a compound when you can already buy it at any grocery store? It's called vinegar.

Acetic derives from the Latin word *acetum*, meaning "vinegar." By definition, vinegar is merely a dilute solution of acetic acid in water.[211] When we consume vinegar, the acetic acid is absorbed and metabolized, giving us a natural boost in AMPK at the dose you might typically get dressing a salad.[212]

In the Take an Acid Trip section of my Amping AMPK chapter in *How Not to Diet*, I cover how vinegar can diminish both visceral and superficial body fat[213] and reduce blood sugars in diabetics on par with antidiabetic drugs[214] by improving the uptake of blood sugar by our muscles.[215] That's an

AMPK effect also seen with exercise.[216] Surprisingly, vinegar plus metformin worked better to control blood sugars than metformin alone, suggesting either additive benefits to further AMPK stimulation (the metformin dose was relatively low) or vinegar benefits above and beyond AMPK.[217]

Vinegar has also been shown to improve artery function[218] and to have other AMPK-activation benefits, such as decreasing blood cholesterol and triglyceride levels.[219] Can it make you live longer? In *C. elegans*, vinegar has a "prominent lifespan-extending effect,"[220] but it's never been tested in people. The Harvard Nurses' Health Study did find that women who consumed at least one tablespoon of oil and vinegar salad dressing five or more days a week had fewer than half the fatal heart attacks compared to women who hardly ever used the dressing. Even after taking the extra vegetable intake into account, they found a 54 percent lower risk of dying from the number one killer of women.[221]

FIBER-RICH FOODS

Don't like the taste of vinegar? Instead of delivering acetic acid through your mouth, you can also supply it to your bloodstream from the opposite direction. You know how vegetables and grains turn sour when they're fermented? Think sauerkraut or sourdough. That's because there are good bacteria like *Lactobacillus* that produce organic acids like lactic acid. Acetic acid is a type of short-chain fatty acid made by the friendly flora in our gut from the fiber and resistant starch we eat. These prebiotics are concentrated in legumes (beans, split peas, chickpeas, and lentils) and whole grains, but fiber can be found throughout the plant kingdom. When we eat whole plant foods, our gut flora can make acetic acid from scratch inside our colons by fermenting fiber. Then, that acetic acid can get reabsorbed back into our bloodstreams. So, we can use the top-down approach to activate AMPK by consuming vinegar or the bottom-up approach by eating fiber.[222]

How much fiber are we talking about? Even eating just the measly minimum recommended intake of fiber of about 30 g a day can result in the production of more than four tablespoons' worth of vinegar in our colon.[223,224] Some inevitably get flushed, so only about 40 percent of the acetic acid produced in the colon gets absorbed,[225] but if we eat enough

healthful foods, it could potentially have a substantial impact on our AMPK status. The sparking of AMPK by colon-produced acetic acid is suspected to play a role in some of the metabolic benefits of a high-fiber diet.[226]

Based in part on studies of human coprolites[227]—fossilized feces (paleopoo!)—our ancient ancestors may have consumed in excess of 100 g of fiber a day.[228] That's more than five times that of the average American today.[229] So, we evolved to be AMPK-activating machines, not only because we were often hungry and active but because our guts were churning out spoonfuls of vinegar every day from all the plants we ate. And, before you ask, no, you can't just take a fiber supplement like psyllium (Metamucil) because it's nonfermentable, meaning our gut bacteria can't eat it. So, although such fiber supplements can improve bowel regularity, they cannot be used to make the key ingredients for AMPK activation.[230]

Food for Thought

The discovery of AMPK is considered to be one of the most important breakthroughs in biomedicine in the last few decades.[231] Because this enzyme is involved in the functioning of the majority of aging-associated regulators, including autophagy, which I discuss next, the importance of AMPK in anti-aging interventions is hard to overestimate.[232]

The drug metformin activates AMPK but carries adverse side effects and may not benefit healthy individuals. AMPK is an energy sensor, so it's activated when we eat less or move more. Some food components, like saturated fat, can suppress AMPK, whereas others, like fiber, can boost it. There are also specific AMPK-activating compounds in barberries, black cumin, hibiscus tea, and vinegar.

To help boost this anti-aging pathway, at each meal, consider:

- reducing consumption of saturated fat (concentrated in meat, dairy, and desserts)

- increasing consumption of fiber (concentrated in legumes and whole grains)
- taking each of the following:
  - 2 teaspoons of barberries
  - a dash (1/12 teaspoon) of ground black cumin
  - ¾ cup hibiscus tea mixed with ¼ cup of lemon verbena tea
    2 teaspoons of vinegar (though *never* taken straight; sprinkle on food or dilute it in the tea)

AUTOPHAGY

When food is scarce, our body shifts into conservation mode, slowing down cell division and turning on the process of autophagy,[233] from the Greek *auto* meaning "self" and *phagy* meaning "to eat." Autophagy means, quite literally, "eating yourself."

TAKING OUT THE TRASH

Upon realizing there isn't much food around, our body starts rummaging through our cells in a salvage operation, looking for anything we don't need —defective proteins, malfunctioning mitochondria, and other stuff that isn't working anymore. It clears out the junk and upcycles it, turning it into fuel or new building materials, thereby renewing our cells. So, autophagy plays two major roles: nutrient recovery and quality control. The conservation of autophagy machinery over a billion years of biological evolution underscores the importance of this universal recycling program,[234] recognized in 2016 with a Nobel Prize awarded for teasing out its secrets.[235]

At any given time, most of our cells are producing and assembling more than 10,000 distinct proteins.[236] Each of them can become misfolded or damaged at any moment and require a cleanup on aisle three. We evolved in a context of scarcity, though, where food was hard to come by. When we'd get to eat next was unpredictable. So, our body expects we'll fall back on hard times any day—maybe even tomorrow—and figures it can put off

cleaning up until then. But, these days, those lean times hardly ever come. Most of us live in nutrient excess, so our body figures, *why bother*? We can just toss the defective protein or broken-down mitochondrion in the corner and make another. So, our cells end up continually hoarding junk.

The buildup of cellular detritus isn't merely wasteful but harmful, too. Out with the old and in with the new doesn't just restock the pantry; it also clears away decay. Our ancient ancestors often ate only once a day or went for several days without any food, so our autophagy switches were constantly getting tripped.[237] Today, in our three-meals-a-day world, our cells no longer need to look under the couch cushions for sustenance, and the trash heaps just pile higher.

In the modern context of not only having relatively easy access to sufficient nutrients but to food in excess, our baseline rate of autophagy is low[238] and slips down even lower as we get older. A decline in autophagic capacity with age has been described in nearly all animals analyzed.[239] This can lead to more accumulation of cellular debris, which can then further impair our aging cells. This may be why inadequate autophagy is not just a consequence of aging but is considered to be one of its causes.

Autophagy is critical for most lifespan-enhancing interventions. Whether through diet, drugs, or genetic manipulations, if autophagy pathways are blocked, so, too, are many pro-longevity effects. What's more, autophagy appears to be not only necessary for life extension but also, in some cases, sufficient.[240] Boosting autophagy alone can lengthen lifespan in mice by an average of 17 percent, as well as improve healthspan.[241] No wonder autophagy is at the forefront of so much longevity research.[242]

FAST OR GO FAST

The most commonly cited inducer of autophagy is dietary restriction, which gives new meaning to the term fasting "cleanse,"[243] but autophagy doesn't really maximally ramp up until twenty-four to forty-eight hours of fasting, which is too long to go unsupervised.[244] (See here, Don't Try This at Home.) However, moderate dietary restriction over the long term may also work, based on muscle biopsies taken from volunteers of the Calorie Restriction Society. See details in see.nf/fast.

Dietary restriction has been called the "safest way" to stimulate autophagy,[245] but that distinction probably belongs to exercise, though it may take sixty minutes or more of moderate to vigorous aerobic exercise (55 to 70 percent VO_2 max).[246] Again, more details in the video. High-intensity interval training didn't seem to make a difference,[247] and to date, data are insufficient to characterize the autophagy response to resistance exercise.[248]

FOODS THAT MAY IMPAIR AUTOPHAGY

As I discussed in the last chapter, we know that the enzyme AMPK activates autophagy. So, anything that suppresses AMPK activation, like saturated fat intake, may also suppress autophagy. Inversely, the enzyme mTOR (see the chapter on mTOR) deactivates autophagy,[249] so anything that activates mTOR, like animal protein,[250] may also suppress the autophagy process. When study participants completely fasted for thirty-six hours and were then given a whey protein drink, their autophagy levels were suppressed significantly more than if they were given even more calories of straight carbohydrate.[251] Some carbohydrate-rich foods, though, notably french fries and potato chips,[252] may inhibit autophagy through another mechanism, acrylamide.

Watch see.nf/acrylamide for details, but basically, acrylamide is a chemical formed when carbohydrates are exposed to particularly high temperatures that can inhibit autophagy, at least in cells in a petri dish.[253] This may explain why high acrylamide exposure is associated with increased mortality.[254] A diminished lifespan among frequent eaters of fast food and salty snacks isn't exactly a revelation, but an experiment I profile in the video comparing the effects of potato chips to boiled potatoes mixed with the same fat and salt does seem to implicate the chemical,[255] though acrylamide isn't the only potentially harmful by-product of deep frying. As one of the earliest geriatric medicine textbooks presciently concluded in 1849, "frying is an abomination."[256]

FOODS THAT MAY BOOST AUTOPHAGY

Any food that activates AMPK should also activate autophagy, so any of the AMPK-boosting foods in the previous chapter should fit the bill. However, autophagy can also be activated directly in pathways independent of AMPK. The most reliable way to kick autophagy into high gear may be to eat less food altogether, but there is a downside to dietary restriction: Starving yourself, as was understated in a major review, "generates discomfort."[257] There is, however, something we can consume that induces autophagy that many find comforting: coffee.

COFFEE

We've long known that alcohol consumption is associated with liver inflammation, but a group of Norwegian researchers made an unexpected finding back in 1986: Coffee consumption is associated with *less* liver inflammation.[258] Subsequent studies conducted around the world replicated their results. In the United States, for example, researchers looked at people at high risk for liver disease—those who were overweight or drank alcohol in excess, for instance—and found that those who drank more than two cups of coffee a day appeared to have less than half the risk of developing chronic liver problems as those who drank less than one cup.[259] The fact that regular coffee consumption seems protective against the development of fatty liver disease[260] gave researchers an idea.

Since autophagy plays such an important role in clearing fat out of the liver,[261] they tested whether caffeine might have cell-cleansing properties. Indeed, it was found to be a potent autophagy stimulant.[262] So, does coffee or caffeine extend the lifespan of model organisms like yeast and worms? Yes[263] and yes.[264] Mice, too. In mice, coffee rapidly triggered autophagy within hours at a human-equivalent dose. Moreover, the autophagy-promoting properties of coffee were independent of the caffeine content—decaffeinated coffee worked just as well.[265] Both regular and decaf also had similar anti-aging effects on another aging pathway (mTOR)—in mice.[266] What about in people?

A systematic review of the health impacts of coffee concluded that "daily coffee consumption should be encouraged" in patients with chronic liver disease.[267] If coffee enhances autophagy, shouldn't its benefits extend to a wide range of diseases? Yes. Intake is also associated with lower risk of kidney disease,[268] along with reduced risk of conditions as varied as gout, type 2 diabetes, skin cancer, and Parkinson's disease. Decaf was also associated with a range of health benefits.[269] The results are all the more remarkable because many of the studies failed to adequately control for smoking and unhealthy food intake, both of which tend to accompany coffee drinking.[270] So, coffee drinkers appeared to be healthier in spite of their tendency for less wholesome habits. Does all this translate into them living longer? Apparently so.

Interventional studies on rats showing that coffee can improve lifespans go back to the 1940s.[271] We only have observational research on coffee and mortality in humans, but, to date, more than twenty studies following more than ten million individuals over time have found that, overall, those drinking three cups of coffee a day had 13 percent lower risk of death from any cause.[272] If practiced throughout adulthood, that would be expected to translate into approximately an extra year of life.[273]

Three cups of decaf appeared to be just as protective, so it's not the caffeine.[274] This is supported by data showing the longevity link extended similarly to those who were genetically slow caffeine metabolizers and others who metabolize caffeine more quickly.[275] If it's not the caffeine, then what is it? Coffee contains more than a thousand bioactive compounds. The polyphenol chlorogenic acid is the most abundant antioxidant in coffee beans,[276] so researchers started there and indeed found that it was able to enhance autophagy in cultured human cells.[277]

How to Brew the Most Healthful Cup

More than a hundred coffees have been tested, and the levels of chlorogenic acids varied by more than thirtyfold. Interestingly, the major contributor widening the range was the coffee purchased from Starbucks, which had an extremely low chlorogenic acid content, averaging ten times lower than the others.[278] This may be because Starbucks roasts its beans so dark.[279]

Caffeine is relatively stable to heat, but a dark roast may wipe out nearly 90 percent of the chlorogenic acid in the beans.[280] The difference between a medium light roast and a medium roast did not appear to matter, though—at least when it came to boosting the total antioxidant status in people's bloodstreams after drinking the coffees.[281]

Don't be fooled by "low acid" coffee. It doesn't help with the acid reflux, heartburn, or stomach upset that plagues some coffee drinkers. The low acid is a reference to low *chlorogenic* acid—which is exactly what we don't want. Low-acid coffee producers use a slow roasting process that destroys the autophagy-activating compound. That's like an orange juice company going out of its way to destroy the vitamin C and then branding its OJ as "low acid." Technically true, since vitamin C is ascorbic acid, but the OJ maker would be bragging about destroying some of the nutrition, and that's exactly what low-acid coffee companies are doing.[282]

Save Room for Milk in Your Coffee?

Adding dairy milk or creamer may undercut some of coffee's benefits. The milk protein casein binds to chlorogenic acid and thereby may block its absorption in the digestive tract.[283] Based on human urine studies, drinking coffee with milk cuts bioavailability of chlorogenic acid, dropping it from 68 percent (in black coffee) down to 40 percent (in a latte).[284] Milk protein can also undercut the benefits of tea,[285] berries,[286] and chocolate.[287]

What about soymilk? In a test tube, phytonutrients in coffee not only bind to proteins in dairy but also in eggs and soy.[288] Eggs haven't been put to the test yet in humans, so the jury's still out on whether having an omelet with black coffee would impair absorption, but soy appears to have been given the all-clear. Soy proteins initially bind up the coffee compounds in the small intestine, but our good bacteria release them so they can be absorbed down in the lower intestine.[289] Other nondairy milks, such as almond-, rice-, oat-, and coconut-based milks, have so little protein

that I'd assume there wouldn't be a binding issue, but they have yet to be directly tested.

The freeze-drying and spray-drying processes used to make instant coffee don't seem to significantly affect levels of chlorogenic acids, but the preparation method used to make fresh coffee does. Brewed coffee has higher chlorogenic acid content than espresso, presumably due to the longer contact time between water and coffee grounds, as well as the greater ultimate volume.[290]

The brewing method also affects the impact of coffee on our cholesterol. Watch see.nf/cafestol to see why paper-filtered is preferable. A study out of Norway following half a million men and women for an average of twenty years appeared to corroborate the cholesterol concern on a population scale. Those drinking paper-filtered coffee had even lower mortality rates than those drinking unfiltered coffee.[291] These findings led some to bemoan the growing popularity of "unfiltered" brews from capsule coffee machines,[292] but the little plastic cups, like K-cups, actually have a paper filter inside. Capsule coffee does end up with more estrogen-like chemicals in it,[293] as one would expect from heating nearly any sort of plastic (BPA-free or not),[294] but the levels found were low compared to established safety guidelines.[295]

Grounds for Concern?

Coffee is not for everyone. People with glaucoma[296] or perhaps even merely a family history of it[297] may want to stay away from caffeinated coffee. Consumption is also associated with urinary incontinence in women[298] and men.[299] There are case reports of individuals with epilepsy having fewer seizures after laying off coffee, so avoiding it is certainly worth a try if you have a seizure disorder.[300] Coffee may also worsen acid reflux disease.[301] Finally, it almost goes without saying that if you have trouble sleeping, you might not want to drink too much caffeine.

Just a single cup of caffeinated coffee at night can cause a significant deterioration in sleep quality.[302]

There are also consistent associations between drinking coffee and certain adverse outcomes during pregnancy, including miscarriage, early preterm birth, and low birth weight. Coffee consumption has not been linked to birth defects, but it may increase the risk of childhood leukemia.[303]

Also, don't stick it up your butt. A recent review on the questionable safety of coffee enemas warned against their use, citing reports of colitis, electrolyte imbalance, rectal burns, and perforation.[304]

Keep in mind that daily consumption of caffeinated beverages can lead to physical dependence. It's no coincidence that Americans alone spend nearly $75 billion annually on the stuff.[305] Caffeine withdrawal symptoms can include days of headache, fatigue, difficulty concentrating, and mood disturbances.[306] Ironically, coffee's tendency to be habit-forming could turn out to be a good thing. If coffee is indeed confirmed to induce autophagy and increase longevity, then a daily habit may ultimately prove to be an advantage.[307]

SPERMIDINE

In 1676, Antonie van Leeuwenhoek, the father of microscopy, was the first person in history to see bacteria. The following year, he saw his own sperm,[308] and a year after that, in 1678, he discovered tiny crystals forming in the semen he had left sitting around.[309] Centuries later, this compound would be recognized as spermine. It and its precursor spermidine are actually found throughout the body, so their names are just an accident of history. It was independently discovered in brain tissue in 1885 and named "neuridine," but when it was revealed to be the same as spermine, naming rights defaulted to the indelicate original.[310]

Spermidine plays a key role in regulating cell growth.[311] It is positively charged, so it naturally binds to negatively charged molecules like DNA.[312]

Spermidine fits neatly in both the major and minor grooves of the DNA helix.[313] Most spermidine in our body is actively bound to our genetic material,[314] stabilizing our genetic code for proper translation.[315] Spermidine is also a potent activator of autophagy.

The spermidine in our tissues is obtained from three sources. Our cells can make it from scratch from an amino acid called arginine, as can certain bacteria in our gut, or we can get it preformed directly through our diet.[316] Certain foods are naturally rich in it. Once ingested, dietary spermidine is rapidly absorbed and circulates throughout our body to contribute to cellular pools.[317] Feed extra spermidine to mice, and they live up to 25 percent longer and have more healthful lives.[318] Similar lifespan and healthspan benefits were also found across other tested species, as detailed in the landmark paper "Induction of Autophagy by Spermidine Promotes Longevity."[319]

The problem is that spermidine levels decline with age. Ours tend to drop by more than half by the time we reach our fifties.[320] This decline is seen across the biological spectrum, but there is a remarkable exception.[321]

The naked mole rat (sometimes referred to by its cuddly nickname, sand puppy) lives an astonishing ten to twenty times longer than other rodents of a similar size without showing any signs of visible aging.[322] They can live for decades without exhibiting typical indications of deterioration, such as loss of fertility or muscle mass. The naked mole rat is considered a "non-aging mammal." This amazing feat may have to do with the maintenance of consistently high levels of spermidine throughout their lifetime, because the same has been found in human centenarians.[323]

Researchers in Italy found that by the time most people reached their sixties and seventies, their spermidine levels had already fallen to about a third of what they measured in middle age. But those living into their nineties and beyond were somehow able to maintain their youthful spermidine levels, presumably by just making more of it internally. However, we could also replenish declining levels *externally* with a spermidine-rich diet. The researchers suggested foods like soybeans and mushrooms,[324] but, as we'll learn, wheat germ is an even more concentrated natural source.

What's particularly encouraging about the rodent studies is that the extra dietary spermidine extended lifespans even when started late in life in older

mice,[325] the human equivalent of changing your diet when you're already in your fifties.[326] Significant anti-aging effects were also found throughout vital organs—in the heart, kidneys,[327] and liver—and in boosted autophagy in the brain.[328]

Wheat Germ vs. Dementia

In see.nf/wheatgermdementia, I review all the trials of spermidine for cognition, including a remarkable study in which those with mild dementia randomized to eat rolls made with added wheat germ (versus wheat bran) experienced cognitive improvements "way beyond all available antidementia treatments so far."[329]

Letting Your Hair Down

Our hair follicles, as one of the most highly active tissues in all of mammalian biology, are like little spermidine-generating machines. In see.nf/spermidinehair, I show how taking the amount of spermidine in a daily half teaspoon of wheat germ[330] can significantly reduce hair shedding (as determined by the so-called pull test) compared to placebo even months after the study ended.[331]

Out-of-Antibody Experience

Long-term immunity requires the maintenance of Methuselahian antibody-producing cells, yet the level of spermidine in our cells drops as we age, a decline in autophagy follows, and the ability of our immune cells to function declines.[332] As I show in see.nf/immuneheart, a restoration of youthful spermidine levels can improve antibody production in immune cells taken from older adults,[333] suggesting that spermidine may help "reverse immune aging."[334]

For the Faint of Heart

In see.nf/immuneheart, I also review the evidence that led to the medical journal editorial "Spermidine to the Rescue for an Aging Heart."[335] The reason people who eat more spermidine tend to have less cardiovascular disease[336] may be that spermidine can restore autophagy in the cells lining our blood vessels that are responsible for healthy artery function.[337]

Higher levels of dietary spermidine were found to correlate with reduced blood pressure and a lower combined incidence of heart attack, stroke, and death from vascular disease. Okay, but the top sources of spermidine in the population studied were whole wheat, apples, pears, and salad.[338] How do we know spermidine intake wasn’t just a proxy for a more healthful diet in general? Only recently did we discover that not only do the apparent benefits appear to be independent of dietary quality but the magnitude of the effect seems unprecedented.

Eight hundred men and women in their forties through eighties were followed for twenty years. Researchers looked at 146 different nutrients in their diet, and the component most predictive of longevity was spermidine. Those who consumed the most spermidine didn’t just have lower risk of dying from cardiovascular disease; spermidine intake was associated with a lower risk of *all* major causes of death, which is what we’d expect from an anti-aging agent. Critically, this survival advantage persisted even after controlling for dietary excellence, meaning it didn’t appear to be just because they were eating more healthful foods in general.[339]

How big of an effect are we talking about? The mortality rate of those in the top third of spermidine intake (consuming more than about 12 mg a day) was compared to those in the bottom third (consuming less than 9 mg a day). The difference in death rate was as if those eating more spermidine were 5.7 years younger.[340] By eating more of certain foods, it’s as if they had effectively turned back the clock nearly six years.

The findings were so extraordinary that, before publication, the researchers sought to replicate their results in an entirely separate cohort of individuals. And, indeed, they arrived at the same conclusion.[341] This led some to propose that, as we age, spermidine approaches the status of a vitamin.[342] When we’re younger, we seem to be able to make enough ourselves, but, as we get older, we need to start ensuring that we’re getting enough through our diet to maintain autophagy into old age. If spermidine is going to be considered an anti-aging vitamin, where is that “vitamin” found?

In developed countries, the average intake of spermidine is approximately 10 mg a day.[343] Some countries in Asia and Europe, especially around the Mediterranean,[344] achieve a per capita daily intake closer to 13 mg or higher,[345] while the United States is down at 8 mg,[346] which may not be surprising since vegetables are the main source.[347]

Swedish researchers calculated that a healthy diet would include 25 mg of spermidine for women and 30 mg for men.[348] If those of us in the United States need to bump up our average daily intake from 8 mg, where are we going to find another 20 mg? Rich spermidine sources fall into three main categories: "unprocessed plant-derived foods" (including mushrooms, though they're technically fungi), certain fermented foods[349] (some bacteria can make it, too, if you recall), and select animal viscera (internal organs).

Which are the best sources? There are a number of different ways that you can rank nutrients in food. You could order them by spermidine per calorie to see which has the best bang for your caloric buck. Or you could sort by spermidine per dollar to see which has the best bang for your actual buck. In the medical literature, the most common ranking is by weight, so you can see which foods are most concentrated with spermidine, ounce for ounce. However, this can be misleading for practical purposes. By this measure, dill, for example, has been singled out for its high spermidine content, ranking as high as chickpeas on a pound-for-pound basis,[350] but one serving of chickpeas (about a third of a can) weighs as much as a hundred servings of dill (five hundred sprigs).[391] On paper, garlic has as much spermidine as potatoes,[392] but it's easier to eat a small baked potato[393] than the same weight in garlic, about seventy-seven cloves.[394,395] So, it's probably most useful to list top spermidine sources by serving.

TOP SPERMIDINE SOURCES

(MILLIGRAM PER 100-GRAM SERVING UNLESS OTHERWISE SPECIFIED)

1. 9.7 mg: tempeh[351,352]
2. 9.2 mg: mushrooms[353,354]
3. 9.2 mg: pig pancreas (1 oz)[355]

4. 8.2 mg: natto (1 oz)[356]
5. 6.1 mg: mango (one, 210 g)[357,358]
6. 5.9 mg: edamame[359,360]
7. 5.8 mg: green peas[361,362]
8. 5.7 mg: cheddar (aged one year, 1 oz)[363]
9. 5.5 mg: lentil soup (1 cup)[364]
10. 5.1 mg: soybeans[365]
11. 4.4 mg: lettuce[366]
12. 4.3 mg: polenta[367]
13. 4.3 mg: corn[368,369]
14. 3.8 mg: soymilk (1 cup)[370]
15. 3.8 mg: mussels[371]
16. 3.7 mg: broccoli[372,373]
17. 3.4 mg: cow intestine[374]
18. 2.9 mg: chickpeas[375]
19. 2.8 mg: cauliflower[376,377]
20. 2.7 mg: celeriac[378]
21. 2.6 mg: yellow peas[379]
22. 2.5 mg: wheat germ (1 Tb)[380]
23. 2.5 mg: french fries[381]
24. 2.4 mg: oysters[382]
25. 2.4 mg: lentils[383]
26. 2.4 mg: adzuki beans[384,385,386]
27. 2.3 mg: eel livers (1 oz)[387]
28. 2.2 mg: salad[388]
29. 2.1 mg: popcorn (50 g)[389]
30. 2.0 mg: kidney beans[390]

On the previous page is an exhaustive list of virtually every food I could find that consistently, on average, reaches 2 mg of spermidine per serving. Note that I didn't restrict the chart based on accessibility or palatability (since that differs individual by individual), nor, necessarily, on healthfulness. (Just because french fries and certain aged cheeses are high in spermidine does not mean the road to longevity is paved with cheesy fries.)

Note also that the list is not necessarily representative of the leading contributory sources of spermidine on a population level. For example, green peas may be the number one source of spermidine in the United States even though they are down at number seven on this list of most concentrated sources.[396] Even though whole-wheat bread has about three times more spermidine than white bread, people may net fourteen times more spermidine from white bread overall, given its popularity. Indeed, one study in Turkey even computed white bread as the leading food source.[397]

Going down the "Top Spermidine Sources" list, you'll notice that soy foods grab four of the top ten spots. Tempeh, which wins the gold, typically comes in 8-oz packages, and just one of those could completely fill the daily 20 mg spermidine gap. Mushrooms take the silver. Interestingly, plain white mushrooms may have twice the spermidine content as "fancier" mushrooms like enoki or shiitake.[398] (Cooking mushrooms does not appear to affect levels.[399])

Up next? Duking it out for most divisive source are pig pancreas and natto, a fermented soy food strong in funk and stringy slime. Speaking of funk, durian fruit, described as having "a sperm-like odor,"[400] is an even more concentrated source of spermidine than mango.[401] It would have made the list had I been playing fair. (For an explanation of my excision of durian fruit with extreme prejudice, you can read about my humorous-only-in-retrospect run-in with durian in *How Not to Die*.)

Although apples and pears represent leading contributors to population-wide intake,[402] they pale in comparison with mangos, which average more than ten times the spermidine concentration.[403] I used a small mango in my calculation, but larger varieties, like Tommy Atkins, Keitt, Kent, or Haden, yield an average of 336 g of peeled, pitted fruit, which would top tempeh as the reigning champ.[404] Two large mangos alone could fill that daily spermidine gap.

Dairy milk has little or no spermidine to begin with, but the bacteria in certain types of ripened cheese make significant amounts. So, while American cheese and mozzarella don't have any, blue cheese can have 1.1 mg of spermidine per ounce,[405] and, as you can see, extra-sharp cheddar ripened at least a year actually makes the list.[406] Cheese in general only averages about 0.6 mg,[407] though, and even some aged varieties, such as Gouda, ripened for six months, are lacking.[408] Yogurt doesn't have any

either,[409] which suggests only certain types of bacteria produce it. Sauerkraut, for instance, doesn't appear to have any more spermidine than fresh cabbage.[410]

Soymilk, however, is a concentrated source[411] and is presumably the only type of milk with significant levels at 3.8 mg per cup. The next beverages don't even come close. Tomato juice has 0.5 mg per cup,[412] followed by high-quality red wines with 0.3 mg per glass.[413] There doesn't appear to be any spermidine in white wine.[414]

While there isn't any spermidine in coffee, tea leaves are said to be "conspicuously rich" in it.[415] They are, pound for pound, but a tea bag usually only has about 2 g of tea so we're talking about 0.3 mg per cup of matcha green tea and less than 0.1 mg per cup of regular green or black tea.

As a certified dark green leafy snob, I was begrudgingly impressed to see lettuce score so high.[416] Lettuce is light, so the 100 g stacks up to 3 cups,[417] but the spermidine in even small side salads could really add up. The popcorn volume was high, too, so much so that I felt I should at least cut the serving size in half—100 g of air-popped popcorn exceeds a dozen cups!

Polenta rounds out the first dozen. The high spermidine content in corn has even caused some to speculate that it may be the reason why maize-raising regions of Japan seem to have such lower mortality rates from Parkinson's disease,[418] a condition caused by the buildup of misfolded proteins in the brain that spermidine-induced autophagy may help clear.[419]

Organic versus conventional cultivation of vegetables does not make much of a difference.[420] Boiling vegetables can leach some spermidine into the cooking water, but it seems to get destroyed only by high dry-heat cooking methods.[421] The same is true for meat. For example, roasting and grilling chicken wipe out about half the spermidine, compared to boiling or stewing, which only causes about a 15 percent decrement.[422] Either way, chicken's contribution is relatively minimal.

While whole plant foods only account for about 10 percent of America's diet,[423] plants provide more than 80 percent of the spermidine in Western countries.[424] Eggs have none, most dairy products have little,[425] and few people are eating animal innards higher in spermidine content. The spermidine in muscle meat is relatively low, averaging 0.4 mg per 3-oz serving and only 0.2 mg in fish.[426] The meat with the most is mussel

muscle. Scallops and clams don't seem to have as much,[427] but oysters and mussels make the chart.[428]

If one wanted to extend the chart down to 1.5 mg per serving, the next entries would be 1.9 mg in a potato (170 g),[429,430,431] 1.8 mg in rabbit liver (1 oz),[432] 1.8 mg in pine nuts (1 oz),[433] 1.7 mg in asparagus,[434] 1.6 mg in peanuts (1 oz),[435] 1.6 mg in cucumber,[436] 1.5 mg in rabbit spleen (1 oz), 1.5 mg in pig lung (1 oz),[437] and 1.5 mg in black-eyed peas.[438,439] Although separate components may not make the cut, a composite food like a PB&J could, with its 1.6 mg in the ounce of peanuts (about 2 tablespoons) and 1.3 mg found in two slices of whole-wheat bread.[440] That's in quarter-can-of-chickpeas territory. A hummus sandwich could score even higher.

Hard to Swallow

This line in a medical journal gave me a double take: "Spermidine is also contained in fruits, such as mango, in semen, and especially in red wine."[441] That's quite the spunky cocktail! Mangos finish cum laude, but wine doesn't actually have much at all. And semen?

You can imagine how giddy headline writers were to the news that spermidine boosts longevity. *Cosmo* ran a column.[442] Provocative titles included "Drinking Semen Might Help You Live Longer."[443]

Since there's only about one calorie per teaspoon of semen,[444] on a spermidine-per-calorie basis, even lentil soup is no match. But, based on an average of five dozen men, each "serving" only contains 0.1 mg, so, nope. Semen doesn't make the chart.[445]

Wheat Germ

The spermidine in semen is a testament (from the Latin *testis*, but for "witness," not "testicles")[446] to its DNA-protective effects. The same is true for wheat germ, which is the tiny plant embryo within the whole-wheat kernel. Though it falls relatively far down the chart in spermidine per

serving, you'll notice it has the smallest serving size, just one tablespoon or 7 g.[447] So, on a volume or weight basis, wheat germ reigns supreme.

It's also the cheapest source of spermidine, as low as two cents per mg. Wheat germ is a by-product of the white flour milling industry and typically just discarded, which may account for its reasonable price.[448] You know something's a bargain when it can even beat out dried beans in nutrient per dollar.

Pop a Spermidine Supplement?

I was surprised to read that spermidine supplements were not commercially available.[449] That couldn't be true. I searched online and *poof*—there it was, a bottle plastered with the word SPERMIDINE. But, if you read the label, you can see it's just wheat germ stuffed into capsules. Not even an extract. Literally straight wheat germ.

On the one hand, it's nice to see supplement manufacturers not trying to concoct some proprietary formula. For example, to meet the turmeric quota in my Daily Dozen (see *How Not to Die*), I often just take the spice in capsule form since I don't always want to curry up my meals. It may be harder to find straight turmeric spice in capsules, as opposed to some patented extract, but if you can, the price premium for convenience is steep.

Unlike turmeric, the taste of wheat germ is pretty neutral, and I've found I can just sprinkle it onto foods. (I mix it with ground flaxseeds, also from my Daily Dozen.) You can buy wheat germ in bulk for as low as $3 a pound. In capsule form, wheat germ comes out to more than $200 per pound, which is at least a dollar per teaspoon as opposed to just a penny or two.

At sufficient doses, wheat germ can also help control cholesterol, triglycerides,[450] diabetic blood sugars,[451] and pain, fatigue, headache, and mood swings associated with painful periods.[452] (Details in see.nf/wheatgerm.) It can also boost *Bifidobacteria* in the gut. A common constituent of commercial probiotics, *Bifidobacteria* are considered one of the proxies for a beneficial balance of good bugs in general[453] and may even have the knock-on effect of adding extra spermidine to the system.

Our good gut flora produce spermidine that can then get absorbed into our bloodstream from our colon and circulate throughout the body.[454] Eating tempeh or sprinkling wheat germ onto dishes can provide periodic bumps at meals, but even better if your microbiome were making it 24/7.[455] In fact, our good gut bacteria probably churn out more spermidine than most of us eat.[456] So, we may be getting less spermidine from the top down than the bottom up, though this may change as we age.

Spermidine levels don't just decline in our bloodstream as we get older but in our stool, too.[457] Feces of thirty-year-olds have more than twice the spermidine concentration of those of eighty-year-olds,[458] and this decline has been linked to changes in our microbiome.[459]

Give people a strain of probiotic *Bifidobacteria*, and you can increase spermidine levels in their stool.[460] The same strain given to mice had the same effect. Enough to prolong their lives? Yes. A boost in spermidine-producing friendly flora was shown to improve the healthspan and lifespan of the mice[461]— even protection from age-induced memory impairment.[462] What about in people?

A symbiotic combination of prebiotics and spermidine-producing *Bifidobacteria* was able to increase spermidine levels in people's blood. This then translated in a randomized, double-blind, placebo-controlled trial to improve endothelial function,[463] thought due to a boost of autophagy.[464] Spermidine-producing bacteria are fiber-feeding,[465] so prebiotics alone would likely foster the growth of more spermidine producers. Then, even if you miss a day, your colonic colleagues can pick up the slack. Since beans and whole grains are leading sources of spermidine and also the fiber and resistant starch our good bugs eat, they may offer a double dose of cellular spring cleaning.

Who Shouldn't Up Their Spermidine?

The lack of reported side effects[466] is not surprising, given that our own body makes so much of it and spermidine's found naturally in some of the very foods associated with health and longevity.[467] But, is it safe for everyone? I note in see.nf/spermidinedownsides who might want to be cautious about attempting to restore youthful spermidine levels. Though spermidine may reduce the risk of getting cancer,[468] because autophagy's nutrient replenishment action could potentially help sustain tumor viability,[469] perhaps people with cancer shouldn't go out of their way to increase their spermidine intake.[470] The other group I would advise caution for are those with kidney failure.[471]

Spermidine Bottom Line

Given the safety and efficacy of spermidine to induce autophagy at achievable dietary doses, it is one of the most promising anti-aging compounds. DrugAge is an extensive online database[472] of more than five hundred lifespan-extending compounds.[473] Among the small subset with the fewest side effects, spermidine had the largest documented lifespan extension.[474] A "predominantly plant-based diet" has therefore been recommended to help counteract the decline in spermidine as we age.[475] Certain foods have more than others, though. While some have suggested the genetic engineering of high-spermidine transgenic potatoes,[476] there are already a plethora of naturally spermidine-rich foods.

Food for Thought

Autophagy is considered the "primary system for cleaning the body" from the inside out.[477] Some food components, like acrylamide, may suppress autophagy, whereas others, like spermidine, can boost the process. Chlorogenic acids in coffee can also help your cells take out the trash. What's more, autophagy can be boosted indirectly by amping AMPK or quelling mTOR.

To help boost this anti-aging pathway, on a daily basis, consider:

- 60 minutes of moderate to vigorous aerobic activity
- minimizing your intake of french fries and potato chips
- trying to consume at least 20 mg of spermidine by incorporating foods such as tempeh, mushrooms, peas, and wheat germ into your diet
- drinking three cups of regular or decaffeinated coffee
- instituting the recommendations to activate AMPK (see the AMPK chapter)
- following the recommendations to suppress mTOR (see the mTOR chapter)

CELLULAR SENESCENCE

Fifty years ago, microbiologist Leonard Hayflick demonstrated that, contrary to what was believed, human cells in a petri dish do not continue to double forever.[478] They only grow and divide about fifty times before entering an irreversible state of arrested replication, known as cellular senescence.[479] Senescence comes from the Latin word *senex*, meaning "growing old."[480] We always have immortal stem cells that can create new cells with a fresh start, but, once they form, they only have about fifty divisions before they, too, are dead in the water. This is a good thing.

This natural "Hayflick limit" helps protect the body against cancer by blocking the proliferation of damaged cells.[481] That's great for successfully getting us through reproductive age and passing along our genes, but what happens when the "natural" human lifespan of about thirty years gets extended to eighty years or more by miracles like sanitation? Our body ends up littered with senescent cells.[482]

ZOMBIE CELLS

Hayflick figured that these nondividing cells might contribute to aging simply because they had lost their capacity to participate in tissue repair and regeneration.[483] Instead, it turns out they *actively damage* surrounding tissues, earning them the moniker "zombie cells."[484] The problem with zombies isn't only that they are no longer productive members of society. They also want to eat your brains.

When we are younger, senescent cells are cleared by our immune system. When our cells reach their limit and are ready to retire, they are programmed to start releasing a cocktail of inflammatory chemicals called the senescence-associated secretory phenotype, or SASP. Inflammation, a process that often carries negative connotations, can sometimes be a benefit. Just like inflammation caused by a splinter draws immune cells out of circulation to a puncture wound, senescent cells make their own funeral arrangements by releasing inflammatory factors to flag themselves for immune clearance.[485] There's a problem, though. As we age, more and more senescent cells are piling up at the very same time that our immune systems are falling into disarray. So, the localized transient inflammation that is usually beneficial, like in the splinter scenario, develops into a detriment—the chronic systemic inflammation that characterizes aging and disease.

Even though the senescent cell burden in aged tissues represents just a small fraction of total cells,[486] they can have an outsized impact through SASP secretion, which can disrupt local tissue architecture and spill out into circulation.[487] What is frequently the largest organ in the human body? Is it the liver? The skin? No. In a growing number of people, it's our adipose tissue—that is, body fat. The inflammation related to obesity, which tends to worsen with age,[488] has been tied to the buildup of SASP-producing senescent fat cells.[489] SASP inflammation may even account for some of the most dreaded side effects of chemotherapy. Chemo works by successfully driving cancer cells senescent, but the ensuing SASP storm can drive bone marrow suppression and heart toxicity.

With all this SASP inflammation, it is no surprise that senescent cells are connected to a spectrum of age-related diseases, including Alzheimer's, Parkinson's, osteoarthritis, osteoporosis, herniated discs, spinal curvature, and loss of muscle mass and kidney function.[490,491] Even cancer, ironically.

Although cellular senescence likely evolved as an anticancer mechanism, late in life the excess inflammation can actively feed tumor growth—as in feed quite literally via angiogenesis, the sprouting of new blood vessels into the tumor.[492] But, how do we know cellular senescence is the cause rather than the consequence of disease?

Young Blood

In see.nf/parabiosis, I detail a macabre set of experiments showing that old animals surgically conjoined like "Siamese twins" to young animals grow healthier, stronger, and smarter,[493] and live significantly longer.[494] To determine if this was due to transmissible bloodborne factors rather than just shared organ capacity, researchers turned to transfusing old animals with young blood. I explore those vampire 2.0 experiments in see.nf/bloodboy.

Yes, the injection of blood from young mice into old improves cognition, for example, suggesting there's some sort of restorative factor in youthful blood, but the injection of blood from old mice into young can make things worse, suggesting there's some sort of debilitating factor in older blood.[495] Or, maybe the old blood is just diluting the revitalizing factor in the young mouse? For that matter, maybe the young blood is diluting the debilitating factor in the old mouse.[496] Amazingly, the latter seems closer to what's happening, as the simple dilution of blood in older animals can replicate much of the regeneration found in the parabiotic and transfusion studies.[497] And indeed, patients with moderate Alzheimer's randomized to blood dilution experienced about 60 percent less cognitive and functional decline over a period of fourteen months compared to a sham, placebo procedure.[498] The advantage over blood transfusions, as the director of the University of Zurich's

Institute of Biomedical Ethics put it: "There is something peculiar about the old literally feeding on the young."[499]

OUT WITH THE OLD

Researchers proved cause and effect by transplanting senescent cells from older mice into younger ones, and all it took were a few to cause persistent age-related physical dysfunction and a quintupling of their mortality.[500] Conversely, clearing even a fraction of senescent cells can profoundly delay tumor development and age-related organ deterioration.[501] The marked extension of healthspan and lifespan through senescent cell clearance sparked a gold rush to identify *senolytics*, compounds that can eliminate senescent cells.[502] In my video see.nf/senolytics, I review both drug and lifestyle approaches.

In short, cellular senescence can be thwarted by preventing our DNA from becoming damaged beyond repair in the first place (see here). Senescent cells can then be eliminated by exercise[503] and caloric restriction[504] (details in see.nf/senolytics), as well as a variety of dietary components.

QUERCETIN

In 1936, Albert Szent-Györgyi, who won the Nobel Prize the following year for discovering vitamin C, suggested that a class of phytonutrients called flavonols should also be considered a vitamin. (He suggested "vitamin P.")[505] The most common flavonol in the diet is quercetin,[506] which is found concentrated in onions, kale, and apples.[507] It's what gives apple peels their bitter taste.[508] Researchers had been testing dozens of different compounds on cells scraped from umbilical cords and then irradiated to force senescence. In 2015, they announced their results: Quercetin was a natural senolytic.[509]

More details in see.nf/quercetin, but, bottom line, quercetin doses as low as the human equivalent of one small apple a week reduced cellular senescence and improved the healthspan of aging mice. For example, they experienced less hair loss, had enhanced heart function, and gained greater

athletic endurance into the equivalent of their sixties.[510] So, we may want to share a few kale stems with our pet mouse, but what about people?

Sources of Quercetin

Quercetin can also be found in its namesake—oak trees, from the Latin *quercus*[511]—but it is considered "widespread in plant-based foods."[512] In fact, quercetin is so pervasive in the plant kingdom that it can even be found in iceberg lettuce.[513] (Lettuce is the fifth leading source of quercetin in the American diet.[514]) Onions have between 20 mg[515] and 100 mg[516] each, apples between 4 mg and 20 mg,[517] a one-pound bunch of kale may have 50 mg, and a cup of tea about 5 mg.[518] Capers have 20 mg per tablespoon, but stay away from high-sodium brands.[519] (I've seen capers in the market with anything between 0 and 200 percent of your entire daily sodium limit per serving.)

Although quercetin supplements procured online tend to be accurately labeled[520] and there are safety data to suggest no significant adverse effects to taking as much as 1,000 mg for as long as twelve weeks, I recommend sticking to dietary sources,[521] as does the Mayo Clinic team who established the field.[522]

Apples and Onions

It's hard to tease out the effects of quercetin from the range of salutary effects attributed to quercetin-rich foods, such as apples and onions. I note in see.nf/applesonions how the wisdom of *an apple a day keeps the doctor away*, a public health aphorism dating back to 1866, seems to have borne fruit.[523] It appears to be less the apple of one's eye than the apple of one's arteries. Significantly better improvement in artery function within hours of eating unpeeled apples than after eating apples that had been peeled[524] is consistent with a quercetin effect, and indeed, even isolated quercetin

supplements can lower blood pressure,[525] cholesterol,[526] and inflammation.[527] Unfortunately, quercetin-rich onion powder failed to improve cognition in elderly with[528] or without[529] Alzheimer's disease. (Details in see.nf/onionpowder.)

Although most of the quercetin supplement studies used doses not easily achievable through diet, even just three-quarters of a teaspoon of fresh onion can acutely improve blood pressure and fluidity compared to placebo,[530] helping to explain why those who consume more quercetin appear to have less than half the risk of dying from heart disease.[531] A modeling study even suggested that prescribing an apple a day could prevent about as many deaths from vascular disease on a population scale as prescribing everyone a cholesterol-lowering statin drug—and with fewer side effects.[532] (Ironically, now that drugs like Lipitor are available in generic form, the drug would likely be cheaper than the fruit.)

A New Wrinkle

The disappointing interventional cognition data were met in 2018 by a report questioning quercetin's senolytic activity. The original quercetin studies in people had been performed on cells from the lining of umbilical cord blood vessels, a convenient source of human tissue. When the experiment was repeated with cells from adult donors, though, quercetin didn't seem to have the same senescent cell–killing effect.[533] However, in 2019, quercetin was found to do something even better.

Werner syndrome is a rare genetic disease characterized by a mutation of a DNA repair enzyme that results in premature aging. When senescent Werner cells were exposed to the levels of quercetin one could get in the bloodstream by eating quercetin-rich foods,[534] they seemed to be rehabilitated rather than eradicated.[535] It appeared as though the senescence was reversed, like waking the living dead. What about aging cells that aren't mutated? A "rejuvenating effect" on senescent cells was found there as

well. In the journal *Experimental Gerontology*, researchers in Greece claimed to have put quercetin to the test topically on volunteers and reported "positive results as regards to [skin] elasticity, moisturization and depth of wrinkles,"[536] but their data do not appear to have been published, which raises concerns about the veracity of the claims.

FISETIN

Given the senolytic success of a quercetin cocktail, researchers started screening other flavonoids.[537] In doing so, they found one that was nearly twice as potent: fisetin.[538] It can increase the lifespan of yeast by 55 percent and fruit flies by 23 percent. Fisetin can also increase the lifespan of mice even when begun later in life.[539] When started at an age roughly equivalent to seventy-five years in humans, fisetin extended the average and maximum lifespans of older mice by about 75 percent. Markers of cellular senescence and SASP were significantly reduced in all analyzed tissues in conjunction with a reduction in age-related pathology.[540] A separate study found that fisetin can also increase long-term memory in mice.[541] What about us?

Like quercetin, fisetin has been shown to have anti-inflammatory effects in clinical trials,[542] but what about senolytic effects? When human fatty tissue that had been removed during routine surgery was exposed to fisetin, there was indeed a reduction of senescence and SASP markers. Given that fisetin is naturally found in the diet, has no reported side effects, and is already sold over the counter in dietary supplements, researchers immediately started designing studies to put fisetin's anti-aging potential to the test.[543] Currently, there are more than a dozen trials in the works, pitting fisetin against a range of age-related conditions, including osteoarthritis, osteoporosis, frailty, kidney disease, cognitive decline, and even COVID-19 complications.[544] The fact that there is so much clinical interest in a natural product that lacks the financial incentives that traditionally drive so much of biomedical research speaks to its promise.

Berried Treasure

Though first isolated from Venetian sumach, fisetin is concentrated in strawberries, the richest known dietary source.[545] This may help explain

why strawberries, but not blueberries (despite having even more antioxidants), were able to more effectively rescue rats exposed to radiation.[546] I run through all the landmark strawberry studies in see.nf/fisetin. In short, randomized controlled trials show that strawberries can improve cognition,[547] cholesterol, inflammation,[548] and osteoarthritis,[549] as well as boost beneficial gut bugs, including *Christensenellaceae*,[550] a newly discovered[551] bacterial family found associated with longevity based on studies of centenarians and supercentenarians.[552] In the video, I also explain why fisetin supplements are not recommended.

PIPPALI

A third natural senolytic compound has been discovered: piperlongumine,[553] found concentrated in a spice commonly sold in Indian grocery stores as pippali (*Piper longum*, also known as pibo in China and long pepper in Europe).[554] I detail what it is and what it can do in see.nf/pippali. I was convinced enough to add it to my daily spice regimen alongside amla (see here), black cumin (see here), and turmeric (see here). Note that the use of pippali during pregnancy and breastfeeding is not recommended.[555]

Food for Thought

Cellular senescence is considered to be one of the foundational hallmarks of aging.[556] The inflammatory SASP, secreted by senescent cells, is thought to be a main driver of tissue deterioration and disease.[557] To prevent cellular senescence in the first place, we can avert DNA damage by following the recommendations in the Oxidation chapter, and, to potentially help clear such cells and their SASP, there are natural senolytic compounds in foods—quercetin, fisetin, and piperlongumine. Although it is not yet clear whether sufficient levels can be reached by eating foods rich in these compounds, such foods are healthful in their own right.

To help slow this aging pathway, on a daily basis, consider:

- consuming quercetin-rich foods, beverages, and seasonings, such as onions, apples, kale, tea, and salt-free capers
- eating fresh, frozen, or freeze-dried strawberries
- seasoning meals with pippali (long pepper)

EPIGENETICS

Until recently, the aging process was considered to be an inexorable decline characterized by the cumulative buildup of molecular damage to key cellular components, particularly our very DNA.[558] Just as the various components of a car eventually break down with time, so do the components of our body. Challenging this assumption were life-forms that could seemingly defy aging by attaining a sort of state of suspended animation, such as date pits unearthed during archaeological digs germinating after thousands of years,[559] plants regenerating from fruits buried by Arctic squirrels 30,000 years before,[560] and bacterial spores viable after tens of millions of years encased in amber or hundreds of millions of years preserved in salt crystals. However, one need not seek exotic examples to demonstrate the uncoupling of biological aging with chronological ("calendar") aging. Instances of the aging clock not only being halted but actively reversed and even reset to zero happen every day.[561]

THE GREAT RESET

Think about it. A baby girl is born with all the eggs she will ever have. It may be decades before one of those eggs is fertilized. That egg could be sitting in her ovaries for twenty, thirty, forty years—all the while, aging just like every other cell in her body. Let's say she gets pregnant at thirty. Upon fertilization, if that egg doesn't somehow rewind its aging clock to zero, then that thirty-year-old egg could lead to the birth of another baby girl with ovaries that are then thirty years and nine months old. By the time she gave birth decades later, the eggs would be more than fifty years old and they

would continue to age and accumulate molecular damage with every successive generation. This is why, necessarily, all manifestations of aging in egg cells must be erased.[562] Otherwise, the eggs in women's ovaries would be millions of years old!

In 1996, we learned that eggs aren't the only cells that can undergo a complete reversal of aging. That was the year a sheep named Dolly was born. The nucleus of an unfertilized egg was removed and, in its place, the nucleus of an udder cell was inserted. ("Dolly is derived from a mammary gland cell," one of the key researchers said unabashedly while explaining her namesake, "and we couldn't think of a more impressive pair of glands than Dolly Parton's.")[563] Then, with a little electric shock, the cell started dividing—no sperm required—and Dolly, the first animal cloned from an adult cell, was born. (Previously, a frog had been cloned from a tadpole cell, earning the researcher the Nobel Prize, but Dolly was the first animal cloned from the cell of an adult.[564])

The world marveled that a genetically identical duplicate of an animal could be created. Since Dolly, thousands of clones have been made of mice, goats, pigs, rats, cows, horses, ferrets, wolves, deer, buffalo, camels, and dogs. Cats, too, the first one predictably named "Copycat."[565] The implications, however, go far beyond replicating particularly productive farm animals or generating Fido 2.0. Hidden within that one mature, specialized cell dedicated to milk production, taken from a sheep's udder, was the full genetic blueprint for the entire animal we'd come to know as Dolly.[566] Furthermore, the cell's age appeared to have rewound back to zero.

There is a lingering misconception that Dolly was beset by some sort of premature aging syndrome. After all, sheep live to be about twelve years old, the mammary cell was taken from a six-year-old,[567] and Dolly died at age six, suggesting that the aging clock had just kept ticking without resetting. But, Dolly died from a viral illness, not old age,[568] and subsequent experience shows clones can have normal lifespans.[569] In fact, mice have been serially recloned—meaning there have been clones made from clones made from clones going out twenty-five generations—and they have all aged normally with respect to lifespan.[570] So, not only can adult cells be dialed back to an embryonic state, but they can effectively be rejuvenated by having any traces of aging wiped clean.[571]

Welcome to epigenetics.

GENES LOAD THE GUN, LIFESTYLE PULLS THE TRIGGER

The term "epigenetics" was coined in the 1940s before we even knew the physical nature of genes, a full decade before Watson and Crick (and Wilkins and Franklin) solved the structure of DNA.[572,573] Epigenetics, which literally means "above genetics," layers an extra level of information on top of the DNA sequence, which on its own is only about 750 megabytes of data[574] encoding 50,000 genes.[575] All our dividing cells are genetically identical, carrying a full complement of our DNA, but each cell doesn't need to express all our tens of thousands of genes. Our nerve cells don't need to be pumping out liver enzymes, and our heart cells don't need to be growing hair. That's where epigenetics comes in—in effect, it's what switches genes on and off. There are a multitude of ways our body does this.[576] I'll talk about sirtuins and microRNAs in their own chapters, but the best-known epigenetic regulator is DNA methylation.[577]

We have enzymes that can strategically add methyl groups directly onto our DNA to silence gene expression. A methyl group is a simple, stable configuration of carbon that can be added to flag stretches of DNA as skippable. It's one of more than a dozen ways DNA can be tagged.[578] We have a separate set of enzymes that can remove these tags to turn the gene back on. There are approximately twenty-eight million common methylation sites along our genetic code, most of which are methylated at any one time.[579] The pattern of methylation is conserved when our cells divide—so a liver cell splits into two new liver cells rather than a bone or muscle cell, for example—and, in this way, methylation patterns in sperm and eggs can be passed down through the generations.[580]

We used to think that once cells matured and had their DNA appropriately methylated to lock them into their specialized functions, that was it.[581] But we now know that our "epigenome," the pattern of methyl markings in our cells, is a dynamic system and responsive to external stimuli. Epigenetics allows organisms to more rapidly adapt to changing environmental conditions.

It can take eons for large-scale shifts in the genetic code to happen, but the genes we already have can be switched on or off within a matter of hours. Epigenetics is how green grasshoppers can turn themselves black after a grassland fire to better camouflage against the charred soil[582] and

how our body determines the number of active sweat glands we have in our skin based on whether we're born in the tropics or in a colder setting.[583] Epigenetics is good news. It means our DNA is not our destiny. No matter our family history, the lifestyle choices we make can effectively turn on and off some of our genes, not only affecting us individually but also our kids and maybe even our grandkids.[584]

In the Gene Expression Modulation by Intervention with Nutrition and Lifestyle (GEMINAL) study, Dr. Dean Ornish and colleagues took tissue biopsies before and after subjects adopted intensive lifestyle changes for three months that included a whole food, plant-based diet. Beneficial changes in gene expression were noted for five hundred different genes. The expression of disease-preventing genes was boosted, and the oncogenes that promote breast and prostate cancer, for example, were suppressed.[585] No matter the genes we may have inherited from our parents, we can affect how those genes affect our health with what we eat and how we live. That's the power of epigenetics. Same DNA, but with different results.

The most striking example of the epigenetic effect of diet on lifespan involves the humble honeybee. Queen bees and worker bees are genetically identical, yet queens may live for three years and lay up to 2,000 eggs a day, while worker bees may live for only three weeks and are functionally sterile.[586] How can this be if there is no difference between them genetically? They have a different diet. When the hive's queen is dying, a larva is picked by nurse bees to be fed a secreted substance called royal jelly. (The workers just get mostly a mixture of honey and pollen adorably named *beebread.*)[587] When the chosen larva eats this jelly, the enzyme that had been silencing the expression of royal genes is turned off and a new queen is born.[588] The queen bee has the exact same genes as any of the worker bees, but simply because of what she ate, different genes are expressed, resulting in dramatic alterations to her life and lifespan. A fiftyfold increase in longevity, thanks to epigenetics.

Live Like a Queen?

If royal jelly can turn a simple larva into a queen who can live more than fifty times longer, should we consider eating

royal jelly ourselves? I review the available evidence in see.nf/royaljelly. Spoiler alert: While it may be the bee's knees for bees, given rare cases of hemorrhagic (bloody) colitis attributed to royal jelly supplements,[589] eating PB&RJs could just end up being a royal pain in the butt.

THE EPIGENETIC CLOCK

There are certain DNA sites on our chromosomes that so predictably methylate or demethylate as we age that it's like clockwork, presenting a potential "molecular crystal ball for human aging."[590] In a remarkable triumph of Big Data, out of the millions of methylation sites in our DNA, a tiny subset so dependably shifts over time that you can predict someone's age within a few years[591] just by strategically measuring the methylation pattern in a few hundred—or even just a few dozen—sites[592] in someone's three-billion-letter genome.[593]

Over the last few years, these "epigenetic clocks" have become established as robust measures of chronological age, surpassing telomere length (see the Telomeres chapter) as the best age predictor.[594] Why invent some costly Rube Goldberg approach to divining someone's age when you can simply ask them? Well, you can imagine forensic applications, the determination of an unidentified victim's age with a blood or tissue sample, but that just scratches the surface.[595] The kicker is that epigenetic clocks don't just track our chronological age but appear to measure our true biological age.[596] In other words, our epigenetic age can better predict our remaining life expectancy than our calendar age.[597] Check out see.nf/clock for the whole wild story.

It's like science fiction.[598] Feed a drop of your blood into some futuristic machine that scans the placement of chemical markers on a strand of DNA and out pops your true age, reflecting a lifetime of lifestyle choices.[599] In addition to predicting time-to-death, epigenetic clocks also appear to foretell healthspan indicators, such as cognitive decline, frailty,[600] arthritis, and the progression of diseases like Alzheimer's and Parkinson's.[601] As you can imagine, the insurance industry has jumped on this, and your premiums may soon be determined by your epigenetic age.[602] But it's not some set-in-

stone fortune teller's curse. You can change the rate at which you age and may soon be able to use epigenetic clocks to track your progress, potentially presenting a radically faster and cheaper way to test anti-aging interventions.[603]

SPEEDING AND SLOWING BIOLOGICAL AGING

Studies of centenarians show that some age so slowly that a 105-year-old may have a DNA methylation age of a 60-year-old.[604] No wonder they lived so long! What can we do to decelerate our epigenetic clocks and slow down aging? Epigenetic clock analyses show that women age more slowly than men,[605] which makes sense since women tend to live longer,[606] a pattern so robust that one demographer quipped, "to be a male is a genetic disease."[607] To catch up, men have to make even healthier changes to their diet and lifestyle.

Cigarette smoke is linked to accelerated biological aging, with marked effects evident even at low levels of exposure.[608] In contrast, both exercise frequency and intensity are associated with a deceleration of aging.[609] What about meditation? Two months of daily practice failed to significantly affect aging rates,[610] and long-term meditators appear to have the same aging rates as nonmeditating controls, though practitioners racking up an average of 6,000 hours of meditation may blunt the increase in epigenetic age acceleration over time.[611]

Until recently, caloric restriction had yet to be tested in people, but it had been shown to slow epigenetic aging in mice and monkeys. Over about a fifteen- to twenty-one-year period of 30 percent dietary restriction, middle-aged rhesus monkeys appeared to epigenetically age seven years less. Even more dramatically, mice at a 40 percent calorie restriction seemed to age only about one year over a period of about three years.[612] In 2018, an aging analysis was published of the CALERIE study, the first major randomized trial of calorie restriction in humans. Using nonepigenetic estimates of biological aging, the control group continued to age at a rate of about one year per year, but in that time, the dietary restriction group only seemed to age by about one *month*. And they achieved this with only a 12 percent calorie restriction, which is like skipping just one donut a day.[613]

Aging rates were slowed in the dietary restriction group independent of weight loss,[614] but obesity has been associated with epigenetic age acceleration in samples of liver tissue[615] and deep abdominal fat.[616] However, even about a hundred pounds of weight loss due to bariatric surgery did not appear to wind back the clock.[617] Maybe we don't just have to eat less, but better.

The lifestyle factor most closely associated with slowing aging—even more than exercise—is a marker of fruit and vegetable intake, blood levels of carotenoid phytonutrients like beta-carotene.[618,619] So, an "epigenetic diet" would focus on consuming more fruits and vegetables.[620] On the other hand, the food most consistently linked to accelerating aging is meat.[621,622] Perhaps this is partly due to the fact that blood levels of by-products of banned pesticides like DDT are themselves associated with both accelerated aging[623] and meat consumption.[624] Long-term exposure to air pollution may also be associated with accelerated aging,[625] but the data are mixed.[626]

WINDING BACK THE CLOCK

The fact that our epigenetic age is a better predictor of lifespan and several diseases of old age than our chronological age is powerful evidence that DNA methylation is inexorably linked with some fundamental cause of age-related decline.[627] Could it be what's actually driving human aging,[628] or is it merely a passive marker of age?[629] Is our epigenetic clock the cause of aging or just the result? If it's an active driver, it's a driver that can go in reverse.

Remember how, in cloning, an adult cell could be reprogrammed to revert it into an embryonic state? Not only were methylation marks erased to free up the whole genome, but all vestiges of aging appeared to vanish. We obviously don't want to reset the clock so far back that we dissolve into an amorphous blob, but might we be able to rewind the clock a little and rejuvenate our cells?

In a Nobel Prize–winning discovery,[630] stem cell researcher Shinya Yamanaka identified what we now refer to as Yamanaka factors, a small handful of DNA-binding proteins responsible for cellular reprogramming that serve, in essence, to return a cell to factory settings.[631] With these tools in hand, an international team of researchers set out to turn back the clock

by reestablishing the regenerative properties of nerve tissue. For example, young kids can actually regrow an entire amputated fingertip, bone and all, but we gradually lose such capacities as we age.[632] The cells that make up the optic nerves that connect our eyes to our brain similarly lose their regenerative properties. With a little Yamanaka factor manipulation, however, the researchers were able to successfully reset the methylation marks to a more youthful state, restoring vision in old mice and rejuvenating human neurons in a petri dish. The cells seemed to have retained a faithful copy of the epigenetic map from earlier in life that could serve as directions to reverse aging.[633]

METHYLATION CALIBRATION

Increasing our access to exercise, fruits, and vegetables while reducing our consumption of tobacco and meat may help slow aging, as evidenced by a deceleration of the epigenetic clock, but what about directly changing DNA methylation? A lot of things affect methylation patterns, but the modifications are hard to interpret. For example, in one study, a high-fat diet caused widespread DNA methylation changes in men within just five days, affecting more than 6,000 genes that were able to only partially reverse six to eight weeks after the participants returned to their usual diets.[634] And, overeating saturated fat causes different methylation changes than overeating polyunsaturated fat, but to what effect?[635] We don't know. Do the epigenetic changes play a role in the ensuing physiological effects, or are they incidental?

We are just starting to tease out the consequences of the epigenetic changes induced by diet and lifestyle. We know now, for instance, that among the consistent methylation differences in vegans compared to omnivores is hypomethylation (less methylation) of a tumor suppressor gene and a gene that encodes a DNA repair enzyme.[636] Since methylation silences genes, unmuzzling them may help account for the lower overall cancer rates among those eating plant-based diets.[637,638] Similarly, in vegetarians, the superoxide dismutase enzyme is less often methylated. That's an antioxidant enzyme that can squelch a million free radicals *per second*.[639] The hypomethylation is associated with a threefold increase in

the expression of that detoxifying enzyme used to explain the "higher protection against chronic diseases in vegetarians."[640]

Beyond tweaking the volume knob of individual genes, there is evidence that large-scale methylation shifts can have health and longevity implications. If you boost the enzyme that actually does the methylating in fruit flies, you can prolong their average lifespan by more than 50 percent. Suppress the enzyme, and you cut short their lifespan. However, this strategy has yet to be shown to work in mammals.[641]

Human DNA methylation is much more complicated. But the fruit fly findings suggest that increasing global methylation capacity may positively affect longevity.

TURN OVER A NEW LEAF

The nutritional factor most widely studied for its epigenetic effects is folic acid.[642] That's the supplemental form of folate, a B vitamin concentrated in beans and greens that is converted into a methyl donor. (Folate comes from the same word root as foliage—*folium*, the Latin word for "leaf.")[643] The methyl group that ends up on your DNA may originate from the folate in your salad, for instance, or the folic acid in a supplement or enriched flour. The recommended daily allowance for most adults is 400 micrograms (µg),[644] yet the average daily intake of older men and women is less than 300 µg and a third don't even get 200 µg.[645] What are the epigenetic implications?

Postmenopausal women had their folate levels moderately depleted by being placed on a relatively low-folate diet to study the epigenetic effects. Even though folate levels didn't fall enough to show clinical signs of deficiency (such as anemia), within two months, the subjects suffered a genome-wide DNA hypomethylation across the board. It was reversed within three weeks, though, upon resuming healthy levels of folate intake.[646] A subsequent study of even older individuals resulted in the same undermethylation but took longer to reverse, underscoring the importance of maintaining adequate levels in the first place.[647]

Even without depletion, a meta-analysis of randomized controlled trials of folic acid supplementation using the most sophisticated methods of laboratory analysis found an increase in global methylation, suggesting that

most of us may not be getting enough in our diet.[648] There's no real benchmark for a "normal" level of methylation, so terms like "hypomethylation" are used in a relative sense,[649] making these changes hard to interpret functionally.[650] But, our ancient ancestors ate a lot more leaves. They likely got twice as much folate as we do today,[651] so the fact that our body puts the extra methyl group availability to use when we get a bump in folic acid levels suggests to me that our folate status may be suboptimal. This is easy to fix, though. For example, just meet my Daily Dozen recommendations for legumes and dark green leafy vegetables. (*Dr. Greger's Daily Dozen* is available as a free app for iPhone and Android.)

Hard as a MTHFR?

So-called MTHFR mutations are a popular scapegoat often used by alternative medicine practitioners[652] to prescribe special supplements (that they not-so-coincidentally may also sell) for a variety of common ailments.[653] MTHFR is an enzyme our body makes to activate folate. A common variant of the MTHFR gene, which has DNA code letter T rather than the more common C at the 677th position, makes for a less functional enzyme. This can have epigenetic implications, as those who got the T variants from both parents (about 10 percent of the global population)[654] have diminished DNA methylation, but only when their folate intake is low.[655] If you get enough folate, your methylation levels are the same regardless of whether you have the T variants. Similarly, those with two of the T variant genes may have higher risk of cancer, but, again, it's only among those not getting enough folate.[656] You don't need a special kind of folate either. The folate in foods and folic acid in supplements and enriched foods are perfectly usable, irrespective of which gene type you have.[657]

Since everyone should be striving to get enough folate, there is no benefit to routine genetic testing to see which variant you have, which is why major medical organizations

in the field recommend against MTHFR testing.[658] The only thing you might do differently if you knew you had a double dose of the less functional enzyme is to be especially careful about alcohol intake. Acetaldehyde, the breakdown product of alcohol, can destroy the folate in our body,[659] so those with double T variants should consider restricting their consumption to less than one drink a day.[660] As everyone should probably be trying to minimize alcohol intake,[661] I agree there's little value in knowing your MTHFR genetics.

FOLIC ACID IS NOT THE SAME AS FOLATE

A review of more than a hundred meta-analyses of population studies shows that those who get more folate in their diet tend to live longer and are protected against cardiovascular disease, several cancers, and a wide range of other chronic diseases.[662] But some randomized controlled trials of folic acid supplements found *increased* cancer risk.[663] As I explore in see.nf/folic, the mystery appears to have been solved when scientists figured out that we aren't rats.

Natural folate isn't shelf-stable, but there's an enzyme in our liver that can convert the stable synthetic folic acid found in supplements into an active form of folate in our body.[664] The original experiments were done on rats, though, and it turns out that their livers are fifty times more efficient at this conversion than ours,[665] so we can end up with unmetabolized folic acid circulating throughout our body,[666] which may impair our anticancer defenses.[667] For example, randomized controlled trials have shown that men taking folic acid supplements significantly increase their risk of developing prostate cancer. Randomized trials have also found that those taking folic acid supplements for more than three years are more likely to develop colorectal polyps.[668] So, natural sources of folate, like beans and greens, may be best, though women who want to get pregnant are still advised to take folic acid supplements, given their proven efficacy for reducing birth defects.[669]

Beyond food and supplements, the third way to improve your folate status is to contract out some of the production to your microbiome. A

folate transporter in our colon appears to be specially designed to absorb folate[670] produced by good bacteria like *Bifidobacterium* when we feed them fiber.[671] Increasing your fiber intake can bolster the growth of little folate factories in your gut.

Food for Thought

Our epigenome, characterized by the pattern of DNA methylation, can be thought of as a lens through which our genetic information is filtered.[672] Unfortunately, it's a lens that can become cloudy as it deteriorates with age. Thankfully, epigenetic changes are reversible, so we may be able to polish it back into focus. Caloric restriction, as well as diet and lifestyle improvements, including physical activity, smoking cessation, and shopping more in the produce aisle than at the meat counter, may all slow the epigenetic clock. Getting sufficient levels of methyl-donor nutrients, such as folate, can also affect global methylation capacity.

To help boost this anti-aging pathway, on a daily basis, consider:

- restricting calories by 12 percent, which would be cutting about 250 calories out of a 2,000-calorie diet (e.g., skipping a piece of pie or cake every day)
- meeting the 400 µg recommended daily allowance of folate, which could be achieved with about a cup of cooked lentils or edamame, a cup and a half of cooked spinach or asparagus, or two and a half cups of broccoli, for example

GLYCATION

You may have heard of the Maillard reaction if you're a foodie or watch cooking shows. It's what gives seared steaks, panfried dumplings, toasted

marshmallows, or freshly baked cookies their distinctive browned look, feel, and flavor. In 1912, the French chemist Louis Camille Maillard discovered, rather by chance, that mixtures of proteins and sugars turn brown upon heating. In the century since, more than 50,000 scientific papers have been published on this "Maillard reaction," in which proteins can become irreversibly glycated, or bonded with sugar.[673] The same reaction can occur at body temperature, leading to an accumulation of advanced glycation end products (AGEs),[674] which we now know are one of the main factors contributing to the aging process.[675]

ADVANCED GLYCATION END PRODUCTS

If you are diabetic, you're familiar with HbA1c, a test that measures blood sugar control, reflecting average blood sugar levels over the prior two to three months. The blood test just reflects the percentage of hemoglobin in your blood that has been glycated. (Hemoglobin is the protein in red blood cells that carries oxygen.) The higher your blood sugars are, the more your proteins are glycated. Since red blood cells last about a hundred days, the test gives you a rolling average over that time.[676]

Diabetes can be diagnosed with an HbA1c of 6.5 percent or higher, meaning 6.5 percent or more of the hemoglobin in the blood has been glycated. A percentage of 5.7 to 6.4 gives a diagnosis of prediabetes, and less than 5.7 is considered normal.[677] So, even if you have normal blood sugars, some proteins and other molecules in your body are being irrevocably glycated. This isn't such an issue for short-lived proteins like hemoglobin, which are rapidly recycled and created anew, but what about long-lived proteins, like the crystallins in the lens of your eye?[678]

Hemoglobin's half-life, the rate at which half gets renewed, is about fifty days. The collagen in your skin has a half-life of more like fifteen years,[679] and the half-life of collagen in the intervertebral discs in your spine is estimated to be at least *ninety-five years*. Similarly, elastin, another connective tissue protein, is formed in infancy and has to last your whole lifespan. Glycation causes proteins to cross-link together, which stiffens our tissues—most critically, our arteries and the heart muscle itself. This impaired elasticity can result in high blood pressure, peripheral artery disease, heart disease, and even cancer. (Stiffness of breast tissue is

associated with an increased risk of cancer.)[680] The acronym for advanced glycation end products was chosen intentionally, to emphasize their role in the aging process.[681]

RAGE OUT OF CONTROL

There are AGEs and then there's RAGE. Advanced glycation end products not only stick our proteins together, they trigger chronic, systemic inflammation. In the search for the mechanism for this response, researchers discovered receptors for AGEs in our body that spark the inflammatory cascade and named them RAGE: receptors for advanced glycation end products.[682] RAGE can function as a master switch. When AGE sparks RAGE, a whole host of inflammatory genes are triggered, along with a promotion of further RAGE expression, which leads to a vicious, cyclical feedback loop that can have profound pathological effects.[683]

As AGEs accumulate in our bones, joints, and muscles, they may contribute to osteoporosis, arthritis, and muscle wasting, the weakening, shrinking, and loss of muscle mass with age.[684] AGEs are implicated in age-related memory decline, impaired wound healing, skin aging, cataracts, Alzheimer's disease, and erectile dysfunction (where the stiffening of penile arteries evidently results in penile unstiffening).[685] AGEs have been found to adversely affect virtually all tissues and organs.[686] As one pathologist put it, "It is hard to find an age-related disease that AGEs are not involved."[687]

The toxicity of AGE accumulation is underscored by the number of defense mechanisms our body employs to prevent their formation.[688] Once they have been formed, though, they're hard to get rid of, so they gradually accumulate and wreak havoc.[689] Over five to six decades, AGE levels in our tissues roughly double.[690] The reason this is seen as not only a marker of aging but an active *driver* of the aging process is that AGE inhibitors have been shown to extend the lifespan of model animals, whereas AGE augmentation can cut lives short.[691] The preferred laboratory animal model of accelerated aging uses *galactose* (a major breakdown product of the milk sugar lactose)[692] to fast-track AGE accumulation.[693] Across the animal kingdom, the slower the rate of AGE formation, the longer species tend to live. The bowhead whale, for example, who, by living more than two

centuries, is probably the longest-living mammal, has exceptionally low rates of AGE accumulation.[694] How can we best keep our levels low?

AGE formation is heat-dependent. At body temperature, the Maillard reaction is exceedingly slow, taking weeks, months, or even years to generate sugar-protein cross-linking.[695] Imagine what would happen if our body, instead of an internal temperature of about 100°F (38°C), hit 200°F, 300°F, or 400°F (93°C, 149°C, or 204°C)? That's what happens when we put meat in the oven. Calling the yellowish then brownish discoloration of cataracts the "AGE food colors of roasted turkey"[696] is not just poetic license. The same AGEs that cloud the pristine clear quality of the lens proteins in your eyes over a period of decades can be formed within minutes on the stove.[697] The burden of AGEs in our tissues appears to be less a matter of how much we make and more a matter of how many AGEs we eat.[698]

DIETARY AGE SOURCES

About a million years ago, our ancestors harnessed fire.[699] When muscle cells are exposed to the high temperatures of flames, they rupture and out spill highly reactive amino acids that combine with blood and body sugars to form AGEs.[700] Like us, animals we eat also have AGEs naturally in their tissues, but high-heat cooking can radically ramp up production.[701] Different cooking methods expose tissues to different amounts of heat and moisture. Poached or steamed chicken, for example, had less than one-fourth of the AGEs of roasted or broiled chicken that had been prepared in drier conditions and at higher temperatures.[702]

Research on rats performed in the 1970s found that diet-derived AGEs weren't absorbed very well, so dietary sources were dismissed as irrelevant —that is, until a quarter century later, when AGE absorption was finally tested in people.[703] The landmark paper, published in the *Proceedings of the National Academy of Sciences*, demonstrated that diet-derived AGEs were indeed absorbed into the human body.[704] Further research showed that dietary AGEs contribute more to the toxic pool of AGEs in our body than our own endogenous production. In other words, our AGE exposure is more from what we eat than what we make.[705] As a result, dietary AGEs have emerged as a burning concern in the food industry.[706] The investigators

suggest eliminating high-AGE foods and high-AGE cooking methods to reduce the body's burden of these toxins.[707]

Researchers got to work testing AGE levels in more than five hundred foods, everything from Big Macs and Hot Pockets to Frosted Flakes and Pop-Tarts.[708] They identified the highest levels in "high-heat-treated meat" and, more generally, in "[a]nimal-derived foods that are high in fat and protein," and determined that the lowest levels are found in vegetables, fruits, whole grains, and milk[709,710] (with the exception of dairy milk–based infant formula Enfamil, which has nearly a hundred times more AGEs than human breast milk).[711] Meat averages about 20 times more AGEs than highly processed foods like breakfast cereals and about 150 times more than fresh fruits and vegetables. Poultry was the worst, containing about 20 percent more AGEs than beef in general.[712]

Based on the most extensively cited[713] AGE food database,[714] which includes hundreds of nonmeat items, the majority of the top fifteen single most AGE-contaminated sources per serving were poultry products, led by oven-fried chicken breast.

Researchers were rather surprised that high-fat and protein-rich foods created more AGEs than starchy and sugary high-carbohydrate foods.[715] After all, AGEs are called "glycotoxins" for a reason.[716] They involve glycation reactions, like the Maillard reaction I mentioned earlier in which sugars bind to proteins. Sugars alone can brown at high heat in a way that may superficially look, smell, and taste similar to products of the Maillard reaction, but that's the result of an entirely different chemical process called caramelization. By definition, Maillard reaction AGEs are created only when amino acids from proteins are involved.[717] For a deeper dive into other AGE rankings, see see.nf/agerank.

HOW TO REDUCE TOXIC AGE INTAKE

Most of the largest AGE food databases used a single AGE (carboxymethyllysine) as a marker for total AGE content,[718] but more than forty individual AGEs have been identified[719] and not all of them are toxic.[720] Some may even be beneficial. A component in roasted coffee beans called melanoidin, for example, may even act as an antioxidant.[721] AGEs from animal-derived foods appear to produce more toxic effects than AGEs

from plant-derived foods.[722] Not only may plant foods average thirty times fewer AGEs; even if you expose proteins to the same amount of AGEs from plant versus animal sources, there are twenty-five times fewer cross-linkages and forty times fewer when compared to poultry AGEs. Plant-derived AGEs also produce less inflammation and fewer free radicals.[723] The AGEs created by the curing of tobacco may be an exception, as the AGEs from cigarettes are implicated in the deleterious effects of smoking.[724]

Even without cutting down on meat, you can significantly cut down on AGE intake by using different cooking methods. High dry-heating methods create the most AGEs, with oven-frying meat worse than deep-frying, which is worse than broiling, which is worse than roasting. Given that there is no threshold temperature, the general recommendation is that the lower the heat, the better when it comes to combating AGE generation.[725] The safest ways of cooking meat are lower temperature moist methods, such as boiling, poaching, stewing, and steaming.[726] Boiled beef has three times fewer AGEs than broiled beef,[727] boiled chicken has five times fewer AGEs than broiled chicken, and boiled eggs have nearly six times fewer than fried eggs. Microwaving from scratch is also relatively safe, found to be on par with boiling.[728]

Much of the focus on reducing dietary AGEs has to do with these kinds of culinary changes.[729] Cooking methods do matter. A raw apple has three times fewer AGEs than one that's been baked, and a boiled hot dog has less than one that's been broiled. But don't lose perspective: A raw apple has 13 units of AGEs compared to a baked apple's 45 units, while a boiled hot dog has 6,736 units compared to a broiled hot dog's 10,143. So, a baked apple still has 150 times fewer AGEs than a boiled frankfurter,[730] and vegetables, even when grilled, have but a fraction of the AGEs of raw meat.[731]

Researchers recommend cooking meat using moist-heat methods like steaming or stewing, but even boiled fish has in excess of ten times more AGEs than a sweet potato roasted for an hour. Even deep-fried potatoes have less than boiled meat. The researchers concluded that daily AGE intake could realistically be cut in half just by modestly reducing meat intake.[732]

Marinating meat with an acidic ingredient, like lemon juice or vinegar, before cooking can significantly decrease the amount of dietary AGEs

produced.[733] This works with both broiling and boiling. Boiling chicken with lemon may decrease AGE content by 15 percent compared to boiling in water alone.[734] Another way to cut down on AGE absorption is to reduce fat content. A high-fat meal increases blood levels of AGEs more than a low-fat meal with the same AGE content and prepared with nearly the same foods but, for example, with reduced-fat cheese in place of a full-fat variety.[735]

CASTING LIGHT ON AGEs

What evidence do we have that cutting down on dietary AGEs will benefit us? Population studies have found that those with elevated AGEs in their blood are at greater risk for anemia, artery and cartilage stiffness, cardiovascular disease, chronic kidney disease,[736] osteoarthritis,[737] and osteoporosis,[738] but most of the studies have focused on the adverse effects of AGEs on our muscles, mortality, and minds. For a run-through, see my video see.nf/ages.

There's a noninvasive way to assess the accumulation of AGEs over time that circumvents the problem of the day-to-day variability in blood levels based on the curious fact that some AGEs that build up in our skin are fluorescent.[739] Using a special detector, long-term AGE exposure can be correlated with frailty,[740] premature death,[741] and accelerated brain shrinkage.[742] In the influential paper "Oral Glycotoxins Are a Modifiable Cause of Dementia … [in] Humans," the reduction of food-derived AGEs is suggested as a feasible, effective strategy to combat our dementia epidemic.[743]

AGEs may help explain why those who eat the most meat were found to have triple the risk of becoming demented compared to longtime vegetarians,[744] but other factors may be contributing. For example, high intake of saturated fat, found mostly in meat, dairy, and junk food, is associated with a 40 percent increased risk of cognitive impairment and a nearly 90 percent higher risk of Alzheimer's disease.[745] Even just a few days on a high-fat, low-carb diet has been shown to cause cognitive dysfunction.[746] There is a problem with all these studies, though. Maybe the correlation between AGEs and chronic disease is just a correlation between

high-AGE foods like processed meat and chronic disease. The only way to prove cause and effect is to put it to the test through interventional trials.

THE AGE DIET TRIALS

Journal articles with titles like "Extended Lifespan in Mice Exposed to a Low Glycotoxin Diet"[747] exemplify the studies that show that lowering dietary AGE intake can improve longevity, whereas increasing AGE intake can impair learning and memory,[748] as well as cut lives short in rodents[749] and other model animals.[750] In one study, for instance, while 76 percent of the mice fed a low-AGE diet lived at least fifty-six weeks, not a single one of the mice fed an AGE-rich diet survived after forty-four weeks.[751]

The negative effect of AGEs is so great it can even trump the benefits of calorie restriction. While lifelong calorie restriction predictably prolongs the lifespan of mice, when they're fed high-AGE food pellets, they not only die sooner than mice eating regular chow but they also do worse in every category tested—inflammation, oxidative stress, insulin resistance, and marked heart and kidney fibrosis (scar tissue buildup).[752] The benefits of reducing food quantity can be undone by reductions in food quality. We'll see this in the next chapter, where the well-being enjoyed by members of the Calorie Restriction Society may be constrained by their relatively high protein intake.

I review the human AGE trials in see.nf/agetrials, but basically, a single meal of broiled chicken causes a "profound impairment" of artery function within hours compared to eating the same amount of boiled chicken. Boiled chicken still impaired arterial function, but significantly less than when the chicken was broiled.[753] This difference was attributed to AGEs, but other heat-generated toxins are also created when meat is cooked, such as heterocyclic amines, which originate mainly from the creatine in the muscle, so it's impossible to say with absolute certainty what caused the difference.[754]

GLYCEMIC LOAD

Even though the majority of AGEs in the body come externally through our diet, AGEs are also formed internally. This normally happens at a slow, continuous rate, but it is sped up in the context of high blood sugars.[755] In

my previous books, I explore the prevention, arrest, and reversal of prediabetes and type 2 diabetes. However, even people with normal fasting blood sugars can get spikes that are too high after eating meals with a high glycemic load.

TAKE A LOAD OFF

In my Low Glycemic Load chapter in *How Not to Diet*, I take a deep dive into the impact different carbohydrate-rich foods have on our blood sugars, focusing on a measure called glycemic load. The higher the glycemic load, the higher our blood sugars tend to spike when we eat them. Here's a breakdown of some common sweet and starchy foods:[756]

Glycemic Load Per Serving

Low ≤ 10	Medium 11–20	High ≥ 20
Beans	Oatmeal	Breakfast Cereals
Chickpeas & Split Peas	Spaghetti	Dates
Fruits	Brown Rice	White Rice
Lentils	Sweet Potato	White Potato
Whole-Grain Bread	White Bread	Raisins

PUTTING LOWER-GLYCEMIC EATING TO THE TEST

In the boiled versus broiled chicken study, even the boiled chicken meal led to some artery dysfunction, whereas a low-glycemic, high-fiber meal can actually improve artery function in the subsequent four hours after consumption.[757] Like AGE studies involving meat reduction, though, it can be difficult to separate out the specific effects of glycemic changes. Many high-glycemic foods are fiber-depleted and highly processed, so you're doing more than just changing glycemic load when you swap them out for beans, fruits, or other low-glycemic foods.[758] A constant challenge with diet studies is that it's hard to change just one thing. It's simple with drug trials because researchers can just give the drug or a sugar pill. Then, if there's a change, they know it was caused by the drug. If only we could somehow stuff a change in glycemic load into a pill. Well, it turns out, we can.

The drug acarbose partially blocks our starch- and sugar-digesting enzymes in the digestive tract, which slows carbohydrate absorption into

our body.[759] When we take the drug with a meal, a high-glycemic meal is effectively transformed into a low-glycemic one—without changing the foods at all.[760] Acarbose is how researchers were able to show that lowering dietary glycemic load leads to weight loss independent of fiber intake,[761] and it can do the same with AGE reduction.

Acarbose has been shown to lower blood AGE levels in diabetics by about 30 percent within twelve weeks.[762] No wonder acarbose has been found to improve the healthspan and longevity of mice, increasing their maximum lifespan by about 10 percent. As drugs go, acarbose has an outstanding safety record.[763] However, flatulence, bloating, and diarrhea are commonly reported.[764] We can reap the upsides of the drug without its downside side effects by simply choosing lower glycemic load carbs, such as legumes (beans, chickpeas, split peas, and lentils), fruits, and intact whole grains.

BE FULL OF BEANS

By 1980, it had already been shown that beans cause an "exceptionally" low blood sugar response, half that of other common foods.[765] But two years later, an extraordinary discovery was published: Legumes can benefit your metabolism hours after consumption[766] or even the following day. If you eat lentils for dinner, your body reacts differently to breakfast eleven hours later.[767] Even if you drink straight sugar water the next morning, your body is better able to handle it if you had lentils the night before. Researchers initially dubbed it the "lentil effect," but when subsequent studies found that chickpeas appeared to work, too, they changed the name to the "second meal effect."[768]

How does it work? We scratch our gut bacteria's backs, and they scratch ours. Good gut flora take fiber we eat and produce short-chain fatty acids for us that get absorbed into our bloodstreams and circulate throughout our systems. So, if we eat a bean burrito for dinner, by morning, our gut bacteria are eating that same burrito and the by-products they create may affect how we digest our breakfast. This helps explain why diabetics randomized to a cup a day of beans, chickpeas, or lentils successfully improved their blood sugar control.[769]

Contrary to popular belief, eating a piece of fruit with a meal would be expected to lower, rather than raise, our blood sugar response,[770] which is why type 2 diabetics are no longer encouraged to restrict fruit intake.[771] A half dozen randomized controlled trials swapped in fruits for other foods, like higher glycemic carbs, and found, on average, a significant improvement in blood sugar control.[772] In fact, those who eschew fruits and go on a ketogenic diet to lower blood sugars may actually make things worse in the long run.

Those going on ketogenic diets may nearly quadruple their saturated fat intake,[773] and saturated fat can impair the action of the blood sugar–lowering hormone insulin. We've known for nearly a century that a high-fat diet can double blood sugar reactions to the same carbohydrate challenge within a matter of days.[774] Even a single meal can do it. Eating a stick of butter,[775] for example, or drinking a milkshake can dramatically increase insulin resistance within hours.[776] But, what if keto dieters stick with the program and avoid carbohydrates to stay in a state of ketosis? AGE levels can skyrocket.

One reason diabetics suffer nerve and artery damage is due to *methylglyoxal*, an inflammatory metabolic toxin that forms at high blood sugar levels. Methylglyoxal is the single most potent creator of AGEs.[777]

Since AGEs are concentrated in high-fat and high-protein animal-based foods, it makes sense that we'd expect high exposure to preformed ones on a keto diet. Similarly, it follows that we'd expect less internal, *new* AGE formation due to presumably low levels of methylglyoxal, given low blood sugars.[778] Surprisingly, Dartmouth researchers found *more* methylglyoxal. After just two to three weeks on the Atkins diet, subjects had a significant increase in methylglyoxal levels and those in active ketosis did even worse, experiencing a doubling of glycotoxin in the bloodstream.[779]

High sugars may not be the only way to create methylglyoxal. One of the ketones you make on a ketogenic diet is acetone. Sound familiar? It's a primary ingredient in nail polish remover. But acetone does more than strip paint and make keto dieters develop "rotten apple breath"[780] and fail Breathalyzer tests.[781] It can oxidize in the blood to acetol, which may be a precursor for methylglyoxal. This may be why nondiabetic keto dieters can

end up with methylglyoxal levels as high as those with uncontrollable diabetes.[782]

What About Natural and Artificial Sweeteners?

When people were randomized to drink beverages sweetened with aspartame, monk fruit, or stevia instead of sixteen spoonsful of sugar[783] (the amount of added sugar in a 20 oz bottle of Coke[784]), they were all found to be equally bad when it came to calorie intake, blood sugars, or insulin spikes throughout the day.[785] Similar results were found for Splenda (sucralose).[786] How is that possible? The mystery is solved in my video see.nf/sweeteners.

HOW TO REDUCE THE GLYCEMIC IMPACT OF GRAINS

In my Wall Off Your Calories chapter in *How Not to Diet*, I explore how the same foods in different forms can have different effects. Steel-cut oatmeal is considered to be a low-glycemic-index food, averaging under 55, whereas the glycemic index of instant oatmeal is 79, which makes it a high-glycemic-index food. Instant oatmeal isn't as bad as some breakfast cereals, though, which can get into the 80s or 90s—even zero-sugar cereals like shredded wheat.[787] How can this be? Modern industrial methods used to manufacture breakfast cereals, like explosion puffing and extrusion cooking, accelerate starch digestion and absorption, which cause exaggerated blood sugar responses.[788] Shredded wheat and spaghetti have the same ingredients—straight wheat—but shredded wheat has twice the glycemic index.[789]

From a glycemic-index standpoint, breads made from sprouted grains[790] with added cracked wheat,[791] whole wheatberries,[792] or rye berries,[793] or made with stone-ground flour are preferable.[794] If you simply just can't live without white bread, toasting it,[795] using sourdough fermentation if you bake your own,[796] and freezing and defrosting it all lower the blood sugar response.

When starch is cooked, then cooled, some of it crystallizes into "resistant" starch—starch that is resistant to being broken down into sugars by the enzymes in our digestive tract, which lowers its glycemic impact.[797] This is why pasta salad can be more healthful than hot pasta, and potato salad better than a baked potato. Some grains—notably sorghum[798] and millet—inherently contain resistant starch, resulting in a 20 to 25 percent lower blood sugar response compared to other grains, such as rice,[799] wheat,[800] or corn.[801]

HOW TO REDUCE THE GLYCEMIC IMPACT OF POTATOES

If you look at most whole plant foods—legumes, nuts, vegetables, and fruits—increased consumption is associated with living a longer life, with about 25 percent less chance of dying prematurely from all causes put together. There appears to be no such protective association with white potatoes, though. Now, potatoes aren't like meat, which may actively shorten your life, but there is an opportunity cost to eating white potatoes, since every bite of a potato is a lost opportunity to put something even more healthful into your mouth that may actively make your life longer.[802]

The reason the consumption of white potatoes may just have a neutral impact on mortality risk is that their fiber, vitamin C, and potassium might be counterbalanced by the detrimental effects of their high glycemic index.[803] Can we have our potatoes and eat them, too, by somehow lowering their glycemic index? There is that cool crystallization trick. By consuming potatoes as chilled potato salad, for instance, it's possible to get nearly a 40 percent lower glycemic impact. To minimize the glycemic index of potatoes, simply precook them and either eat them cold or reheated in the microwave.[804] (I call it the nip-and-nuke method.) The vinegar in that potato salad may even have an additional benefit.

STRIKE A SOUR NOTE

Randomized controlled trials involving both diabetic and nondiabetic subjects suggest that blood sugar control may be improved by adding two teaspoons of vinegar to a meal, effectively blunting the post-meal blood sugar spike by about 20 percent.[805] So, the effects of these high-glycemic foods may be blunted by adding vinegar to rice (like the Japanese do to

make sushi) or dipping bread in balsamic vinegar, for example. The combination of chilling before eating and adding vinegar to make potato salad was found to have an additive effect.[806] See see.nf/lemony for a comparison to the effects of lemon juice.

SPICE THINGS UP

As you can see in the Glycemic Load Per Serving chart (see here), the simplest way to stick to a lower glycemic diet is to try to stick to foods that were grown, not made. If you are going to eat high-glycemic foods, vinegar isn't the only way to help blunt the blood sugar surge. For example, if you eat berries with your meals, they can act as starch blockers by inhibiting the starch-digesting enzyme.[807] This then slows the absorption of blood sugars into your system. So, if you're preparing a high-glycemic breakfast, add blueberries to your pancakes or top your bowl of Franken Berry with actual berries.

On the other end of the culinary spectrum, onions can do the same thing. When subjects downed about three tablespoons of corn syrup, their blood sugars shot up over the next hour and a half from their baseline of about 90 mg/dL up to around 130 mg/dL before their bodies were able to tamp them back down. However, when they ate a quarter of an onion with that corn syrup, their sugars only went up to about 115 mg/dL.[808] After eating a whole onion, their blood sugars only reached 105 mg/dL, and two onions resulted in only about a five-point increase to 95 mg/dL. Simply by eating onions, their blood sugars hardly went up at all, similar to what one might experience on an antidiabetes drug.

Spices can also be helpful. An Indian curry with 6 g of spices (about one tablespoon) cut the blood sugar response to white rice by 19 percent, compared to no added spices, and 12 g of spices cut the glycemic impact by 32 percent.[809] You can also drink your spices. Have some ginger tea with two slices of refined flour white bread, and you drop the bread's glycemic index by nearly 30 percent. Cinnamon tea works even better, with nearly a 40 percent drop in glycemic response. Even regular unsweetened green tea cuts the glycemic impact by about 20 percent.[810] Of course, not eating white bread in the first place would work even better.

What about drinking herbs? Chamomile is one of the most widely used medicinal plants in the world—and for good reason.[811] When type 2 diabetics drank a small cup of chamomile tea after their meals for a few months, they got significant improvement in long-term blood sugar control compared to drinking the same volume of warm water[812] or when pitted head-to-head against black tea.[813] And the side effects? All good—lower LDL cholesterol and triglycerides,[814] a decrease in inflammation,[815] and improved sleep, mood,[816] and antioxidant status.[817] Chamomile tea and green tea appear to share the same mechanisms for blood sugar control: blocking the transport of sugars through the intestinal wall.[818]

Slave to the Rhythm

In my Chronobiology chapter in *How Not to Diet*, I explore how our ability to keep our blood sugars under control deteriorates as the day progresses.[819] Thanks to our circadian rhythm, a meal eaten at 8:00 at night can cause twice the blood sugar response as an identical meal eaten at 8:00 in the morning.[820] Even eating lunch earlier, rather than later, can make a significant difference.[821] So, if you simply have to have refined grains and sugary foods, giving in to your craving might be less detrimental in the morning.[822]

WALK IT OFF

Since active muscles can siphon off excess blood sugars, exercise timing can complement meal timing. When type 2 diabetics were randomized to a leisurely twenty-minute stroll (about 2 mph) either before or after dinner, researchers found that after-dinner walking can comparatively blunt blood sugar spikes by 30 percent.[823] Thanks to some tactical timing, the same meal and the same amount and intensity of exercise can give us a significant bonus effect on blood sugar control. Exercising after a meal can bring down blood sugars just as effectively as some blood sugar–lowering drugs,[824] and even just a short ten-minute walk after eating may make a difference.[825] See

my Exercise Tweaks section in *How Not to Diet* for specifics on optimal timing.

Food for Thought

AGEs are considered "gerontotoxins,"[826] meaning aging agents (from the Greek *geros* for "old age," as in *geriatric*), and are implicated in a wide spectrum of age-related diseases. In a sense, we are all slowly being cooked alive. AGEs are formed endogenously at body temperature, especially with high blood sugars, but their buildup in our tissues is largely determined by the AGEs we eat (or smoke), which are formed at much higher temperatures when some foods are cooked at high heat (or tobacco is cured).

Rather than addressing dietary change, however, the medical field has focused on inventing drugs to combat AGEs. Lifestyle approaches are said to have "zero commercial value,"[827] and an argument is made that "stewed chicken would be less tasty than fried chicken.…"[828] Why not have your KFC and eat it, too, by taking Kremezin, the drug that blocks AGE absorption every time you eat to reduce the absorption of the toxins?[829] It turns out the drug is just a preparation of activated charcoal,[830] like what's used for drug overdoses and when people are poisoned. I'm sure chasing your KFC with some ipecac would lower your AGE levels, too! A safe level of dietary AGE intake has yet to be established, but animal studies show even cutting intake just by 50 percent can lead to a longer life.[831]

The best way to reduce absorption of AGEs is to reduce your exposure in the first place.

To help slow this aging pathway, on a daily basis, consider:

- stopping smoking[832]
- avoiding the very worst foods, such as bacon and hot dogs[833]

- eating an "AGE Less" diet by emphasizing lower AGE foods, such as fruits and vegetables[834]
- cooking high-protein foods using relatively low heat and high humidity methods, such as boiling or steaming rather than broiling or frying
- favoring raw nuts and seeds over roasted or toasted
- choosing lower-glycemic-load foods

IGF-1

A major breakthrough in our thinking about aging happened in the early 1990s. Aging was generally considered to be a hopelessly intractable problem.[835] We just wear out, the thinking went, in a haphazard and passive process of wear and tear. Then, in 1993, a single genetic mutation was found to double the lifespan of *C. elegans*,[836] the roundworm oft used in aging research. Instead of all worms being dead by thirty days, some lived for sixty days or longer in one experiment. As principal investigator Cynthia Kenyon recalled, the "mutants were the most amazing things I had ever seen. They were active and healthy and they lived more than twice as long as normal. It seemed magical but also a little creepy: they should have been dead, but there they were, moving around."[837]

This lifespan extension was the largest reported to date in any organism. These Methuselahian worms were touted as medical marvels, "the equivalent of a healthy 200-year-old human,"[838] all because of a single mutation. That was particularly surprising. Presumably, aging is caused by multiple processes affected by many genes. How could knocking out a single gene double lifespan?

DON'T GEAR THE REAPER

What is this so-called Grim Reaper gene—one that so accelerates aging that, if it's knocked out, the animals live twice as long? It is the worm equivalent of the receptor to human insulin-like growth factor 1 (IGF-1),[839] a potent growth hormone structurally similar to insulin. Mutations of that same receptor in humans may help explain why some people live to be a

hundred and others don't.[840] It was a stunning discovery, the first life-extension pathway to be defined. We learned that aging is controlled by hormone signals conserved evolutionarily from tiny worms all the way up to us.[841]

Interference with the signaling in the IGF-1 pathway has since been shown to extend the lives of a variety of species.[842] Mice that have had IGF-1 disrupted live 42 to 70 percent longer.[843] Marveled Kenyon, "Some of these long-lived mutants are breathtaking; in human terms, they look like forty-year-olds when they are actually eighty or even older." The dialing down of growth-hormone signaling is thought to shift the body's priorities from growth to maintenance and repair, thereby extending survival.[844] The decline in IGF-1 levels as we get older may even be nature's way of sustaining us into old age.[845]

CENTENARIAN SECRETS

The majority of long-lived rodent models have lower levels of IGF-1.[846] What about people? Centenarian humans have lower IGF-1 levels in their blood, but is it cause or effect? IGF-1 levels decline as we age, so did the growth hormone cause centenarians to live long lives, or did living long lives cause the low IGF-1 level?[847] It's not as if you can compare them to controls of the same age who *aren't* centenarians. This led researchers to look at the IGF-1 levels of the offspring of centenarians so they could compare them to age-matched controls, and, indeed, the children have lower IGF-1 levels, too.[848] This suggests that lower IGF-1 levels may have given the centenarians the advantage.

Hundreds of different common human genetic variants have been studied, and this same pathway consistently implicated in extending lifespans in other animals is the very one associated with longevity and reduced risk of the major causes of death.[849] There is a single IGF-1-lowering gene variant that adds as much as ten years or so to life expectancy if you inherit it from both parents.[850]

Those lucky enough to be born with genetically lower IGF-1 levels are more likely to live to be nonagenarians.[851] Then from age ninety, low IGF-1 levels[852] and activity[853] have been found to subsequently predict their future survival. Interestingly, there are two mutations linked to centenarianism in

Ashkenazi Jews—my heritage—that lead to *elevated* IGF-1 levels, but the mutations are in the IGF-1 receptor, so the elevated levels are presumably due to their body's futile attempt to overcome the enfeebled receptor.[854] Either way, the dampening of IGF-1 signaling appears to be a human-longevity mechanism.[855]

Is it just the luck of the draw whether we're born with good genes? Regardless of what our genetically determined baseline level of IGF-1 activity is, we can ramp it up or tamp it down, depending on what we eat.

The Taller Live Shorter

Dog lovers may know that smaller breeds tend to live longer than larger ones.[856] Tiny toy poodles average nearly twice the lifespan of the Great(est) Dane.[857] This makes sense when you realize that a major determinant of the difference in breed size is IGF-1.[858] The same phenomenon is observed in other species.[859] Asian elephants are smaller than their African cousins and typically live longer, and smaller horses, rodents, and cows generally outlive larger ones, too. What about people?

Bigger used to be better. Taller height was once an indicator of socioeconomic status and superior childhood living conditions, which translated into improved longevity.[860] However, now that relatively few kids are stunted by malnutrition, that baseline welfare allows inborn factors to shine through. These days, shorter stature predicts a longer lifespan.[861] In fact, this may help explain the gender differential in life expectancy. Men, on average, are about 8 percent taller than women and have about an 8 percent shorter lifespan.[862]

The relationship between a taller stature and a shorter life is driven mainly by increased cancer rates. That could help explain why, in general, men have more than a 50 percent increased risk of developing cancer compared to women.[863] Each additional inch in height is associated with

about a 6 percent increased risk in dying from cancer.[864] This could just be because bigger people simply have more cells to potentially turn malignant.[865] After all, those with more skin might have a greater chance of developing skin cancer.[866] But the connection between height and cancer could also be because of cancer-promoting growth hormones like IGF-1.[867]

The Ashkenazi centenarians with the IGF-1 mutation were, on average, about an inch shorter, but the difference in height was not statistically significant.[868] This suggests we may be able to enjoy all the longevity benefits of dampening IGF-1 while still having a shot at the NBA.

CANCER BOOSTER

Each year, you are reborn. You destroy and create anew nearly your entire body weight in cells every year. About fifty billion of your cells die each day, but about fifty billion new cells are born.[869] Of course, there are times that you need to grow, such as during infancy or puberty, but your cells don't grow in size as you mature—they grow in number. As an adult, you may have around forty trillion cells, four times more than when you were a child.

During periods of growth like puberty, you need a net growth of cells, creating more than you retire, but that's not the case in your later years. Of course, you still need your cells to grow and divide, but extra cell growth in adulthood can mean the development of tumors.

How does your body maintain its balance? It sends hormones—chemical signals—to all your cells. IGF-1 is one of those key signals for regulating cell growth. When you're a child, the growth hormone's levels go up to power your development, but they decline when you reach adulthood, cueing your body to stop producing more cells than it puts out to pasture.

If your IGF-1 levels stay elevated after you're old enough to vote, your cells will continue to get the message to continue to grow and divide. As you might expect, the higher the IGF-1 in your bloodstream, the higher

your risk for developing some cancers, such as breast,[870] colorectal,[871] and prostate.[872] (That doesn't seem to be the case, though, with lung,[873] ovarian,[874] or pancreatic cancer.[875]) In the Harvard Nurses' Health Study, premenopausal women younger than fifty in the upper third of IGF-1 levels had nearly five times the risk of developing breast cancer compared to those in the lower third.[876] In fact, before there was successful chemotherapy, surgeons would treat advanced breast cancer cases by not only removing the ovaries but operating on the brain to remove the patient's pituitary gland, which orchestrates growth hormone production in the body.[877]

Those with a tendency to have lower IGF-1 levels are less likely to get cancer in the first place,[878] and cancer survivors with lower levels are more likely to survive longer.[879] It's not the original tumor that tends to kill you; it's the metastases.[880] As a growth factor, IGF-1 doesn't just make tumors grow;[881] it helps cancer cells separate from the main tumor, infiltrate surrounding tissues, and invade the bloodstream.[882] IGF-1 is what helps breast cancer get into the bone,[883] liver, lung, brain, and lymph nodes.[884] It's involved every step of the way, facilitating the transformation of normal cells into cancer cells to begin with, then nurturing them to survive, proliferate, self-renew, grow, migrate, invade, and, finally, stabilize into new tumors. It even helps new tumors hook up their blood supply.[885]

Centenarians, however, seem to be endowed with a peculiar resistance to cancer.[886] As you age, your risk of developing and dying from cancer grows every year—until you hit eighty-five or ninety. Interestingly, that's when your cancer risk begins to drop.[887] At age sixty-five, we are a hundred times more likely to have a tumor than we are at age thirty-five, but if you don't get a cancer diagnosis by a certain age, you may never get one.[888] Centenarians appear ten times less likely to die from malignant tumors than people in their fifties and sixties (4 percent versus 40 percent, respectively).[889] What appears to account, at least in part, for this relative resistance to cancer among centenarians? Less IGF-1.[890] So, lowering IGF-1 activity could have the dual benefit of decreasing cancer risk while increasing longevity.

Cancer-Proofing Mutation

The primacy of IGF-1's role in tumor biology is demonstrated by a natural experiment involving a genetic defect that causes severe, lifelong, IGF-1 deficiency called Laron syndrome. The first case of this syndrome was reported in the *Israel Journal of Medical Sciences*,[891] but the largest affected population is in a remote area of Ecuador.[892] Jews fleeing the Spanish Inquisition in the fifteenth century escaped to South America and brought the gene mutation with them, causing this disparate geographic distribution.[893]

Lifelong IGF-1 deficiency not only gives people with Laron syndrome a small stature but it also appears to make them effectively cancer-proof.[894] Only a single case of (nonlethal) cancer was described among nearly five hundred affected individuals.[895] That's a cancer rate one hundred times lower than people without Laron syndrome, and without a single cancer death.[896] Most malignant tumors are covered in IGF-1 receptors. Without any IGF-1 around, the tumors may not be able to grow and spread.[897]

When we're kids, we need growth hormones to grow, but what if, as a child, we could get all of the growth hormones we needed to grow to a typical height and then downregulate hormones like IGF-1 once we reach adulthood? Turning off excess growth signals could potentially keep our cellular life-and-death balance sheets balanced to prevent cancer and settle us into repair-and-maintenance mode to prolong our lives. It turns out that we can do just that. We can suppress IGF-1 activity—not with surgery or medication but through simple dietary choices.

HOW TO REDUCE IGF-1 LEVELS WITH DIET

Unsurprisingly, drug companies have come up with a variety of IGF-1-blocking chemo agents, including ones with cute names like *figitumumab* and not-so-cute side effects like "early fatal toxicities."[898]

How can we reduce IGF-1 levels naturally?

Complete fasting can do it. Consuming nothing but water for five days can temporarily cut your levels in half.[899] (Don't try this at home, though. See here.) This is why cancer patients often fast for a few days before and after chemotherapy. The reduction in IGF-1 makes cancer cells more vulnerable to being killed off. How do we know that the fasting benefit is due to the IGF-1 reduction? Because restoring IGF-1 eliminates the starvation-induced vulnerability of cancer cells.[900]

Fasting is the poster child of unsustainability, though. If you fast long enough, you're guaranteed to stop aging—because you'll be dead. Avoiding the finality of long-term fasting fatality is the impetus behind creating fasting-*mimicking* diets designed to lower IGF-1 levels by eliminating the key dietary component that drives them up to begin with: animal protein.[901]

In rodents, calorie restriction alone reduces IGF-1 levels,[902] but in humans, unless protein consumption is also reduced, even severe caloric restriction doesn't work. Researchers were only able to get subjects' IGF-1 levels to budge after the protein intake of calorie-restriction practitioners was cut from typical American quantities down closer to the recommended daily allowance.[903]

At intakes far exceeding recommended consumption, protein from plants and animals equally raises IGF-1 levels,[904] but at more reasonable levels, animal protein appears to be the main culprit. Men[905] and women who avoid meat, egg, and dairy proteins have significantly lower IGF-1 levels even when moderately exceeding protein recommendations.[906] When people switch to a plant-based diet, their IGF-1 levels can drop significantly in less than two weeks.[907] However, just adding more plant foods,[908] cutting out meat,[909,910] or switching to fish may not help.[911,912] It's not all or nothing, though. A study of women carrying the BRCA mutation who are at high risk for breast cancer found that IGF-1 levels could be lessened by simply reducing, but not completely eliminating, animal product consumption across the board.[913]

Even a single serving of chicken breast a day would be expected to significantly raise IGF-1 levels in the blood.[914] When it comes to aggravating IGF-1, chicken may be worse than beef, but that's based on rat studies and has yet to be tested in people.[915] More than a half dozen randomized controlled trials have shown that dairy consumption increases IGF-1 in as little as a week.[916] Perhaps the strangest was a study out of

Denmark in which IGF-1 levels were lowered successfully by switching people from two-thirds of a gallon of milk every day for ten days to two-thirds of a gallon of Coca-Cola.[917] I do believe that's the only study where people show a benefit from drinking twenty-five liters of Coke!

The relationship between milk consumption and IGF-1 is so consistent that the link has reached a P value of 10^{-27}.[918] In science, *P value* refers to the chance of getting a result that extreme if in fact there really was no such effect. It's used to determine how likely you would be to get the same results by random chance. How small of a chance is 10^{-27}? The probability that the association between milk consumption and IGF-1 is just a fluke is less than the chances of winning the lottery not once, not twice, but three times in a row, then subsequently getting struck and killed by lightning.[919]

IGF-1 may help explain the relationship between dairy consumption and prostate cancer,[920] but the reason those who drink the most milk appear to live shorter lives on average and are more likely to die from cancer may have more to do with the animal fat rather than the animal protein, since those findings were absent for low-fat milk.[921]

The bump in IGF-1 from dairy intake may be partly due to the absorption of preformed IGF-1 already in the milk.[922] After all, the whole point of milk is to put a few hundred pounds onto a calf in a matter of months,[923] so it shouldn't be surprising that it has high levels of growth-stimulating hormones.[924] Bovine IGF-1, which is identical to human IGF-1,[925] isn't affected by pasteurization.[926] While oral consumption of IGF-1 has been shown to be absorbed into the circulation of rats, pigs,[927] and presumably calves, similar studies have yet to be done on humans. Regardless, the protein in dairy can cause a surge in our own IGF-1 production, something less likely to happen when consuming protein from plants.[928]

ANIMAL VS. PLANT PROTEIN

The varying effects of animal versus plant protein appear to be due to different profiles of amino acids, the building blocks of proteins.[929] When you were a kid, did you love Tinker Toys as much as I did? I still remember how excited I was unwrapping a huge Tinker Toy set on my sixth birthday. I dumped out the new load of raw building materials onto the floor in front of

me and couldn't wait to start scaling up. Our liver responds with just as much excitement when faced with a bunch of protein building blocks.

Although some IGF-1 is made locally in various tissues, our liver is responsible for approximately 75 percent of the IGF-1 that circulates throughout our body.[930] So, what happens when we consume a load of protein? Our liver starts pumping out IGF-1 to tell all the cells in our body that it's time to grow to use up the excess. With so much extra protein to work with, our liver sends the signal to our cells to be fruitful and multiply.

The problem is that tumors may be some of the new additions spurred by this growth hormone. When you're a fully grown adult, cell growth is something we want to slow down, not accelerate. The goal, therefore, would be to maintain adequate, but not excessive, protein intake. But animal protein appears to send a different signal to our livers than most plant proteins. Why is protein from an animal associated with increased levels of IGF-1, but not protein from a plant?[931] Let's go back to Tinker Toys.

Let's say you want to build a really big cube, and a pile of little cubes is dumped in front of you. Nice, right? You start stacking them together and are done in no time. What if, instead, you got a bunch of pyramid shapes? Each of the pyramids can certainly be broken down into the constituent sticks and connectors. You'd still have all the essential elements to construct your big cube, but you probably wouldn't be as excited to dive into the pile of pyramids because so much more work would be involved breaking them down first. Basically, it's the same with your liver and IGF-1.[932]

All plant proteins and nearly all animal proteins are complete proteins, containing all nine essential amino acids.[933] (The only incomplete protein in the food supply is the animal protein collagen [gelatin], which is missing tryptophan.[934]) So, while you couldn't live on Jell-O and marshmallows, all other dietary proteins, whether from plants or animals, contain all the essentials you need. When you hear about high- versus low-quality proteins, that's referencing the relative proportions of the different essential amino acids. The more closely the proportion matches our own proteins, the higher quality it's considered to be.

In a sense, there's only one truly "perfect protein" for us—human flesh. Failing that, any flesh will do. We don't practice species cannibalism, but by practicing kingdom cannibalism (Animalia) or, if we eat our fellow

mammals, class cannibalism (Mammalia), we're getting protein that more closely mirrors our own than, say, a kidney bean. This is not necessarily a good thing.[935]

When a big load of incoming animal proteins hits our liver, it's analogous to the head start with the pile of Tinker Toy cubes: The protein's meat and we're meat, so we start pumping out IGF-1 to speed up cell division to use up the excess. When we get plant proteins, though, they're like the pyramids. Our body can break them down into all the essential amino acids we need, but they just don't stimulate the same kind of real estate boom that animal protein does. This phenomenon doesn't appear to affect muscle mass, as those afflicted with acromegaly (a form of high-IGF-1 giantism) aren't disproportionately muscular,[936] and people injected with IGF-1 twice a day for a year don't experience an increase in lean mass or muscle strength.[937] But the IGF-1 surge associated with animal protein consumption may very well affect lifespan and cancer risk.[938]

What About Soy Protein?

What about the few plant proteins that have amino acid profiles similar to animal proteins, like soy? One of soy's selling points is that it has "high-quality" protein, but when it comes to IGF-1, so-called higher quality may mean higher risk. Is that the case with soy-based protein?

We know that the consumption of animal protein is associated with significantly higher levels of IGF-1, while the consumption of non-soy plant protein is associated with significantly lower levels.[939] Soy protein falls in the middle, with no significant association with IGF-1 levels either way. This suggests that if we simply replace animal protein with soy protein, we may not see as dramatic a drop in IGF-1 as achieved by replacing meat, eggs, and dairy with a variety of proteins from plants other than soybeans. This was confirmed in a Stanford study: Switching from regular beef, pork, and chicken to plant-based (Beyond Meat) beef, pork,

and chicken analogs made from soy and pea protein only caused an insignificant (3 percent) drop in IGF-1.[940]

Interventional studies showed that adding large quantities of soy protein supplements (40 g a day) increased IGF-1 levels,[941,942] but eating a couple of daily servings of actual soy *foods* did not.[943] The cutoff appears to be about 25 g of soy protein a day.[944] Of course, the main reasons we care about IGF-1 are cancer and longevity, and, if anything, soy consumers appear to be protected from cancer. A recent systematic review and meta-analysis found a 12 percent reduction in breast cancer death associated with each daily 5 g increase in soy protein intake, such as three-quarters of a cup of soymilk or two tablespoons of soy nuts.[945] Soy food intake also seems to be protective against prostate cancer.[946] And, in terms of longevity, as we'll explore in Part II, the two longest-lived formally studied populations on Earth, the Okinawa Japanese[947] and the vegetarian Seventh-day Adventists in California, tend to eat soy foods on a daily basis.[948]

QUIT COLD TURKEY

IGF-1 may help explain why people's lives appear to be cut short when they eat some low-carb diets but not others.[949] Twin Harvard cohorts found that vegetable-based low-carb diets were associated with lower mortality rates, while those based on animal sources increased the risk of premature death by 23 percent and the risk of dying specifically from cancer by 28 percent.[950] Even just substituting 5 percent of calories of animal protein with protein from plants, such as beans or nuts, may be associated with a 14 percent lower risk of dying prematurely (and a 19 percent lower risk of dying specifically from dementia).[951] Egg protein (found mostly in the egg white) appears to be the worst. Replacing just 3 percent of egg protein with plant protein may be associated with a 24 percent lower risk of premature death in men and a 21 percent lower risk in women.[952]

When a dream team of longevity researchers, including Luigi Fontana and Valter Longo, followed a nationally representative sample of thousands of Americans over age fifty for an average of eighteen years, they found that those under sixty-five with high protein intakes had a 75 percent increase in overall mortality and a fourfold increase in the risk of dying from cancer. When the protein sources were split up into plant versus animal, however, the overall mortality risk was found to be limited to the consumption of animal protein.[953] The sponsoring university described the study with a memorable opening line: "That chicken wing you're eating could be as deadly as a cigarette."[954]

The researchers explained that, compared to someone on a low-protein diet, the quadrupling of risk for cancer death from eating a diet rich in animal proteins during middle age is a mortality risk comparable to smoking. And when they say "low protein," that is just compared to what most people eat. The "low protein" group was actually getting the *recommended* amount of protein, 0.8 g per kg of healthy body weight, or about 50 g a day for someone weighing about 140 pounds—preferably from plants to keep IGF-1 activity low.[955] Overall, the amount of life lost from each burger is estimated to equate to smoking two cigarettes.[956]

Two Risks Don't Make a Right

What was the response in the scientific community to the revelation that, as the *Guardian* headline put it, "Diets high in meat, eggs, and dairy could be as harmful to health as smoking"? One nutrition scientist said that it was "potentially dangerous" to compare the effects of smoking with the effects of animal foods because a smoker might think, "Why bother quitting smoking if my cheese and ham sandwich is just as bad for me?"[957]

This reminds me of a famous Philip Morris cigarette ad that tried to downplay the risks of smoking. It argued that if you think secondhand smoke is bad (increasing the risk of lung cancer by 19 percent), drinking one or two glasses of milk every day may be three times as bad (a 62 percent

higher risk of lung cancer). So, it concluded, "Let's keep a sense of perspective." The ad went on to say that the risk of cancer from secondhand smoke may be "well below the risk reported … for many everyday items and activities."[958]

That's like saying we shouldn't worry about getting stabbed, because getting shot is so much worse. (Note: Philip Morris stopped throwing dairy under the bus after it acquired Kraft Foods.)

CANCELING CANCER

One of the ways our body tries to protect us from cancer is by releasing a binding protein into our bloodstream to tie up any extraneous IGF-1. Think of it as our emergency brake. Let's say you've managed to downregulate production of new IGF-1 through diet. What about all that excess IGF-1 still circulating from the bacon and eggs you may have eaten the day before? No problem: The liver releases a snatch squad of binding proteins to help take it out of circulation.

The release of IGF-1 triggered by animal protein consumption may explain why you can so dramatically bolster the cancer-fighting power of your bloodstream within weeks of switching to a plant-based diet. After only eleven days of cutting back on animal protein, your IGF-1 levels can drop by 20 percent and your levels of IGF-1 *binding protein* can jump by 50 percent. After study subjects ate plant-based for less than two weeks, researchers dripped their blood onto some cancer cells growing in a petri dish and found that it suppressed cancer growth 30 percent better than before. This has been demonstrated on both prostate cancer and breast cancer cells.[959] The remarkable strengthening of cancer defenses is attributed to the dietary changes in IGF-1. How do we know? If you add back to the cancer cells the amount of IGF-1 that had been banished by plant-based eating, the cancer cell growth comes surging back.[960] Participants in this intervention also added a walking component to their routines, but when it comes to IGF-1 binding and killing off cancer cells, even 3,000 hours in the gym appear to be no match against some walking plant-eaters.[961]

The cancer-suppressing effect seems so powerful that, in a randomized controlled trial, Dr. Ornish and colleagues appeared to be able to slow, stop, and even reverse the progression of early-stage, non-aggressive prostate cancer without chemotherapy, surgery, or radiation—just a plant-based diet and lifestyle program. After one year, the subjects' bloodstream was nearly eight times better at suppressing the growth of cancer cells.[962] Biopsies showed a downregulation of critical cancer genes, effectively the switching off of the expression of cancer growth genes at a genetic level.[963] If you instead eat a lot of dairy after a prostate cancer diagnosis, for example, you may suffer a 76 percent higher risk of death overall and a 141 percent increased risk of dying specifically from your cancer.[964] The reduction in IGF-1 from the reduction of animal protein intake may explain why vegans —those who don't eat meat, eggs, dairy, or other animal products—have been found to have lower rates of all cancers combined.[965]

A Food That Lowers IGF-1

Are there any foods that actively lower IGF-1? A retrospective[966] and snapshot-in-time study suggested that tomato consumption may be associated with lower IGF-1 levels.[967] One fruitful trial (funded by a lycopene supplement company) of colon cancer patients and lycopene, the red pigment in tomatoes, got people's hopes up.[968] Six other such studies done to date, however, fell flat on their face.[969] There appears to be no overall effect of lycopene supplementation on IGF-1 levels.

Flaxseed reduces IGF-1 levels in rats[970] but failed to do so when it was put to the test in people.[971] Similarly, green tea worked in mice,[972] but neither green tea[973] nor green tea supplements did the same in us.[974] Seaweed may help, though. Giving postmenopausal women just 5 g a day of alaria (*Alaria esculenta*) cut the IGF-1 bump caused by a 67 g protein load by 40 percent.[975]

IGF-1 AND LONGEVITY

Epidemiological studies have found both high *and* low IGF-1 concentrations associated with a shorter lifespan,[976] prompting editorial titles such as "IGF-I: Panacea or Poison?"[977] I take a deep dive into the data in see.nf/igf1, showing how the correlation between low IGF-1 levels and mortality can be a case of reverse causation, as both acute and chronic illness can lower IGF-1 levels to create the spurious appearance of harm.[978] Mendelian randomization methods can help tease this out, studying what happens when people are effectively randomized at birth to genetically have lower or higher lifelong IGF-1 set points. Such studies show that IGF-1 may indeed causally increase the risks of age-related ailments such as heart disease,[979] osteoarthritis,[980] and diabetes.[981] This may help explain why type 2 diabetes risk appears to be increased by animal protein intake but decreased by consumption of plant protein.[982]

As we'll see in the Anti-Aging Eight section, protein restriction alone can improve longevity, but it is possible to separate out the effects of IGF-1 and protein intake. As I noted earlier in the chapter, those who won the genetic lottery to have lower IGF-1 levels without even having to work at it are more likely to survive into their nineties[983] and even live through that decade,[984] and have a longer lifespan overall.[985]

Beyond genetics, there are interventional studies showing a reduction of total protein intake down to recommended levels[986] and/or switching from animal to plant protein sources has a variety of metabolic benefits.[987] However, the prospective study by Longo and colleagues that found the positive association between decreased protein intake and decreased mortality in middle age appeared to flip at around age sixty-five into a negative relationship. This could be due to reverse causation—for example, frail adults may be more likely to be malnourished. Nevertheless, the researchers recommended a protein intake of at least 10 percent of calories after age sixty-five, which would be 50 g on a 2,000-calorie-a-day diet, preferably from plants.[988]

Food for Thought

Insulin-like growth factor 1 is considered to be of cardinal importance for cancer expansion,[989] so downregulating IGF-1 activity not only has the potential to slow the aging process[990] but may be a way to turn anti-aging genes against cancer.[991] IGF-1 is cranked up on high-protein diets and by animal protein in particular. This helps explain the benefits of more plant-oriented eating,[992] as well as why consuming a diet with a relatively low proportion of protein is considered critical for lifelong health.[993]

To help slow this aging pathway, on a daily basis, consider:

- striving to stick to the recommended daily intake of protein of 0.8 g per healthy kg of body weight (0.36 g per pound), which translates to about 45 g a day for the average-height woman and about 55 g a day for the average-height man
- choosing plant-based protein sources whenever possible

INFLAMMATION

In recent years, one of the most medically important discoveries was recognizing the potential role of inflammation in many chronic diseases, including at least eight of the top ten leading causes of death.[994] The magnitude of this new understanding has been compared to the discovery of the germ theory centuries ago, which revolutionized how we prevent and treat infectious diseases.[995]

For most of our time on Earth, infections were a primary cause of death and disease. Without soap, sanitation, or water purification, we were under constant barrage, racked with chronic parasitic infestations from within and attacked on all sides by microbial threats. Without antibiotics, a scraped knee could end up being a mortal wound, which is why our immune systems evolved to be on high alert, erring on the side of overreaction rather than under-reaction.[996] Sometimes, though, that can do us more harm than

good. For example, head trauma may kill hundreds of thousands of brain cells, but the ensuing inflammatory response may kill millions of brain cells or the patient themself.[997]

META-INFLAMMATION

Inflammation evolved to be beneficial. When you get a splinter in your finger, for example, and the digit turns red and gets warm, painful, and swollen, that inflammation is your body's natural reaction to tissue damage or irritation. Its purpose is to trigger the healing process, not a disease process.

Your body's reaction to that splinter is an example of acute inflammation, a localized, temporary, direct response to infection or injury focused on resolving a problem. Chronic inflammation, also called *metabolic inflammation*, or *meta-inflammation* for short, on the other hand, is systemic, persistent, and nonspecific and appears to perpetuate disease.[998] It has a low-grade, smoldering quality that can be picked up on blood tests showing abnormally high levels of inflammatory markers like C-reactive protein (CRP).

Ideally, CRP levels in the blood are under 1 mg/L,[999] but, in the presence of infection, it can skyrocket within hours up to 100 mg/L or more.[1000] Today, our highly sensitive CRP blood tests can measure levels to a fraction of a point, which has led the medical community to recognize that having baseline levels of just 2 or 3 mg/L may place us at increased risk of catastrophes like heart attacks and strokes. Baseline CRP levels below 1 mg/L denote lower risk, but most middle-aged Americans have levels that exceed this level,[1001] suggesting that most suffer from chronic inflammation —chronic inflammation that tends to worsen with age.

INFLAMMAGING

As we get older, our immune system gradually deteriorates in a process known as immunosenescence.[1002] This plays a part in explaining why pneumonia, for example, moves up from being the tenth leading cause of death when we're in our fifties and early sixties to being the eighth leading cause when we're sixty-five and older.[1003] It's why latent viruses can

reemerge, like chickenpox erupting as shingles after lying dormant for a half century. It also explains why vaccines don't work as well as we age. The annual flu vaccine is only about 50 percent effective among those who need it most.[1004]

On the flip side, the activated immune cells of eighty-year-olds produce significantly *more* pro-inflammatory signals.[1005] This suggests the worst of both worlds—a decline in the part of the immune system that fights specific infections and an aggravation of nonspecific overreactions that can lead to inflammation.[1006] This progressive increase in pro-inflammatory status is now recognized as a major feature of the aging process, formalized in 2000 into a concept called "inflammaging," a chronic low-grade inflammation that may be responsible for the further decline and onset of disease in the elderly.[1007,1008]

CRP levels rise as we age and are associated with reduced survival, poorer physical and cognitive performance,[1009] diminished feelings of vitality,[1010] and a range of age-related diseases, including Alzheimer's, Parkinson's, cardiovascular disease, diabetes, and chronic kidney disease.[1011] Inflammaging is also thought to play a key role in degenerative disc disease in our spine[1012] and the loss of muscle mass and strength as we age.[1013]

CRP is the most widely studied inflammatory biomarker for predicting remaining lifespan.[1014] Having higher CRP levels in your blood may increase your risk of dying prematurely by 42 percent. However, interleukin 6 (IL-6), the most important trigger for CRP production, may be an even better predictor.[1015] Interleukins are chemical messengers used to communicate between (*inter*-) white blood cells (-*leuk*ocytes).

In our youth, blood levels of IL-6 are typically low or may even be undetectable, but they begin to increase when we're around fifty to sixty. As a potent pro-inflammatory agent, elevated levels are considered to be one of the most powerful predictors of disease and death in the elderly.[1016] Researchers looked at single blood samples from healthy individuals aged sixty-five and older and found that if their IL-6 levels were in the highest quarter of values, their risk of dying may be 40 percent over the next five years, compared to less than 10 percent among those with values in the lowest quarter.[1017] IL-6 even seems predictive at extreme ages. Centenarians with an IL-6 level in the lowest third of values are three times more likely

to be alive nearly five years later, compared to the highest third.[1018] IL-6 appears to be a cause, rather than just a consequence, of life-threatening disease since those born genetically predisposed to higher IL-6 levels are less likely to survive to old age.[1019]

Save Your Skin

Which organs do you think are our largest? Maybe our lungs, liver, or intestines? Those weigh about five pounds each. Our skin, on the other hand, weighs about twenty pounds.[1020] How might our skin contribute to inflammaging?

As young as age forty-five, we start to lose hydration in the outermost layer of our skin, as our skin's barrier function starts to deteriorate.[1021] Barrier breaches can then trigger inflammation that can spill over into the bloodstream. Would topical application of some kind of skin cream be able to lock in moisture and prevent this inflammation? When aged mice were rubbed with petroleum jelly three times a day for ten days, the inflammatory markers went down not only in their skin but throughout their bodies.[1022] This prompted a 2019 study in which researchers put it to the test in people.

Elderly men and women (average age seventy-eight) were randomized to a twice-daily application of 3 mL (about two-thirds of a teaspoon) of an emollient to their skin for a month. Remarkably, not only did the blood levels of inflammatory markers like IL-6 drop significantly compared to elderly controls who didn't moisturize their skin but they dropped down to levels close to that of younger individuals (average age thirty-two).[1023] This suggests that applying skin lotion may be a simple way to dampen systemic inflammation.

HOT AND HEAVY

Inflammation is considered to be an important indicator and driver of aging,[1024] but where is all this inflammaging coming from? Some have suggested chronic infections, such as Epstein-Barr virus or cytomegalovirus (CMV), but preindustrial populations of forager-horticulturalists and hunter-gatherers don't appear to have suffered from inflammaging despite large infectious exposures. We've already covered two implicated sources of inflammaging: the buildup of dietary advanced glycation end products[1025] (the Glycation chapter) and senescent cells spewing SASP[1026] (the Cellular Senescence chapter). Our age-related decline in autophagy machinery (the Autophagy chapter) can also lead to what's been dubbed "garbaging."[1027]

Our immune system may start reacting to the cellular detritus that can build up as we age, and that has led some to speculate that inflammaging—and even part of the aging process itself—may be an elaborate autoimmune, autoinflammatory reaction.[1028] This would be consistent with the fact that two years of modest caloric restriction cut inflammation markers such as CRP by 40 percent. This dramatic anti-inflammatory effect could have been due to a boost in autophagy that cleared out inflammatory cellular debris or simply as a consequence of their weight loss.[1029]

Dozens of studies have found that obesity is strongly associated with increased levels of inflammatory markers, such as CRP, in the blood.[1030] But is the inflammation a cause or a consequence of obesity? We once thought that fatty tissue was simply a passive depot for the storage of excess fat, but we now know that it plays an active role in secreting inflammatory chemicals. Fatty tissue is able to expand so rapidly that it may even outpace its own blood supply and become starved of oxygen.[1031] (An electrode can be inserted directly into an obese belly to measure how low oxygen levels may fall compared with individuals at a healthy weight.[1032]) This oxygen deprivation is thought to contribute to the death of fat cells. But this is not a good thing; fat cell death draws out inflammatory cells like macrophages, a type of roaming white blood cell found in pus, to try to clean up the debris. Indeed, belly biopsies from obese individuals show macrophages swarming throughout the fat.[1033] Then, the macrophages appear to get stuck and fuse together into giant cells, which are a hallmark of chronic inflammation seen in resistant infections like tuberculosis or around foreign bodies our body

can't clear.[1034] All this is occurring while inflammatory compounds spill out into general circulation.[1035] As such, obesity appears to lead to systemic inflammation, rather than the other way around.[1036,1037]

Unsafe at Any Feed

Dietary cholesterol may also contribute to inflammation in body fat that can spill over into our bloodstream.[1038] Body fat is a major site for cholesterol storage in humans.[1039] Our fat cells can accumulate high levels of free cholesterol, which cannot be broken down by our cells and is toxic at high concentrations.[1040]

We've known since 2014 that dietary cholesterol promotes the swelling of fat cells and belly fat inflammation in monkeys,[1041] but there weren't any human studies until 2019, when researchers took biopsies from vegetarians and meat eaters. Vegetarians generally consume significantly less cholesterol than do omnivores. Although eggs are the single largest source of cholesterol in the American diet, more than any individual type of meat, the number one overall source of cholesterol is meat in general (with twice as much cholesterol coming from white meat as from red).[1042] So, researchers expected to find less inflammation in the biopsies from vegetarians than from meat eaters, and they did. Not only did the vegetarians' thigh fat average fewer than half of the pro-inflammatory macrophages compared to biopsies taken from omnivores, the meat eaters had 80 percent greater expression of tumor necrosis factor, a potent inflammatory marker, in their abdominal fat.[1043]

Preeminent Harvard nutrition professor Mark Hegsted once wrote that if cholesterol were introduced as a new food additive, the conclusion would almost certainly be that it could not be considered safe at any level,[1044] if only because

> any intake of dietary cholesterol above zero increases the risk of our number one killer, heart disease.[1045]

As we get older, we experience an increase in visceral fat, the deep abdominal fat that coils around and infiltrates our internal organs, bulging out our belly. The increase in fat mass alone may contribute to inflammaging,[1046] but, as they age, even *individual* fat cells spill out more pro-inflammatory mediators like IL-6 compared to younger fat cells.[1047] So, loss of body fat with chronic caloric restriction may play a role independent of autophagy induction, though it appears to work disproportionally better than weight-loss surgery at reducing inflammation over the same general time frame. Bariatric surgery alone causes about a 60 percent drop in both excess body weight[1048] and CRP,[1049] whereas just a 10 percent drop in body weight in the nonsurgically calorie-restricted group was associated with a 40 percent drop in CRP.[1050]

Visceral fat isn't the only place in the gut that can spill out inflammatory factors. As we age, our microbiome changes. We start to take on opportunistic pro-inflammatory bacteria at the same time that our gut permeability ("leakiness") is increasing, which leads to the seepage of bacterial components into our bloodstream.[1051] Thankfully, as we'll see, all these contributors to inflammaging can be mediated by diet.

THE DIETARY INFLAMMATORY INDEX

The widespread meta-inflammation that occurs throughout our lives appears in part to be the reaction by our immune system to many unhealthy aspects of daily living—from environmental factors, like traffic pollution and toxic chemicals, to our everyday lifestyle choices, including factors such as cigarettes, sleep, chronic stress, and level of physical activity.[1052] However, we may introduce into our body the *primary* driver of meta-inflammatory chronic disease multiple times a day—every time we eat.[1053]

How can we tell if a food is pro-inflammatory or anti-inflammatory? Simple. We can just watch what happens to the levels of C-reactive protein and other inflammation markers after someone eats it. By doing so, we can

also assess the impact of individual nutrients, whole foods, meals, or entire dietary patterns.

Researchers scoured thousands of such experiments and developed a scoring system called the Dietary Inflammatory Index.[1054] It's very straightforward: The more pro-inflammatory foods we eat on a daily basis, the higher our score, and the more anti-inflammatory foods we eat, the lower our score. Our goal is an overall negative score, which we can achieve if we eat more anti-inflammatory foods than pro-inflammatory ones. In other words, an anti-inflammatory diet.

Generally, components of animal products and processed foods, like saturated fat, trans fat, and cholesterol, were found to be pro-inflammatory, while constituents of whole plant foods, such as fiber and phytonutrients, came up strongly anti-inflammatory.[1055] It shouldn't be a surprise, then, that the Standard American Diet (SAD) scores as pro-inflammatory. This reached a peak in the early aughts during the Atkins craze, but we still run hot[1056] and have the elevated disease rates to show for it.

Higher Dietary Inflammatory Index scores have been linked to impaired kidney,[1057] lung,[1058] and liver function[1059] and a higher risk of cardiovascular disease.[1060] Those eating more inflammatory diets also appear to experience faster aging at a cellular level.[1061,1062] Pro-inflammatory diets are also associated with the development of frailty[1063] and increased risk of falls in the elderly.[1064]

Pro-inflammatory diets don't only impact our physical health. A recent review concluded that every study that looked at the Dietary Inflammatory Index and cognitive performance found that diets with higher inflammatory potential were linked to impaired memory and cognitive dysfunction.[1065] Inflammatory diets have also been associated with worse mental health, including higher rates of depression, anxiety, and impaired well-being,[1066] as well as lower sleep quality.[1067]

What about cancer? Eating more pro-inflammatory foods has been tied to higher risk of prostate,[1068,1069,1070] breast,[1071,1072] endometrial,[1073] and ovarian cancers.[1074] Higher Dietary Inflammatory Index scores are also associated with heightened risk of esophageal,[1075] stomach,[1076] liver,[1077] pancreatic,[1078] colorectal,[1079] kidney,[1080] and bladder[1081] cancers, as well as non-Hodgkin's lymphoma.[1082]

Overall, eating a more inflammatory diet has been associated with 75 percent increased odds of having cancer and 67 percent increased risk of dying from it.[1083] Not surprisingly, those eating more *anti*-inflammatory diets appear to live longer lives[1084,1085,1086,1087] with less functional disability.[1088] A meta-analysis of a dozen cohort studies, where populations are followed over time, found that those scoring at the higher end of the Dietary Inflammatory Index had a 23 percent higher risk of dying prematurely compared to those at the lower end.[1089]

You've Got to Move It Move It

Lifelong, voluntary wheel-running dampens inflammaging in mice,[1090] but what about in men and women? There have been more than twenty controlled interventional studies on the effect of exercise on inflammation in older adults, and they've consistently shown a beneficial, anti-inflammatory effect.[1091] The IL-6 levels of active older adults may be about 30 percent lower than sedentary age-matched individuals.[1092] Sadly, nearly eight out of ten American adults fail to meet the national physical activity guidelines.[1093]

PRO-INFLAMMATORY FOODS

The food components that rate as most pro-inflammatory are saturated fat and trans fat. In the United States, the top five sources of saturated fat are essentially cheese (including pizza), desserts like cake and ice cream, chicken dishes, pork, then burgers.[1094] With the ban on added trans fat, the only remaining sources in the food supply are the small amounts found naturally in meat and dairy and what's created during the refining of vegetable oils.[1095]

The inflammatory effects of saturated fat can manifest after a single meal. We've known for nearly twenty years that within hours of eating a high-fat meal (Sausage and Egg McMuffins were used in the original study), your arteries can stiffen, cutting in half their ability to relax normally.[1096] Unhealthy meals don't just cause damage decades down the road but right here and now, within hours of going into your mouth. How do we know it was the fat and not the junky refined carbs in the English muffin? Because you can also cause a spike in inflammation by drinking straight cream, which has zero carbs and is mostly saturated butter fat.[1097] And, just as this inflammatory state starts to calm down five or six hours later, it's time for lunch, when we may once again whack our arteries with another load of saturated fat. This cycle leaves many Americans trapped in a dangerous pit of chronic, low-grade inflammation. It's no wonder dietary saturated fat has been considered an "accelerator of the aging process."[1098]

After just one meal high in saturated fat, IL-6 levels can double within six hours,[1099] approaching levels associated with twice the risk of premature death.[1100] Why is saturated fat so pro-inflammatory?

Palmitic acid, the predominant saturated fat in the American diet[1101] and concentrated in meat and dairy,[1102] directly induces an inflammatory response. Drip some onto human white blood cells in a petri dish, and they start spewing out inflammatory chemicals.[1103] But, saturated fat may also help endotoxins leak through the gut wall into your circulation.[1104] Endotoxins are highly pro-inflammatory structural components of certain types of bacteria, like *E. coli*. As such, the highest levels of these endotoxins are found in foods with high bacterial loads, like meat.[1105] (Fresh hamburger, for example, has been shown to contain approximately a hundred million bacteria per quarter pound.[1106]) Endotoxin activity can be detected in your bloodstream just one hour after eating a high-fat meal.[1107] It's no wonder your body reacts so strongly!

The theory has its critics, though, who argue that since we already have so many bacteria and their endotoxins living in our large intestine, ingesting a few more endotoxins from our food shouldn't matter much in terms of causing systemic inflammation.[1108] After all, we have about two pounds of pure bacteria down where the sun don't shine, so we may already have a

whole ounce or so of endotoxin in us. Given that a lethal dose of intravenously injected endotoxin can be just a few millionths of a gram, we could theoretically have a million lethal doses inside our body. The apparent paradox, though, is explained by compartmentalization.[1109] It's all about location, location, location.

Poop is harmless in our colon, but feces shouldn't be injected into our bloodstream, or eaten, for that matter, particularly with fat, as that can promote the absorption of endotoxins high up in the small intestine.[1110] The palmitic acid in animal fat can both disrupt the barrier function of the gut lining, which, in effect, makes it leakier,[1111] and directly ferry endotoxins into our lymph vessels, which eventually dump into our bloodstream.[1112] The same goes even if the poop is well cooked.

You can boil endotoxins for two straight hours with no detriment to their ability to induce inflammation.[1113] Yes, you can kill off any bacteria if you boil your poop soup long enough, but that doesn't destroy their endotoxins. In other words, even when you cook the crap out of meat, you can't really cook the crap out of meat.

Ironically, even when slaughterhouse workers trim off visible fecal contamination, which can occur when the animal's digestive tract is ruptured during the evisceration process,[1114] the trimming can lead to an increase in certain fecal bacteria, thought to be caused by cross-contamination from one carcass to the next.[1115] Then, even when properly stored in refrigeration, endotoxins start accumulating along with the bacterial growth.[1116]

Bust Your Chops

The highest levels of endotoxins have been found in meat and dairy, and the lowest levels in fresh fruits and vegetables—but that was testing *whole* fruits and vegetables.[1117] Most spoilage organisms cannot penetrate the plant's surface barrier to then go on to spoil its inner tissues. That's why fruits and veggies can be out in the orchards and fields all day in the hot sun. Once you cut them open, though, and bacteria can gain access to the inner tissues, the

produce can start to spoil within a matter of days.[1118] What does that mean for the prechopped veggies conveniently stocked in grocery stores?

Watch see.nf/precut for details, but basically, endotoxins can build up in refrigerated prechopped vegetables to the point of neutralizing their anti-inflammatory benefits.[1119] The prechopped veggies did not cause inflammation, like in the meat, eggs, and dairy studies, but they did appear to extinguish some of the plant's anti-inflammatory effects.[1120] It's still better to eat prechopped vegetables than no veggies at all, but chopping your own might be the more healthful option.[1121]

BLUNTING THE ENDOTOXIN SURGE

Not all high-fat foods cause inflammation. More than a dozen studies have shown that nuts, for example, don't increase inflammatory markers,[1122] even if you eat handfuls of them a day.[1123] Spreading half an avocado on a beef burger may even blunt some of the inflammation caused by the meat.[1124]

Some reviews purport to show a drop in inflammatory markers when consuming wild game,[1125] which is about as lean as you can get, but that's only compared to store-bought meat. If you eat some really fatty meat, all the common markers of inflammation—CRP, IL-6, and tumor necrosis factor alpha (TNF-α)—shoot up within hours of consumption. What if you instead eat a kangaroo steak, which is extremely low-fat, on the order of elk or moose?[1126] The same thing happens—a rise in all three inflammatory markers—but to a significantly lesser extent.[1127] This would suggest that venison, for example, would cause less inflammation than chicken, which, these days, contains two to three times more calories from fat than from protein and ten times more calories from fat than it had a century ago.[1128] (Note that this may depend on how the deer was shot. Standard rifle bullets can disperse millions of microscopic lead fragments into wild game,[1129] and lead exposure may also be pro-inflammatory.[1130])

"[T]he most obvious solution to this metabolic endotoxinemia appears to be to reduce saturated fat intake," concluded endotoxin scientists.[1131] In the United States, that would mean prioritizing cutting down on the top

three sources: cheese, desserts, and chicken.[1132] However, "the Western diet is not conducive to this mode of action," the scientists wrote, "and it is difficult for patients to comply with this request." If that's the case, there is a way to blunt some of the endotoxin surge: Eat fiber-rich foods with your meals.

Researchers randomized people to eat the same McDonald's Sausage and Egg McMuffin breakfast bomb with or without a high-fiber breakfast cereal. The fiber seemed to glom onto the endotoxins, preventing that bump of endotoxemia three hours after the meal. The fiber also reduced the oxidative stress, the free radicals generated by such a meal. Of course, the best way to mediate the impact is to skip past the golden arches altogether, but adding fiber-rich foods may at least make your sad meal a little happier.[1133]

Don't Get Hyper

Animal fat can be inflammatory, but so can animal protein. Check out my *How Not to Die* kidney disease chapter. I describe in detail how a high intake of animal protein can profoundly influence normal human kidney function by inducing *hyperfiltration*, a dramatic increase in our kidneys' workload. Within hours of consuming meat, our kidneys rev up into that hyperfiltration mode. Beef, chicken, and fish all appear to have similar effects.[1134] An equivalent amount of plant protein, though, causes virtually no noticeable stress on the kidneys,[1135] which can translate into the preservation of ailing kidney function.[1136] Why does protein from animals cause that overload reaction while protein from plants doesn't? Because of inflammation. Researchers found that the hyperfiltration response disappeared when study participants were given a powerful anti-inflammatory drug along with animal protein.[1137]

NEU5GC

There's even an inflammatory animal *sugar*. Watch my video see.nf/neu5gc to learn how an acidic sugar called Neu5Gc could be a "Trojan horse" in meat and dairy contributing to the higher rates of cancer, heart disease, and autoimmune diseases.[1138] To quell the inflammation caused by this foreign sugar, the researchers suggest "reduction of dietary Neu5Gc intake and accumulation through simple diet-based interventions."[1139]

Since humans and plants don't make Neu5Gc, does that mean we can only choose between cannibalism and veganism if we want to avoid exposure? No. Already, transgenic pigs have been engineered without Neu5Gc for organ transplants, so one suggestion is that we could use "genetically modified livestock as a source of red meat."[1140] Or, we could stick to eating animals that naturally don't express it in the first place. Neu5Gc is found in most mammals, amphibians, and fish,[1141] with the highest levels in caviar,[1142] but it is rare in birds and reptiles.[1143] Among mammals, the highest levels were found in goat meat,[1144] but, in terms of "potential candidates for human consumption,"[1145] levels were low in venison and missing entirely from the muscles of kangaroos and dogs (but not cats).[1146] Another suggestion would be to take some kind of Neu5Gc-blocker every time we eat meat. The researchers acknowledge that "[i]n practice, it would be hard to arrange for such an antidote to be easily available as part of every meal.…"[1147]

POURING SALT ON THE WOUND

Excess sodium raises not only your blood pressure[1148] but also the level of inflammation in your body. It's hard to control people's food intake long-term to study the effects—unless, of course, you can lock people in a space capsule. Mars520 was a 520-day space flight simulation designed so we could see how people might do on the way to Mars and back. For up to months at a time, the nascent astronauts were put on different levels of salt, and the findings clearly showed that a drop in sodium intake leads to a drop in inflammation.[1149] This has implications for inflammatory diseases such as asthma,[1150] multiple sclerosis,[1151] psoriasis,[1152] lupus,[1153] and arthritis.[1154] For more details, see my video see.nf/saltinflammation.

ANTI-INFLAMMATORY FOODS

In the Dietary Inflammatory Index, the spice turmeric is the single most anti-inflammatory food, followed by ginger and garlic, and tea, green or black, is the most anti-inflammatory beverage. In terms of the most anti-inflammatory food *components*, the top two are fiber and flavones.[1155] Dietary fiber, found in all whole plant foods, is most highly concentrated in whole grains and legumes, such as chickpeas, beans, lentils, and split peas.[1156] Flavones are plant compounds concentrated in fruits, herbs, and vegetables,[1157] with apples, oranges, parsley, celery, and bell peppers the leading sources in the American diet,[1158] while chamomile tea is the most flavone-filled beverage.[1159]

FIBER SOOTHES THE SAVAGE BEAST

How and why is fiber so anti-inflammatory? Check out see.nf/fiber for the full story, but basically, we feed the good bacteria in our gut with prebiotics like fiber, and they feed us right back with short-chain fatty acids like butyrate, the primary fuel of the cells lining our colon. The good bacteria in our gut feed us and try to keep us healthy because they have a pretty good thing going. Our guts are warm and moist, and food magically keeps coming down the pipe. If we die, though, they lose all that. If we die, they die, so it's in their best evolutionary interest to keep us happy.[1160] But there are bad bugs, too, like cholera that causes diarrhea. They have a different strategy: The *sicker* they can make us, the more explosive the diarrhea, for example, the better their chances of spreading to other people and into other colons. They don't care if we die, because they don't intend on going down with the ship.[1161]

So, how does the body keep the good bacteria around while getting rid of the bad? Think about how tricky this is. We have literally trillions of bacteria in our gut, so our immune system must constantly maintain a balance between tolerating good bacteria and attacking bad. Wouldn't there need to be a way for our good bacteria to signal to our immune system that they're the good guys? Yes, and there is. That signal is the fiber breakdown product butyrate. Researchers found that butyrate suppresses the inflammatory reaction and tells our immune system to stand down, saying in effect, "The good guys are on board, so all's well."[1162] (This does not

apply to fiber supplements like Metamucil, which are nonfermentable, that is, inedible, to our good bacteria.[1163])

We're not just talking about intestinal inflammation. If you eat some whole grain barley for supper, by the next morning, your good gut bacteria are having it for breakfast, releasing butyrate into the bloodstream[1164] to exert broad anti-inflammatory activities throughout the body.[1165] This may explain why those eating fiber-rich foods are less likely to develop inflammatory conditions from knee pain[1166] and osteoarthritis[1167] to lung inflammation and respiratory diseases like COPD (chronic obstructive pulmonary disease).[1168] Most important, those who eat more fiber-rich foods live longer lives.

ALL IN ONE PIECE

An analysis of ten studies encompassing more than ten million person-years of data found that higher intake of dietary fiber compared to lower intake was associated with a 15 percent lower risk of premature death from all causes combined.[1169]

But since fiber is concentrated in some of the most healthful foods on the planet—fruits, vegetables, whole grains, beans, and nuts—how do we know that fiber intake isn't just a proxy for a healthy diet in general and the survival benefit isn't merely due to the myriad other beneficial components in whole plant foods? If you remember, we ran into a similar conundrum trying to tease out the benefits of eating foods with lower glycemic loads. The solution we turned to was acarbose, the starch-blocking drug that slows the digestion of carbohydrates.

Fiber is just a carbohydrate chain we can't digest, so acarbose can effectively turn some of the regular starch we eat into fiber. Indeed, those taking acarbose end up with more starch in their stool, which provides a bounty for our good gut bacteria.[1170] That's why acarbose can increase the level of good bugs like *Bifidobacterium*,[1171] *Lactobacillus*, and *Prevotella*.[1172] This all means more anti-inflammatory butyrate entering the bloodstream,[1173] and it also gives researchers a tool to test out the fiber–inflammation–longevity connection.

Just as you can enable rats to live longer by feeding them fiber,[1174] you can enable mice to live longer by feeding them acarbose while keeping their

diets the same. Why do we suspect the survival benefit is not just a blood-sugar effect? Because the lifespan enhancement correlated with fecal concentrations of butyrate. A single fecal sample taken several months before death (the equivalent of several years for humans) could predict the mouse's likely lifespan.[1175] How can we replicate the effects of acarbose without taking a drug?

Switching from refined grains to whole grains would ferry more fiber down to our colon, but taking the next step and switching to *intact* whole grains (groats) wouldn't only give us more fiber but also sneak down a load of starch. To see why powdered grains can starve our microbial selves, check out my video see.nf/intact. Researchers found that subjects fed the same amount of the same foods doubled their stool size when fed intact versus ground grains.[1176] Our stool is not primarily composed of undigested food. Most of it—about 75 percent—is pure bacteria,[1177] more than a trillion per tablespoon.[1178] No matter how well we chew intact plant foods, when we eat the way nature intended, we transport an array of starch and other prebiotic nutrients down to our good bacteria, who get fruitful and multiply. Production of short-chain fatty acids increases, and we get to bask in all the anti-inflammatory benefits of butyrate.

Centenarian *Anti*-Inflammaging

Since inflammation has a critical role in aging, wouldn't you expect centenarians to have somehow escaped inflammaging? That isn't the case, though. As expected, at their advanced age, people more than a hundred years old have high blood levels of inflammatory compounds. So, what sets them apart? A counterbalance of an equally high blood level of *anti*-inflammatory compounds.[1179] This response is known as *anti-inflammaging*. "[I]f inflammaging is a key to understand aging," an Italian research team suggested, "anti-inflammaging may be one of the secrets of longevity."[1180]

Interleukin 10 (IL-10) may be the most potent anti-inflammatory cellular messenger in our blood. Is there a

way to boost IL-10 levels?[1181] Eat more fiber. Butyrate "massively" enhances secretion of IL-10,[1182] so raising IL-10 blood levels is as easy as swapping out refined grains in favor of whole grains.[1183] A type of fiber called *beta-glucan* in brewer's, baker's, and nutritional yeasts has been found to boost IL-10. The amount found in two daily tablespoons of nutritional yeast triples IL-10 levels within four weeks.[1184] However, if you have Crohn's disease[1185] or the skin condition known as *hidradenitis suppurativa*,[1186] I caution against the use of nutritional yeast due to potential immune reactivity (see see.nf/crohns for details).

Based on three decades of studying more than a thousand centenarians, researchers identified "a provegetarian diet, rich in vegetables and legumes" as a common denominator. Part of the centenarians' aging success may have been due to an anti-inflammatory boost from all that fiber, but their diets also contained "relatively little meat and animal fat,"[1187] so it's hard to tease out the decisive dietary factors.

PLANT YOURSELF

Given that saturated fat ranks as the single most pro-inflammatory food component and fiber as the single most anti-inflammatory food component,[1188] an anti-inflammatory diet would be one centered around whole plant foods.[1189] See details in see.nf/plantshift, but basically, dozens of interventional trials that put different diets to the test in thousands of individuals have shown that more plant-based diets were more effective in lowering systemic inflammatory markers such as C-reactive protein.[1190]

A completely plant-based diet can help lower CRP levels by 30 to 40 percent within just a few weeks in both adults[1191] and children,[1192] but it need not be all or nothing. Simply swapping out a few servings a week of meat for beans, split peas, chickpeas, or lentils can lower your CRP, IL-6, and TNF-α by about a third within two months.[1193] What if you just add plant foods to your regular diet? Five a day aren't enough. Five daily servings of fruits and veggies don't appear to be sufficient to make a

difference, but if you get eight servings a day, you can significantly drop your CRP levels compared to those who eat close to the American average,[1194] a paltry two servings a day.[1195] That's one of the reasons my Daily Dozen recommends a minimum of nine daily servings.

Of course, not all plant-derived foods are anti-inflammatory. If all you do is boost your intake of vegan junk like white bread, soda, and cake, you can end up even more inflamed.[1196] Are any plants particularly potent?

What About Fish?

First and foremost, an anti-inflammatory diet in clinical practice "focuses on eating whole, plant-based foods."[1197] But just as all plant-derived foods are not anti-inflammatory, all animal foods are not necessarily pro-inflammatory. Omega-3 fatty acids found in fish, for example, score as an anti-inflammatory component in the Dietary Inflammatory Index,[1198] even though they only appear to help among those with chronic disease.[1199] When healthy people were given fish oil supplements equivalent to eating about a serving of salmon, one can of tuna, or ten fillets of tilapia every day[1200] for weeks or months, overall, there was no benefit in terms of reducing key inflammatory markers.[1201]

The consumption of fish itself doesn't appear to affect markers of inflammation[1202] or lower inflammatory disease mortality—unlike plant-based omega-3 sources like nuts.[1203] Perhaps the benefits of the omega-3s are offset by the industrial toxins that now contaminate much of the aquatic food chain.[1204] That could also help explain the association found in the Harvard Nurses' Health Study between the consumption of non-dark-meat seafood (such as canned tuna, shrimp, scallops, and lobster) and higher inflammatory markers in the blood.[1205]

A study followed 10,000 Norwegian men for four decades and found that those eating berries more than fourteen times each month were significantly more likely to be alive at the end of the investigation.[1206] Higher intake of anthocyanins, berries' brightly colored pigments, has been associated with anti-inflammatory effects,[1207] but it takes interventional studies to prove cause and effect. I review dozens of such studies in my video see.nf/berryinflammation, showing that common berries like blueberries[1208] and strawberries[1209] can significantly reduce markers of inflammation.

This is not just an antioxidant effect. Free radicals can disfigure proteins in our body to the extent that they become so unrecognizable by our immune systems that our own body attacks them as foreign.[1210] We can help mitigate this inflammatory autoimmune response by saturating our body with sufficient antioxidants. High-antioxidant fruits and vegetables, such as berries and greens, have been found to douse systemic inflammation significantly better than the same number of servings of more common low-antioxidant fruits and veggies, like bananas and lettuce.[1211] However, no anti-inflammatory benefit was found for antioxidant vitamins and minerals like vitamins C and E, beta-carotene, or selenium,[1212] which takes us back to the bright red, blue, and purple anthocyanin plant pigments.

Dozens of randomized controlled trials on anthocyanin-rich supplements (mostly berry extracts) have demonstrated anti-inflammatory effects.[1213] This may be why red-fleshed plums beat out yellow-fleshed apricots in reducing CRP blood levels[1214] or why even super healthful fruits like mangos may be powerless against the inflammation caused by eating a meal of fatty meat,[1215] whereas a half dozen studies combined have shown that pomegranates, a fruit packed with ruby red anthocyanins, can bring down inflammation over time.[1216]

The anti-inflammatory effect of berries is so potent that you can actually feel it if you push yourself. The bioflavonoids in citrus can help with muscle fatigue during a tough workout[1217] (see.nf/citrus), but the anthocyanins in berries may help you deal with post-exercise inflammation. Muscle biopsies confirm eating berries can significantly reduce exercise-induced inflammation,[1218] which translates into faster recovery times.[1219] Watch see.nf/soreness for details. Antioxidant supplements, however, don't

appear to help.[1220] In fact, men doing arm curls with added vitamin C ended up with *more* muscle damage and oxidative stress.[1221]

Optimizing recovery from a workout is considered to be the "holy grail of exercise science,"[1222] but what about discernible effects on inflammatory conditions of aging, such as arthritis? Tart cherries have been successfully used to treat gout.[1223] Delicious dietary treatments are more than welcome, as some gout drugs can cost $2,000 per dose,[1224] carry no clear-cut distinction among nontoxic, toxic, and even lethal doses,[1225] and can cause a rare side effect in which your skin detaches from your body.[1226] (Of course, the best way to deal with gout is to try to prevent it in the first place with lower alcohol consumption[1227] and a more plant-based diet.[1228]) As I detail in see.nf/berryinflammation, the most common inflammatory joint disorder, osteoarthritis of the knee, can also be mitigated with berry treatment.

How to Lose Count

Considering the anti-inflammatory effects of plant foods and their components, it's no surprise that a pooling of more than twenty studies shows that those eating more plant-based diets have lower CRP levels—especially among those eating purely plant-based.[1229] This has been confirmed with two dozen interventional studies that, overall, found that randomizing people to plant-based diets reduces systemic inflammation within a matter of months or even weeks.[1230] However, plant-based diets can be so effective at causing weight loss that some of the drop in inflammation may be indirect.[1231] Even when weight is taken into account, though, compared to those randomized to eat the American Heart Association's recommended diet, which includes more fruits and vegetables but also low-fat animal products like skinless chicken breast, skim milk, and egg whites, those randomized to an exclusively plant-based diet got a 33 percent drop in CRP within eight weeks.[1232]

In addition to lower CRP levels, those eating more plant-based also tend to have lower white blood cell counts,

considered to be a "stable, well-standardized, widely available and inexpensive measure of systemic inflammation."[1233] As I explore in my video see.nf/whitecount, a higher white blood cell count may be an important predictor for cardiovascular disease incidence and mortality, decline in lung function, cancer mortality,[1234] diabetes,[1235] and premature death in general.[1236] Even within the normal range, every drop of just one point may be associated with a 20 percent drop in the risk of premature death.[1237]

How can we lower it? As I discuss in my follow-up video see.nf/idealcount, avoiding secondhand smoke can drop your white count by about half a point,[1238] losing about a quart of excess body fat can lower it by about one point,[1239] and exercising one to two hours a week for two months can drop it about a point and a half,[1240] as can eating a whole food, plant-based diet.[1241]

GO GREEN

The Low Inflammatory Foods Everyday (LIFE) Diet is based on Dr. Joel Fuhrman's high-nutrient-density principles, which includes a daily green smoothie and is packed with other fruits and vegetables.[1242] The LIFE Diet successfully lowered CRP, but participants were also encouraged to limit their consumption of all animal products. However, even looking only at those who drank the green smoothie each day without making any other changes to their usual diet saw an astounding 40 percent reduction in CRP within just one week, claimed to be the fastest diet-induced reduction in CRP ever reported in the medical literature. Here's Dr. Fuhrman's recipe if you want to try it yourself: half a pound of dark green leafy vegetables (such as baby kale), two and a quarter cups of blueberries, one banana, one tablespoon of unsweetened cocoa powder, one tablespoon of ground flaxseeds, half a cup of water, and half a cup of either plain or vanilla soymilk or unsweetened vanilla almond milk.[1243]

The secret to the green smoothie may lie in how it's made. High-speed liquification may enhance the liberation of nutrients. If you blenderize

spinach, for example, the bioavailability of its beta-carotene is boosted by nearly 50 percent compared to mincing it, and you get closer to 90 percent more than if you ate the leaves whole.[1244] The same amount of food, but greater or lesser levels of nutrients make it into your bloodstream depending on how you prepare it. The chlorophyll itself may also play a role. It's been found to be anti-inflammatory in a petri dish[1245] and in animal studies,[1246] reducing "paw volume"—that is, how swollen their paws get when injected with some inflammatory irritant. However, the anti-inflammatory effects of chlorophyll have yet to be tested clinically.

Cruciferous vegetables, which encompass kale, collard greens, and others in the broccoli family, may be particularly anti-inflammatory,[1247] which could help explain why they are also more closely associated with living a longer life compared to other veggies.[1248] Special cruciferous compounds appear to inhibit NF-κB, which is a central mediator of inflammation that regulates a battery of pro-inflammatory genes, though it may take eating about two pounds a day to significantly drop IL-6 levels within two weeks.[1249] However, even just about an ounce of broccoli sprouts a day can significantly reduce CRP levels and cut IL-6 in half.[1250] They can easily be sprouted at home year-round in a mason jar for about twenty-five cents a cup.

Hot Tomato

Have any vegetables other than greens been shown to lower inflammation in people? Purple-fleshed potatoes,[1251] tomato juice[1252] and tomato paste[1253] (but not tomato extract supplements[1254]), and shiitake mushrooms.[1255] Details in see.nf/veggies.

GRAIN OF TRUTH

Consistent with recommendations from leading cancer[1256] and heart disease[1257] authorities, I suggest getting at least three daily servings of whole grains. A meta-analysis of eleven studies estimated that such intake would translate into a 17 percent lower overall risk for mortality.[1258]

(Amusingly, the authors had a typo, writing instead about "risks for morality." Angel food cake versus devil's food cake?)

The findings aren't surprising, given that whole grain consumption has been associated with a lower risk of dying from cardiovascular disease, cancer, diabetes, and inflammatory diseases in general.[1259,1260] Put simply, millions of people around the world every year could potentially save their own lives by eating more whole grains.[1261] Interventional trials are required to establish cause and effect, though. I review the randomized controlled trials in see.nf/grains, which found that anti-inflammatory effects may be limited to certain subgroups.

THE FLAX OF LIFE

Like whole grains, nuts are linked to lower inflammation in population studies,[1262] as well as lower risks of death from inflammatory disease[1263] and all causes put together.[1264] The interventional trial data, however, are underwhelming. Only two of six of the inflammatory markers tracked in longer-term trials responded to nut consumption.[1265] Certain seeds hold more promise in this dimension.

Watch see.nf/sesame to learn what a quarter cup of sesame seeds a day can do for knee osteoarthritis pain[1266] and see.nf/oxylipins to see what happens when people are randomized to muffins with flaxseeds versus placebo muffins.[1267] Though flaxseeds also reduce conventional inflammatory markers,[1268] the mechanism by which ground flaxseeds reduce blood pressure appears to be through the reduction of oxylipins, pro-inflammatory compounds thought to be involved in inflammaging that rise with age.[1269] But middle-aged adults randomized to eat muffins containing ground flaxseed were able to drop their oxylipin levels down to what one would expect to see in a twenty-year-old within just four weeks.[1270]

THE SPICE OF LIFE

Spices have been used for centuries to treat inflammatory disorders.[1271] If you recall, turmeric is scored as the most anti-inflammatory food in the Dietary Inflammatory Index.[1272] In vitro, curcumin—the pigment in the spice responsible for its bright yellow color—has an anti-inflammatory profile that is stronger and broader than that of the powerful anti-

inflammatory corticosteroid drug prednisolone.[1273] Many turmeric preparations have proven to be beneficial for inflammatory diseases of the joints,[1274] lungs,[1275] skin,[1276] and gut,[1277] including purified curcumin, turmeric extracts, and about a daily half teaspoon of the plain spice you can buy at your local market.[1278] Although curcumin from turmeric doesn't appear to blunt the acute pro-inflammatory effects of a milkshake,[1279] for example, when taken over time, randomized controlled trials clearly show a drop in a variety of inflammatory markers.[1280,1281]

Ginger and garlic follow turmeric as the most anti-inflammatory foods in the Dietary Inflammatory Index.[1282] A meta-analysis of more than a dozen randomized controlled studies lasting four to twelve weeks using a half teaspoon to one and three-quarters teaspoons of ground ginger found a significant reduction in inflammatory markers.[1283]

Ginger powder has been used to successfully treat rheumatoid arthritis[1284] and osteoarthritis.[1285] Its pain-reducing effects are on par with ibuprofen,[1286] and it is protective[1287] rather than damaging to the stomach lining.[1288] One-eighth of a teaspoon of powdered ginger, which can cost a single penny, can work as well as the migraine headache drug Imitrex without the medication's side effects.[1289] Taking a third of a teaspoon up to a full teaspoon each day for a few days before your period was shown to significantly lessen menstrual pain and dramatically stanch heavy bleeding.[1290] Dried ginger powder is expected to work better than fresh, since the most potent anti-inflammatory components are dehydration products formed during the drying process.[1291]

Garlic powder can also reduce inflammation blood markers.[1292] Compared to placebo, a third of a teaspoon a day was found to significantly improve pain intensity, tender joint count, fatigue, and disease activity among women with active rheumatoid arthritis.[1293] Any significant side effects? Just body odor and bad breath.[1294]

Anti-inflammatory effects have also been documented for cloves, rosemary,[1295] dill,[1296] cinnamon[1297] (choose Ceylon, not cassia[1298]), and cocoa (except when given with milk).[1299] Details in see.nf/spicy.

Chamomile Tea May Be *Too* Anti-Inflammatory During Late Pregnancy

The single most anti-inflammatory beverage in the Dietary Inflammatory Index is tea.[1300] Green tea is so anti-inflammatory it can be used for pain control as a mouthwash after wisdom tooth surgery.[1301] Chamomile tea is so anti-inflammatory that it may not be safe to drink regularly during late pregnancy, for fear it might prematurely constrict the fetal ductus arteriosus, a temporary blood vessel that the body keeps open with inflammatory compounds to allow the fetus to "breathe" in the womb.[1302] For details, see my video see.nf/thirdtrimester.

ANTI-INFLAMMATORY DRUGS

If inflammation plays a key role in the aging process, what about taking over-the-counter anti-inflammatory drugs like aspirin?

ASPIRIN

Aspirin has been shown to extend the lifespan of mice and other model organisms.[1303] It's been around in pill form for more than a century and is perhaps the most commonly used medication in the world.[1304] We've been using its active anti-inflammatory ingredient, salicylic acid, for thousands of years, though, in its natural form (as an extract of willow tree bark) to ease pain and fever.[1305] One reason it remains so popular despite the existence of even better anti-inflammatory painkillers today is that it's used on a daily basis by millions of people as a blood thinner to reduce the risk of a heart attack.

The benefits of taking a daily aspirin must be weighed against the risk of internal bleeding complications. My video see.nf/aspirin runs through all the numbers. In short, taking an aspirin a day is generally not recommended for those without a known history of heart disease or stroke,[1306] particularly among the elderly, as the risk of bleeding complications increases sharply in

individuals over seventy years of age.[1307] How can we get the anti-inflammatory effects without the bleeding risk?

Aspirin is actually two drugs in one. It's technically acetylsalicylic acid. Within minutes of swallowing aspirin, enzymes in our gut split it apart into an acetyl group and salicylic acid.[1308] The acetyl group is what inactivates our platelets and thins our blood. If we could consume salicylic acid directly, we could combat inflammation without the risk of bleeding. That's exactly what we can do with diet.

Vitamin S

In my *How Not to Die* chapter on avoiding iatrogenic (doctor-induced) death, I note in the aspirin discussion that the willow tree isn't the only plant that contains salicylic acid precursors. They are widely found throughout the plant kingdom in many fruits and vegetables.[1309] In fact, the blood levels of people eating plant-based diets actually overlap with some of those taking low-dose aspirin,[1310] but they can end up with a significantly *lower* risk of ulcers[1311] due to gut-protective nutrients prepackaged in plants along with the salicylic acid.[1312]

Whole,[1313] organic,[1314] unpeeled[1315] plants have higher concentrations of these aspirin phytonutrients. Standouts include beets, green peas, avocados, dates, nuts, cocoa,[1316] lentils, and buckwheat, but herbs and spices contain the highest concentrations.[1317,1318] Dried basil,[1319] chili powder,[1320] coriander,[1321] dried oregano, paprika, and turmeric are rich in the compound, but cumin has the most per serving. A single teaspoon of ground cumin may have more salicylic acid than a baby aspirin.[1322,1323]

The spicier the better. A spicy vegetable vindaloo has been calculated to contain four times as much salicylic acid–type compounds as a milder Madras-style veggie dish. Approximately one in four vegetarians tested in rural India had blood levels above the lower end of those taking aspirin every day.[1324] This may help explain why India, with its traditionally spice-rich diets, has among the lowest worldwide rates of colorectal cancer[1325]—the cancer that appears most sensitive to aspirin's effects.[1326]

The benefits of salicylic acid are another reason you should strive to choose organic produce. Because a plant uses the compound as a defense hormone, its concentration may be increased when it is bitten by bugs. Pesticide-laden plants aren't nibbled as much, which may be why they

appear to produce less salicylic acid. In one study, for example, soup made from organic vegetables was found to contain nearly six times more salicylic acid than soup prepared from conventional, nonorganically grown ingredients.[1327]

Given the strength of the aspirin evidence, some in the public health community talk of a widespread "salicylic acid deficiency" and have proposed that the compound be classified as an essential vitamin: "Vitamin S."[1328] Whether it's the salicylic acid or a combination of other phytonutrients that accounts for the benefits of whole plant foods, the solution is the same: Eat more of them.

Food for Thought

Aging can be thought of as an inflammatory disease.[1329] A single measurement of inflammatory markers, such as CRP or IL-6, can predict physical and cognitive performance, as well as remaining lifespan in elderly individuals. In a study of thousands of individuals followed over time, only about a third of those with age-related diseases starting out with a CRP above 10 mg/L were alive five years later, whereas, among those with a CRP of 3 mg/L or lower, only about a third were dead within the same time frame.[1330]

Thankfully, excess inflammation can be extinguished through changes in diet. Those eating lower on the Dietary Inflammatory Index in middle age are more likely to age successfully, which is defined as living independently with no major chronic diseases, no symptoms of depression, no function-limiting pain, and good overall self-perceived health —good social health, good physicality, and good mental function.[1331] The associated extension of both healthspan and lifespan suggests anti-inflammatory may be synonymous with anti-aging.[1332]

To help slow this aging pathway, on a daily basis, consider:

- reducing dietary and endogenous exposure to inflammatory AGEs (see the Glycation chapter)
- reducing senescent cell SASP inflammation (see the Cellular Senescence chapter)
- boosting autophagy to help clear out inflammatory cellular debris (see the Autophagy chapter)
- applying an emollient skin lotion
- avoiding pro-inflammatory food components, such as saturated fat, endotoxins, Neu5Gc, and sodium, by minimizing intake of meat, dairy, tropical oils, and salt (one lousy breakfast could double your C-reactive protein levels within four hours before it's even lunch time[1333])
- eating foods shown to be anti-inflammatory, such as legumes, berries, greens, sodium-free tomato juice or tomato paste, oats, flaxseeds, turmeric, ginger, garlic, cinnamon, cocoa powder, dill, green and chamomile teas, and other fiber-, anthocyanin-, and salicylic acid–rich foods

mTOR

It sounds like science fiction. Bacteria in a vial of dirt taken from a mysterious island create a compound that prolongs life. Researchers called it rapamycin—named after the bacteria's home, the mystical Easter Island, known locally as Rapa Nui and famed for its rock-carved figures.[1334] Rapamycin inhibits an enzyme that came to be known as mTOR, or "mechanistic target of rapamycin." mTOR has since been characterized as a "master determinant of lifespan and aging."[1335]

OVER THE HILL AND PICKING UP SPEED

What does the enzyme actually do? mTOR is the major regulator of growth in animals,[1336] and its activation drives increases in both cell size and cell

number.[1337] When we're young, mTOR is a life preserver, buoying our development, but when we're older, it can act like a block of cement chained to our ankles, pulling us under.

The action of mTOR has been described as the engine of a "speeding car without brakes." In this analogy, aging is a hurtling car that enters the low-speed zone of adulthood and wreaks havoc because it does not and cannot slow down. Living organisms don't have brakes because they've never needed them. In the wild, animals don't often live long enough to experience aging. Most die even before reaching adulthood, and the same used to be true for humans. Most Londoners, for example, apparently didn't even survive to age sixteen during the seventeenth century.[1338]

In the face of early-age mortality, living beings need to grow as fast as possible to be able to reproduce before dying from external causes. The best evolutionary strategy may be to run at full speed. However, once we pass the finish line, once we win the race to pass on our genes, we're still careening forward at an unsustainable pace, thanks in part to this enzyme. In our childhood, mTOR is an engine of growth, but, in adulthood, it can be thought of as the engine of aging. Nature simply selects for the brightest flame, which in turn casts the darkest shadow.

This is the so-called trade-off theory of aging, a concept technically known as *antagonistic pleiotropy*, in which a gene can have a positive effect when we're young and a negative one when we're old. That explains how genes with deleterious effects late in life can persist in a population.[1339] For example, the pro-inflammatory "Alzheimer's gene" appears to protect us against some childhood infections, major killers throughout most of human existence.[1340]

Unconstrained, mTOR plows full steam ahead, revving up construction pathways to churn out cellular building blocks for new growth and canceling any plans for renovation or demolition. To preserve growth at all costs, mTOR actively suppresses autophagy, countermanding cellular cleansing and rejuvenation.[1341] In the Autophagy chapter, I explained how this can lead to accelerated aging. Conversely, putting the brakes on mTOR and slowing things down appear to decelerate the aging process, extending life and health. Inhibiting mTOR is considered to be the best validated aging regulator.[1342]

The soil bacteria collected from Easter Island weren't making rapamycin to slow down aging but rather to slow down the growth of their natural enemy, soil fungi,[1343] just like fungi make penicillin to wipe out competing bacteria. Fungi, from yeast on up, have mTOR-equivalent genes, as do all plants and animals. mTOR is the universal growth regulator of advanced life-forms.[1344] So, while rapamycin originally drew attention as an antifungal drug, we soon learned it had many other effects.

UNIVERSAL ANTI-AGING DRUG

Dozens of published studies have demonstrated that, by slowing down mTOR, rapamycin extends both the average and maximum lifespans of laboratory mice.[1345] What if you aren't a rodent? Rapamycin appears to be a universal anti-aging drug that lengthens lifespan in all animals and other organisms tested to date,[1346] the only known drug to do so.[1347] It can even work when started in midlife.

The original experiment, conducted by the National Institute on Aging's Interventions Testing Program and published in 2009, was delayed because the researchers were having difficulty keeping rapamycin stable in food pellets for mice. (It can't just be dissolved in their drinking water because it's fat soluble.[1348]) By the time the experiment was up and running, the mice were six hundred days old, which is equivalent to sixty human years.[1349] Even though the mice started the drug so late in life, their lifespan was extended by about 12 percent, which could equate to more than seven additional years of human life.[1350]

Initially, it was debated whether rapamycin was a true anti-aging intervention or "merely" a potent anticancer agent, lengthening lifespans simply by preventing cancer formation.[1351] mTOR signaling is hyperactive in up to 80 percent of human cancers, where it plays a pivotal role in sustaining tumor growth.[1352] When rapamycin was used clinically to prevent the rejection of organ transplants (by suppressing the proliferation of immune cells that attack the new organ), a peculiar side effect was found:[1353] It made cancer disappear. In a set of fifteen patients who had biopsy-proven Kaposi sarcoma, a cancer that often affects the skin, all cutaneous sarcoma lesions disappeared in all subjects within three months after starting rapamycin therapy.[1354] As mTOR is the master regulator of

cellular growth, the reduction in cancer incidence is unsurprising, but subsequent studies have shown that rapamycin can do so much more.

In animal models, it extends healthspan, too.[1355] Rapamycin has been shown to ameliorate age-related declines in cognitive and physical function,[1356] regenerate the periodontal bone that holds teeth in place,[1357] and prevent hearing loss,[1358] artery dysfunction,[1359] and tendon stiffening.[1360] It can even rejuvenate the hearts of aged mice.[1361] Remarkably, health and longevity benefits could be achieved with intermittent or transient dosing, such as receiving one dose every five days[1362] or just for a few months during middle age.[1363]

As a dog dad, I was excited to read about the Dog Aging Project, where pawrents brought their middle-aged canine companions to be randomized to a low rapamycin, high rapamycin, or placebo group for ten weeks. As in the mouse studies, rapamycin appeared to at least partially reverse some age-related heart dysfunction in the dogs without any untoward side effects. Anecdotally, most of the owners of the dogs who covertly got the rapamycin reported their pets displayed increased activity and energy compared to only a minority of those whose pooches got slipped the placebos.[1364] It was time to try rapamycin in humans. I cover all the rapamycin trials to date in see.nf/rapamycin. Bottom line? It is not ready for prime time as an anti-aging drug. Is there any way to suppress mTOR without taking meds?

CALORIE RESTRICTION

For an organism to reach reproductive age as soon as possible, it certainly makes sense to plow full steam ahead, but there are times one has to slow down out of necessity. When we were evolving, we didn't have the luxury of Uber Eats and Instacart. Periodic famine was the norm. Those who didn't slow their roll (in terms of cellular growth) during times of scarcity might not live long enough to pass along their genes. That's why we evolved a braking mechanism triggered by caloric restriction.

Remember AMPK, our fuel gauge enzyme? When our tank is drained, AMPK switches us to energy conservation mode, in part by shutting down mTOR via two separate mechanisms to ensure we don't continue spending wildly while we have pennies in the bank. AMPK and mTOR can be

thought of as the yin and yang of nutrient sensing and growth control.[1365] One goes up as the other goes down, based on nutrient availability.

Suppression of mTOR may be a central mediator of the lifespan-extending effects of dietary restriction.[1366] mTOR may explain why women hospitalized for anorexia were found to have half the risk for breast cancer.[1367] The severe caloric restriction caused by their disorder may have tamped down the very mTOR expression that has been noted in breast cancer tumors and associated with more aggressive disease progression, as well as a lower survival rate among breast cancer patients.[1368] Of course, as one of the deadliest psychiatric disorders,[1369] anorexia nervosa also carries tremendous risk, but serious long-term caloric restriction is no cakewalk either.

Caloric restriction has been heralded by some as a fountain of youth,[1370] but negative side effects may include dangerously low blood pressure, infertility, slower healing of wounds, menstrual irregularities, sensitivity to cold, and loss of strength, bone, and libido, as well as "psychological conditions such as depression, emotional deadening, and irritability." You're also walking around starving all the time. In the infamous Minnesota Starvation Study that used conscientious objectors as guinea pigs during World War II, many of the volunteers suffered a preoccupation with food, constant hunger, binge eating, and many emotional and psychological issues.[1371] Even researchers who study caloric restriction rarely practice it themselves.[1372] There's got to be a better way to suppress mTOR.

PROTEIN RESTRICTION

The breakthrough came when scientists discovered that the benefits of eating less may not be coming from restricting calories but, rather, from restricting protein. A comprehensive, comparative meta-analysis of dietary restriction in animal models found that the proportion of protein intake was more important for life extension than was the degree of caloric restriction.[1373] In fact, just reducing protein intake without any changes in caloric intake has sometimes been shown to have effects similar to restricting calories.[1374] Rats fed a diet of about 8 percent protein live almost 40 percent longer than rats fed a diet that's around 20 percent protein.[1375]

It makes sense that protein intake can drive mTOR activation. It's not enough to have energy (calories); construction crews need building materials. Yes, insufficient calories can shut down mTOR by cranking up AMPK, but calories aren't the primary inducer of mTOR activity—amino acids are, the building blocks of proteins.[1376] That's good news. Protein restriction is much easier and safer to maintain than dietary restriction, and it may be even more powerful because it suppresses mTOR *and* IGF-1, the two pathways thought responsible for the longevity and health benefits of caloric restriction.[1377]

A small handful of amino acids are particularly important: methionine and the three branched-chain amino acids (BCAA), isoleucine, leucine, and valine[1378] (so named since they happen to have fatty side-chains branching off from their central structure). Restriction of these specific amino acids recapitulates many of the beneficial effects of protein restriction, which itself is the fulcrum of caloric restriction, and restricting only methionine is sufficient to extend life in a lab.[1379] So, restricting all calories to boost lifespan via mTOR suppression is like fasting to manage a peanut allergy. It works, but it's unnecessary overkill.

Where are these mTOR-accelerating amino acids concentrated? In animal proteins. There is more mTOR-stimulating leucine in whey protein than in a comparable amount of wheat protein.[1380] Those eating strictly plant-based diets still tend to exceed overall protein requirements but end up taking in about 30 percent fewer BCAAs (including leucine) and 47 percent less methionine than omnivores. This translates into significantly lower levels in their blood, perhaps helping to explain the longer lives[1381,1382] and lower cancer rates among those eating more plant-based.[1383] (Tryptophan is the only other amino acid for which restriction alone can promote longevity, delay tumor onset, and increase average and maximum lifespans in rats.[1384] It is also found in lower levels in the diets and bloodstreams of those eating plant-based diets.[1385])

This may also help explain the longevity of long-living populations like that of Okinawa, Japan, who had about half the mortality rate of Americans from major age-related diseases. The traditional Okinawan diet is heavily plant-centric. Only about 10 percent is protein, and less than 1 percent is made up of animal products, the equivalent of one serving of meat a month and one egg every two months.[1386] Their longevity is surpassed only by

those regularly eating no meat at all, the vegetarian Adventists in California,[1387] who have perhaps the highest life expectancy of any formally described population in history.[1388]

Individuals eating plant-based have the additional advantage of more easily avoiding palmitic acid, the saturated fat found mainly in meat and dairy that has also been shown to activate mTOR.[1389] A note of caution: Those following a plant-based diet who do not ensure a regular, reliable source of vitamin B_{12}, either through supplements or B_{12}-fortified foods, may have elevated levels of a methionine breakdown product called *homocysteine*.[1390] Homocysteine is also an mTOR activator,[1391] but it can be detoxified with adequate B vitamin intake.

LEUCINE RESTRICTION

To combat the diet-induced mTOR boost, some researchers have suggested that drugs could be developed to block some of the intestinal absorption of the offending amino acids.[1392] It makes more sense to me to just eat less of them in the first place. Leucine may be the most effective mTOR activator and is concentrated where it makes the most sense for growth promotion: in milk.[1393] Whey proteins contain the highest amount of leucine, 75 percent more than beef.[1394] A whey protein beverage can significantly boost mTOR activation within an hour of ingestion.[1395]

Bovine milk has more than three times the leucine of human milk,[1396] which is reasonable because calves grow about forty times faster than human babies.[1397] (Baby rats double their weight in five days, so it's understandable that rat milk has more than ten times the leucine compared to ours.[1398]) Different animals have different amounts of leucine in their milk, appropriate for the growth and development needs of their offspring. No animal—except humans—drinks milk after weaning.

Milk is not a simple beverage. It has a highly sophisticated hormone-signaling system designed to activate mTOR.[1399] When we drink the milk of a faster-growing species, especially later in our life, there is concern we may "over-stimulate" mTOR signaling.[1400] One early, visible manifestation of excessive mTOR stimulation may be acne.

Acne is considered a disease of Western civilization, as it was rare or even nonexistent in places like Okinawa.[1401] The acne-aggravating effects of

milk drinking were first noted more than a century ago.[1402] Those who consume the most dairy have more than double the odds of developing acne as those who consume the least.[1403] Seventy-five to 90 percent of commercial dairy products in the marketplace comes from pregnant cows, so this may relate to the hormone content in milk, but mTOR alone appears to increase risk, in part by promoting the production of sebum, the oily sebaceous gland secretion.[1404]

Acne is considered the prototypical mTOR-driven skin disease.[1405] The fact that up to 85 percent of teens in Western countries exhibit acne implies overactivated mTOR signaling[1406] and offers an explanation why a history of acne has been associated with both breast[1407] and prostate cancer risk.[1408] mTOR is upregulated in nearly 100 percent of advanced human prostate cancers,[1409] which may help explain why milk consumption has been found to be a major dietary risk factor for both the development[1410] and spread of prostate cancer.[1411]

Milk drinkers also appear to live shorter lives, unless they drink fermented (soured) milk.[1412] In the fermentation process, the lactic acid bacteria break down some of the galactose, branched-chain amino acids, and bovine microRNAs[1413] (see here), which may explain why yogurt intake doesn't carry the same risk.[1414]

A CUP OF TEA AND BROCCOLI

Is there anything we can eat to dampen mTOR activity? Tomato powder decreases mTOR activation in aging rats[1415] and a tomato extract slowed mTOR in human breast cancer cells in a petri dish,[1416] but they have yet to be clinically evaluated. Broccoli compounds, however, have been put to the test.

There's a compound called DIM, which is formed when the cruciferous vegetable compound indole-3-carbinol hits our stomach acid,[1417] and it's been shown to suppress mTOR activation.[1418] Sulforaphane, another product of consuming vegetables in the broccoli family, also cools down mTOR,[1419] which may help explain why those who eat their greens live, on average, longer, more healthful lives.[1420]

Given that hyperactive mTOR signaling may play a role in autism,[1421] researchers from Johns Hopkins and Harvard conducted a double-blind,

randomized, placebo-controlled trial with an amount of sulforaphane equivalent to a few cups of broccoli a day in young men with autism[1422] and showed benefits no drug has ever matched.[1423] (Details in see.nf/autism.)

Is there anything we can drink to dampen mTOR activity? Exposing yeast cells to the level of caffeine that would be found in your bloodstream after a cup of coffee led to an inhibition of TOR activity sufficient to extend life.[1424] In mice, both caffeinated and decaffeinated coffee consumption was able to downregulate mTOR to a similar extent, suggesting there's something other than caffeine in coffee that may be helping.[1425] Similarly, green tea contains the flavonoid EGCG that itself suppresses mTOR activity at physiologically relevant concentrations.[1426] This could help explain why a topical 2 percent green tea lotion can cut the number of pimples in half[1427] and why green tea consumption is associated with living a longer life.[1428]

WHAT ABOUT MUSCLE MAINTENANCE?

If dietary changes are so good at suppressing mTOR, might we be concerned about rapamycin-style side effects? The enzyme is part of two different protein complexes—mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 is the aging accelerator, whereas mTORC2 actually appears to be protective. Unfortunately, rapamycin inhibits both, and with mTORC2 disruption come many of its adverse effects. Protein restriction, however, targets only mTORC1, so you get the best of both worlds.[1429] Is there any downside to dietary mTOR suppression?

mTOR signaling is required for the bulking of muscle mass in response to resistance exercise,[1430] raising the possibility of, as one rehabilitation medicine journal editorial title put it, "The mTOR Conundrum: Essential for Muscle Function, but Dangerous for Survival."[1431] However, the suggestion that leucine restriction might accelerate the rate of muscle loss with aging does not seem to be supported. Higher mTOR activation in men may help explain why they tend to live shorter lives than women,[1432] yet men experience a higher rate of age-related muscle loss.[1433] And, giving months of leucine supplements with meals to elderly men did nothing to increase muscle mass or strength.[1434,1435]

In mice, blocking mTOR with rapamycin *protects* aging muscle. Mice genetically engineered to overstimulate mTOR suffer a catastrophic collapse of muscle mass, which is prevented by mTOR inhibition. This suggests that, if anything, mTOR may drive detrimental muscle aging.[1436]

Food for Thought

The enzyme mTOR is recognized as a major driver of aging,[1437] the "Grand ConducTOR" of aging, if you will.[1438] (mTOR seems to bring out the punny side of study authors: "TORwards a Victory over Aging"[1439] or, my favorite, "The Magic 'Hammer' of TOR."[1440]) Perhaps more so than any other single anti-aging strategy, mTOR inhibition disrupts a panoply of degenerative processes,[1441] explaining why the mTOR-blocking drug rapamycin is currently the most effective pharmacological approach ever devised for targeting aging.[1442] Nonpharmacological approaches to slowing this "pacemaker of aging"[1443] include the restriction of certain amino acids, such as methionine and leucine, protein restriction in general, or full dietary restriction.

To help slow this aging pathway, on a daily basis, consider:

- following all the steps to boost AMPK from here
- striving to stick to the recommended daily intake of protein, 0.8 g per healthy kg of body weight (0.36 g per pound), which translates to about 45 g a day for the average-height woman and about 55 g a day for the average-height man
- choosing plant-based protein sources whenever possible

OXIDATION

Earl Stadtman, revered biochemist and recipient of the National Medal of Science, the highest honor for scientific achievement in the United States, once said, "Aging is a disease. The human lifespan simply reflects the level of free radical damage that accumulates in cells. When enough damage accumulates, cells can't survive properly anymore, and they just give up."[1444]

This concept, first proposed in 1972[1445] and known today as the mitochondrial theory of aging, suggests that, over time, free radical damage to our mitochondria leads to a loss of cellular function and energy. Our mitochondria are the power source for our cells. Think about charging your phone over and over; its capacity diminishes every time you recharge it. Similarly, as our power plant mitochondria accumulate free radical damage, they may also lose function over time.

HULK SMASH

For a refresher on what exactly free radicals are and how they are formed, see my comic-book characterization of the quantum biology of oxidative phosphorylation in the brain disease chapter in *How Not to Die*. Suffice it to say, free radicals tend to be unstable, violently reactive molecules with an unpaired electron.

Electrons, tiny building blocks of matter, like to travel in pairs. Free radicals try to pair their unmatched electrons by stealing electrons away from any molecule in their path.[1446] This can have varying effects, depending on what kind of molecule is mugged. When fat is attacked, cell membranes can be disrupted.[1447] When enzymes are targeted, they can become inactivated.[1448] When other proteins are damaged, they can unravel and create new structures that our very own immune system may attack as foreign, thus leading to a form of autoimmune inflammation.[1449] And, when free radicals rip electrons from our DNA, our genes can become mutated and our DNA strands literally broken.[1450] Thankfully, our body has an array of antioxidant defenses that can harmlessly donate spare electrons and thereby defuse free radicals.

An imbalance between excess free radicals and inadequate antioxidant defenses is known as oxidative stress. According to the theory, the resultant cellular damage essentially causes aging. So, aging and disease are conceptualized as the oxidation of our body. Those brown age spots on the back of your hands? Oxidized fat and protein under the skin. Oxidant stress is thought to be why we get wrinkles[1451] and become more forgetful,[1452] and why our organ systems break down as we get older. In sum, the theory goes, we're rusting.[1453] (Rust is the oxidation of metal.) That's the rationale for eating more antioxidants, but does that actually work? Despite 20,000 published reviews of more than a quarter million papers on antioxidants,[1454] it remains a controversial topic.[1455] First, let's examine if the theory about oxidation and aging is even true.

THE ONLY THEORY THAT EXPLAINS THE SPREAD

More than three hundred theories of aging have been proposed.[1456] Although none has achieved general acceptance,[1457] the mere fact that the mitochondrial theory has persisted for nearly half a century lends it a certain weight.[1458] Its origins can even be traced back decades earlier than Stadtman's proposal in the 1970s—back to when scientists noted a parallel between many of the manifestations of aging and the DNA-damaging effects of radiation exposure.[1459] This led to the free radical theory of aging of 1956, the proposal that aging was due to the accumulation of oxidative tissue damage.[1460] Then, with the realization that mitochondria were the major source of cellular free radical formation, it morphed into the mitochondrial theory.[1461]

Any successful theory of aging must be able to solve a fundamental mystery: *Why do the maximum lifespans of animals vary so widely?* There is a two hundredfold difference among mammals. Some shrews may only live for a year, while bowhead whales can reach two hundred years or more[1462]—and they're only the second-longest living animal.[1463] The ocean quahog, a clam in the North Atlantic, can live to be more than five hundred years old.[1464] That's *thousands* of times that of some other invertebrates that may only survive a few days. Just one theory of aging can account for the only known parameters that can explain this spread: the mitochondrial theory.[1465]

This theory proposes that the lower the rate of mitochondrial free radical production, the longer animals live. This is not a matter of metabolic rate. Bats and birds, for example, have high metabolisms yet relatively high longevity. The mitochondria of long-lived species simply appear to be more efficient. They often leak fewer electrons, which correlates with less oxidative damage to mitochondrial DNA.[1466] (Mitochondria have their own tiny loops of DNA commonly thought to code for just thirteen proteins,[1467] separate from the bulk of DNA coding of the more than 20,000 genes in the cellular nucleus.[1468]) Thankfully, mitochondrial efficiency is not some immutable characteristic. We may be able to reduce our mitochondrial free radical production rate through exercising,[1469] as well as by making a single dietary tweak—lowering our intake of the amino acid methionine.[1470]

HOW TO LOWER METHIONINE INTAKE

The methionine content of tissues is linked tightly to maximum lifespan among mammals. The lower the methionine, the longer the longevity. This makes sense within the mitochondrial theory, since methionine is the protein component most susceptible to oxidation.[1471] High methionine levels don't just make you vulnerable to oxidative stress, though—they actively cause it. This can even be demonstrated in a test tube. When methionine is dripped onto isolated mitochondria, they start churning out more free radicals.[1472] To see if diet can dial it down, researchers put it to the test.

In rodents, a dietary restriction of 40 percent less food decreases the rate of mitochondrial free radical generation and increases lifespan. This was found to be due to the drop in protein intake. Rather than restricting diet across the board, just cutting protein had the same effects, whereas fat or carbohydrate restriction alone affected neither free radical formation nor longevity. In turn, the beneficial effects of protein restriction on mitochondrial function were found to be due to the drop in the single amino acid methionine.[1473] Restricting all dietary amino acids except methionine had no effect on mitochondrial free radical flux or DNA damage, but restriction of just methionine did both.[1474] This led to the conclusion that the electron leakiness of mitochondria appeared to be controlled by the amount of methionine in the diet.[1475]

Within a period of seven weeks, restricting the intake of methionine in rats lessened electron leakage, free radical formation, and mitochondrial DNA damage.[1476] Consistent with the mitochondrial theory, this appeared to slow aging, as evidenced by a reduction in the incidence of a range of degenerative age-related ailments and an extension of lifespan.[1477] As discussed in chapters on other anti-aging pathways, such as autophagy (see here), there are many ways dietary restriction can prolong life, but methionine restriction alone is thought to account for about 50 percent of the lifespan extension attributed to full dietary restriction.[1478]

There are three ways to lower methionine intake. We can decrease our overall intake of food, but that can leave us hungry, and we can also lower methionine by just decreasing our overall intake of protein.[1479] Many Americans get more than twice as much protein as is needed,[1480] so it could be a matter of going from excessive intakes to the recommended intake.[1481] Doing so has been shown to offer a variety of metabolic payoffs within a matter of weeks, thought due to the concurrent drop in branched-chain amino acid intake.[1482] Speaking of bonus benefit, the third way to reduce our methionine intake is by swapping out animal protein for plant protein.[1483] (See the methionine sources graph here.)

At one time, the comparably low methionine content in legumes (beans, split peas, chickpeas, and lentils) had been considered a nutritional disadvantage, but longevity researchers have concluded that the newly discovered multitude of benefits ascribed to methionine restriction "ironically converts such 'disadvantage' into a strong advantage."[1484] This is consistent with data showing legume consumption may be the most important dietary predictor of survival in older people around the world,[1485] a cornerstone of longevity Blue Zones diets.[1486] Plant-based diets are said to make methionine restriction "feasible as a life extension strategy."[1487]

WHAT ABOUT ANTIOXIDANT SUPPLEMENTS?

Antioxidant supplements are a multibillion-dollar industry[1488] and frequently touted as having anti-aging benefits, despite hundreds of studies failing to find clear evidence of such effects.[1489] Those taking antioxidant supplements don't appear to live any longer.[1490] What's more, when put to the test in randomized controlled trials, beta-carotene, vitamin A, and

vitamin E supplements seem to *increase* mortality.[1491] In effect, supplement users may be paying to live a shorter life.

My video see.nf/antioxsupplements explains why. For example, supplements contain only a select few antioxidants, whereas our body relies on hundreds of them, all working together to create a network to help dispose of free radicals.[1492] High doses of a single antioxidant may upset this delicate balance.[1493] Rather than working in isolation, antioxidant compounds can act synergistically.[1494] In essence, the whole (food) may be greater than the sum of its parts.[1495]

As I explain in the video, the bottom line is that the close proximity or even physical contact between mitochondrial DNA and the source of free radical formation likely explains why antioxidants can't seem to slow the rate of aging,[1496] but that doesn't mean antioxidants can't prevent age-related diseases linked to oxidative damage to the 99.999995 percent[1497] of our DNA *outside* the mitochondria.

FREE RADICALS ACCELERATE AGING

Our nonmitochondrial DNA is compartmentalized inside the cell nucleus, out of the direct line of fire from the mitochondria, but it is still subject to constant assault from free radicals. Each day, our genome suffers an estimated 70,000 hits, manifesting largely as single-stranded breaks in the DNA double helix. Thankfully, we have an array of DNA repair mechanisms (the subject of a Nobel Prize in 2015) that may be able to fix a break before the cell divides and passes along the DNA lesion as a mutation.[1498] Unfortunately, our DNA repair capacity declines with age,[1499] which may explain the accumulation of DNA damage seen in older individuals[1500] (though centenarians tend to escape with relatively less oxidative damage).[1501] Why do we believe this is not just a consequence of aging but a cause of it? The most compelling evidence is that most of the rare genetic syndromes of premature aging are caused by mutations of DNA repair genes.[1502] Parallels have also been drawn with the long-term effects of cancer treatment.

Radiation therapy and genotoxic chemotherapy work by purposefully creating free radical–induced DNA damage to kill rapidly dividing cancer cells. All exposed cells are affected, though, not just cancerous ones. If

DNA damage is a driver of aging, one would expect such cancer survivors to suffer prematurely from age-related disability, and that indeed appears to be the case, with survivors experiencing conditions such as arthritis decades earlier than expected. Twenty percent of survivors of childhood cancers have a heart attack or stroke by age fifty compared to only one percent of their siblings by that age. Ten percent of seniors aged sixty-five or older suffer from frailty, a disabling loss of endurance and strength. That's the same percentage of pediatric cancer survivors suffering from frailty in their thirties. Whether arising from congenital deficiencies in DNA repair or exposure to genotoxic agents, the consequence of excess DNA damage appears to be the same: accelerated aging.[1503]

Oxidative stress has been implicated in hair graying;[1504] the development of cataracts, arthritis, frailty, and neurodegenerative, cardiovascular, kidney, and pulmonary diseases;[1505] cognitive decline; age-related macular degeneration;[1506] and muscle loss.[1507] Lowering antioxidant defenses in mice results in accelerated hearing loss, cataract formation, and cardiac dysfunction, whereas increasing antioxidant capacity affects the reverse,[1508] delaying age-related disease.[1509] So, in this aging pathway, lifespan modulation may require quelling free radical formation, but healthspan enhancement may be achieved through bolstering our antioxidant defenses to help quash the resulting oxidant stress.

OUR ORIGINAL DIET

The paleo diet view of human nutrition posits that the agricultural revolution over the last 10,000 years is but an evolutionary eye blink and humans are adapted to Paleolithic diets heavy with lean meat.[1510] Why stop there? If our entire evolutionary timeline were scaled down to a year, the last 200,000 years of Stone Age humanity would be but a few days, representing just the last 1 percent of the roughly twenty million years we've been evolving since our common great ape ancestor.[1511]

During our truly formative years, perhaps the first 90 percent of our existence before we learned how to use tools, our nutritional requirements reflected an ancestral past in which we ate mostly leaves, flowers, and fruits,[1512] similar to that of our fellow great apes.[1513] This could explain why

fruits and vegetables are not only good for us but are, in fact, vital to our survival.[1514]

Humans are one of the few mammals so adapted to a plant-based diet that if we don't eat enough produce, we could actually die from scurvy, a disease of vitamin C deficiency.[1515] Most other animals make their own vitamin C, but why would our body expend all that effort to do the same when we evolved hanging out in the trees and eating fruits and veggies all day long?[1516]

Presumably, it's not a coincidence that the few other mammals unable to synthesize their own vitamin C—such as guinea pigs, fruit bats, and some rabbits—are all strongly herbivorous, just like the great apes.[1517] Data from human fossilized feces deposited in the Stone Age tell us that we may have been getting up to ten times more vitamin C and ten times more dietary fiber than we do today.[1518,1519] Are these incredibly high-nutrient intakes simply an unavoidable by-product of eating whole plant foods all the time, or might they actually be serving some important function, like antioxidant defense?[1520]

Plants create an impressive array of antioxidants from scratch to defend their own structures against free radicals in the firestorm of photosynthesis.[1521] There is a reason plants can lounge about in the sun all day long without getting sunburned (which in us is an inflammatory reaction to the DNA damage created in part by UV ray–induced free radicals).[1522] The human body must defend itself against the same types of pro-oxidants, so we, too, have evolved an array of amazing antioxidant enzymes that are effective—but they aren't infallible. Indeed, free radicals can breach our defenses and cause cumulative DNA damage with age.[1523] This is where plants can come in.

Plants make antioxidants so we don't have to. Since antioxidant-rich foods traditionally formed such a major part of our ancestral diet, we didn't have to evolve that great of an antioxidant system. We could just let the plants in our diet pull some of the weight, like giving us vitamin C so we didn't have to be bothered to make it ourselves.[1524] Using plants as a crutch may well have relieved the pressure for further evolutionary development of our own defenses. So, we became dependent on getting massive quantities of plant foods in our diet, and, when we don't, we may suffer adverse health consequences.

At what point in our evolutionary history did we stop consuming enough antioxidant-rich plants? Even during the Stone Age, this may not have been a problem. Only recently did we start giving up on whole plant foods.[1525] Today, paleo and low-carb followers may actually be eating more vegetables than those on standard Western diets.[1526] Great! The problem isn't that people want to cut their carb intake by swapping out junk food in favor of vegetables. The concern is the shift toward animal-sourced foods. According to NYU nutrition professor emerita Marion Nestle, if there is one takeaway from anthropological studies of ancestral diets, it's that "diets based largely on plant foods promote health and longevity.…"[1527]

WHICH FOODS HAVE THE MOST ANTIOXIDANTS?

In many ways, our prehistoric ancestors consumed a larger amount of antioxidants than we do but had less need for them. In modern life, we are surrounded by new pro-oxidant stresses—from air pollution and cigarette smoke, to alcohol and junk food, and pesticides and industrial chemicals.[1528] This makes it even more important to buttress our inherent antioxidant defenses with antioxidant-rich foods. Today, we have the advantage of being able to get seasonal produce, such as frozen berries, from around the world at any time of the year, making it much easier to have a steady intake of antioxidants in our diet.

Given that the total antioxidant capacity of our diet correlates with a lower risk of getting[1529] and dying from cancer[1530] and all causes of death put together,[1531] scientists set out to find the most antioxidant-rich foods. Sixteen researchers from around the world published a database of the antioxidant power of more than 3,000 different foods, beverages, supplements, herbs, and spices. They tested everything from Cap'n Crunch cereal to the crushed dried leaves of the African baobab tree to see what has the most antioxidants. They even tested dozens of brands of beer. (Santa Claus beer from Eggenberg, Austria, tied for the most antioxidant-rich brew.)[1532] Beer actually represents Americans' fourth-largest source of dietary antioxidants.[1533] Check out the chart to find out where your favorite foods and beverages rank in see.nf/antioxidantlist.

There is no need to post the entire 138-page chart on your refrigerator. Just remember this simple rule: On average, plant foods contain sixty-four

times more antioxidants than animal foods.[1534] As the researchers noted, "antioxidant-rich foods originate from the plant kingdom while meat, fish and other foods from the animal kingdom are low in antioxidants." Even iceberg lettuce, which is 96 percent water[1535] and the least healthy plant food I can think of, contains seventeen units (micromoles per decagram using a modified FRAP assay) of antioxidant power. To give you some perspective, some berries have more than one thousand units, making iceberg pale in comparison. But compare iceberg's seventeen units to some common animal products. Fresh salmon has only three units of antioxidant power, chicken as few as five units, and skim milk and a hard-boiled egg have just four units each. "Diets comprised mainly of animal-based foods are thus low in antioxidant content," concluded the research team, "while diets based mainly on a variety of plant-based foods are antioxidant rich, due to the thousands of bioactive antioxidant phytochemicals found in plants which are conserved in many foods and beverages."

Among plant foods, berries average about ten times the antioxidant power of other fruits and vegetables, and are beat out only by herbs and spices. Cherries may have up to 714 units, but there is no need to cherry-pick individual foods to boost your antioxidant intake. Simply strive to include a variety of fruits, vegetables, and salt-free seasonings at every meal. That way, you can continuously flood your body with antioxidants to help ward off age-related disease.

BOOSTING BLOOD ANTIOXIDANT CAPACITY

Just as you can measure the amounts of antioxidants in foods and beverages, you can measure the antioxidant level in the bloodstream. Compared to most foods in the produce aisle, the antioxidant level in our body is kind of pitiful. Like meat, we don't even make it up to iceberg lettuce level![1536] Then again, meat is what we're made of, so I guess it's not that surprising.

Rather than just measuring the antioxidant power of a food in a test tube, tracking the change in antioxidant capacity of our blood after eating provides confirmation that antioxidants are effectively being absorbed into our system. Antioxidant supplements may not be able to move the needle[1537] or decrease oxidative DNA damage,[1538,1539] but fruits and vegetables can do

both.[1540,1541,1542] And the greater our blood antioxidant status, the longer we tend to live.[1543]

Bloodstream antioxidant capacity may just be a marker of healthier eating in general,[1544] but at least one study found that the mortality benefit persisted independent of fiber intake.[1545] This suggests that we aren't living longer just because we're eating more whole plant foods in general, though tea may be a confounder. Tea has no fiber and is the single leading contributor of antioxidants in the American diet.[1546] Tea consumption alone is associated with a longer lifespan,[1547] so it would be interesting to see if the protective antioxidant association with premature mortality would survive after controlling for tea intake.

ANTIOXIDANT-RICH FOODS AT EVERY MEAL

Every meal is an opportunity to tip the balance in a pro-oxidant or antioxidant direction. Eating a single meal deficient in antioxidant-rich foods can leave us in a pro-oxidant state for hours, coinciding with a drop in antioxidants in our blood as our body's stores are slowly used up.[1548] (Details in see.nf/antioxidantmeals.) We don't want to slide backward every day and end up with fewer antioxidants in our body than we woke up with. This is especially important in the context of increased oxidative stress due to illness, secondhand smoke, air pollution, or sleep deprivation.[1549]

There was a remarkable study published in the *Journal of Biomedical Optics* that detailed a novel experiment in which German researchers noninvasively tracked people's antioxidant levels using an argon laser to measure, in real time, the fluctuating antioxidant levels in their skin. Their most important finding was that antioxidant levels can plummet within two hours of a stressful event and may take up to three *days* to get back to normal.[1550] Hours to lose, but days to recover, so healthier eating is especially important when we anticipate we'll be stressed, sick, or tired. Ideally, we would be having antioxidant-rich foods at every meal and snack.

HOW TO REDUCE DNA DAMAGE

Sadly, most Americans eat a lot of pale foods—white bread, white potatoes, white pasta, and white rice—but colorful foods are often better for us

because of their antioxidant pigments. Blueberries are one of the most vividly tinted foods, and the data don't disappoint. A half cup of blueberries is able to blunt the drop in antioxidant capacity of our blood in the hours after consuming a berry-free sugary breakfast cereal (though a quarter cup cannot).[1551] Over time, those randomized to twice-daily blueberry smoothies halved the levels of a potent free radical in their blood within six weeks, which could then translate into enhanced DNA protection.[1552]

Researchers drew blood from people before and after they ate two cups of defrosted frozen blueberries and exposed their white blood cells to free radicals in the form of hydrogen peroxide.[1553] The blueberries significantly reduced the ensuing DNA damage within an hour of consumption. However, the protective effect was transient. DNA vulnerability returned within two hours, so again, we should aim to eat supercharged antioxidant-rich foods multiple times a day.

In a test tube, lemons, persimmons, strawberries, broccoli, celery, and apples all conferred DNA protection to human cells, but that presumes that the active components would get absorbed into the bloodstream at the concentration found to be protective.[1554] There are, however, foods that have been demonstrated to reduce DNA damage when actually eaten:

- one daily ounce of mixed nuts (walnuts, almonds, and hazelnuts) can reduce damage within twelve weeks,[1555]
- five teaspoons a day of tomato paste within just two weeks,[1556]
- three-quarters of a cup of microwaved frozen spinach[1557] or one cup of other cooked green leafy vegetables a day within three weeks,[1558]
- about four daily teaspoons of spinach powder within two weeks,[1559]
- two cups a day of steamed brussels sprouts within six days,[1560]
- a single serving of watercress within two hours,[1561]
- about one and a half cups of green tea[1562] or tomato,[1563] orange,[1564] blood orange,[1565] or carrot juice[1566] within hours to weeks, and
- eight kiwifruit within four hours[1567] or one kiwifruit a day for three weeks (with no significant difference found between eating one, two, or three a day).[1568]

Kiwis,[1569] cooked carrots,[1570] and green tea[1571] have the additional distinction of being able to facilitate DNA repair, something previously presumed not to be readily affected by diet.[1572] Can we just take a pill? A supplement containing the same amounts of alpha- and beta-carotene as the carrots failed to achieve the same effect.[1573]

Whole-food extracts of apples,[1574] oranges,[1575] spinach,[1576] and blueberries[1577] have been shown to increase the lifespan of *C. elegans*, and there are individual phytonutrients, such as gallic acid, that can not only extend *C. elegans* lifespan[1578] but also reduce human DNA damage within days[1579]—and do so at the daily dose found in a half cup of strawberries, half a mango, or a few tablespoons of carob powder, though whole foods may work even better.[1580] Whole apple extract has been found to extend the average lifespan of *C. elegans* by 39 percent, which is twice that of individual apple fractions or single apple phytonutrients,[1581] such as quercetin, which only prolonged average lifespan by 15 percent.[1582] Lemon-infused water—not even the whole fruit—increased the lifespan and healthspan of mice compared to a lifetime of drinking regular water,[1583] and amla,[1584] cinnamon,[1585] cocoa,[1586] and turmeric[1587] have all been shown to extend the longevity of fruit flies. In humans, the daily dose of antioxidants associated with a 7 percent lower risk of premature death can be found in about one cup of cooked spinach or just two-thirds of a cup of blackberries.[1588]

SPICE IT UP

Spices are the most potent DNA protectors. Just one week of eating about two teaspoons of rosemary or sage a day, one and a half teaspoons of ground ginger or cumin, three-fourths of a teaspoon of paprika, or even just a tenth of a teaspoon of cooked turmeric can protect against breakage of our strands of DNA.[1589] A daily quarter teaspoon of amla—dried Indian gooseberry powder—was also found to decrease oxidative DNA damage.[1590] This is to be expected, as ounce for ounce, dried herbs and spices pack the greatest antioxidant punch.[1591]

Herbs and spices max out at ten times the antioxidant power of nuts and seeds, for example. Of course, it's easier to eat an ounce of nuts than it is to eat an ounce of nutmeg, but some herbs and spices are so off-the-charts that

even just a small pinch can go a long way. For example, adding a single teaspoon of dried oregano to a bowl of whole-wheat spaghetti with marinara and steamed broccoli nearly doubles the antioxidant power of the dish. Even just two-thirds of a teaspoon of marjoram would offer the same boost. A half teaspoon of cinnamon more than quintuples the antioxidant content of a bowl of oatmeal,[1592] and we have verification of bioavailability. A dozen randomized controlled trials have shown that cinnamon—both the cassia and Ceylon varieties—can increase the antioxidant capacity of our bloodstream and reduce free radical damage at doses ranging from just half a teaspoon to one and a half teaspoons a day.[1593]

Don't forget fresh herbs. A tablespoon of fresh lemon balm leaves approximately doubles the antioxidant content of a salad of lettuce and tomato, as does half a tablespoon of oregano or mint or even three-fourths of a teaspoon of marjoram, thyme, or sage.[1594] When you're whipping up a dressing, keep in mind that dozens of randomized controlled trials have shown that small doses of ginger[1595] and garlic[1596] can increase the antioxidant capacity of your bloodstream and decrease free radical damage, so try to include one or both.

The leader of the pack? Cloves. One of my favorite ways to enjoy them only takes a few minutes to prepare. I simply microwave a sweet potato and then mash it up with some cinnamon and just a pinch of cloves, which gives it a delicious pumpkin pie profile. An inexpensive, simple, easy snack with more antioxidants than people on a standard American diet may get in a whole week.[1597]

What about cocoa? Consumption of cocoa has been found to decrease markers of oxidative stress[1598] as well as lower blood pressure.[1599] Dark chocolate can do the same for us, but not white chocolate[1600] or milk chocolate.[1601] Cocoa may, however, be able to neutralize the pro-oxidant effects of dairy milk,[1602] whereas soymilk can actually bring down free radical damage[1603] (though rice milk may make things worse).[1604]

Not Worth Your Salt

Sodium is a commonly neglected pro-oxidant dietary component. I cover this in depth in my video see.nf/salty,

but basically, a single typically salted meal can significantly suppress artery function within thirty minutes[1605] by suppressing a powerhouse antioxidant enzyme in our body called *superoxide dismutase*,[1606] which can ordinarily detoxify a million free radicals per second.[1607]

DNA-PROTECTING BEVERAGES

Although eating whole fruits is best, randomized controlled trials have found a reduction in free radical damage after consumption of tart cherry,[1608] orange,[1609] pomegranate,[1610] tomato,[1611] wheat grass,[1612] and low-sugar cranberry juices.[1613] Grape juice can also improve the antioxidant capacity of the blood.[1614] What about wine?

Red wine can acutely improve blood antioxidant capacity[1615]—even to the extent of buffering (but not eliminating) the spike in oxidation caused by a Mediterranean meal including fried fish.[1616] However, chronic wine consumption doesn't seem to help. When smokers were randomized to drink about two glasses of red wine, white wine, or dealcoholized red wine every day for weeks, only those drinking the nonalcoholic wine experienced a drop in markers of oxidant stress.[1617] This was presumed to be due to the known pro-oxidant effects of alcohol ingestion.[1618]

Smokers who drink alcohol were found to suffer twice the chromosomal damage compared to teetotaling smokers, but, other factors being equal, smokers who drink green tea suffer about a third less. (Even better are those who don't smoke at all, who have ten times less damage.)[1619] Though neither coffee[1620] nor green tea[1621] can block the oxidant stress induced by a high-fat meal, both green and black teas can increase the total antioxidant capacity of the bloodstream within just thirty minutes of ingestion, which can last for at least two hours. (Green tea is about 50 percent better at boosting than black.)[1622] Although the data on the effects of adding milk to your tea are mixed, most studies have shown that taking your tea with dairy decreases or even completely inhibits tea's antioxidant properties.[1623]

Within just one hour, a single cup of green tea can significantly boost the activity of the initiating DNA repair enzyme that fixes oxidative DNA damage, and drinking two cups a day for a week boosts it even more.[1624]

Within four weeks, drinking a mug (300 mL) of green tea every day improves DNA resistance to free radical damage in the first place.[1625] Tea is in fact so DNA-protective that it can be used to store fresh samples of sperm until they can be properly refrigerated.[1626]

HOW PRO-OXIDANTS CAN HAVE ANTIOXIDANT EFFECTS

Ironically, the rallying of antioxidant and DNA repair defenses appears to be a consequence of green tea's mild *pro*-oxidant qualities, a phenomenon paralleled to physical training.[1627] It's been called the "exercise-induced oxidative stress paradox."[1628] Ultramarathon runners may generate so many free radicals during a race that they can damage the DNA of a significant percentage of their own cells.[1629] Why would an apparently healthy act (exercise) lead to detrimental effects? Because exercise in and of itself is not necessarily the healthy act; it's the recovery period afterward.[1630] For example, exercise training has been shown to enhance antioxidant defenses by increasing the activities of our antioxidant enzymes. So, athletes may be taking hits to their DNA during a race, but, a week later, they don't just go back to the baseline level of DNA damage. Day-to-day DNA damage drops even lower, presumably because the prior exertion had revved up their antioxidant defenses.[1631]

In this way, the mild oxidative stress of green tea and exercise can be seen as beneficial, similar to vaccination. By challenging the body a little, we might induce a response that's favorable in the long run. The concept that low levels of a damaging entity can upregulate protective mechanisms —the whole "that which doesn't kill us makes us stronger" notion—is known as *hormesis*.[1632] (See here.)

Taking antioxidant pills, such as vitamin C and vitamin E supplements, can block that boost in antioxidant enzyme activity caused by physical activity and thereby blunt some of the ensuing health benefits, but eating antioxidant-rich foods may offer the best of both worlds.[1633] While vitamin C supplements seem to impair physical performance,[1634] fruits[1635] and vegetables[1636] can have ergogenic benefits, enhancing performance without undermining the protective adaptation response.[1637] In fact, fruits and veggies may even boost exercise benefits. Both black currants[1638] and lemon verbena,[1639] an antioxidant-rich herbal tea, were shown to protect against

exercise-induced oxidative stress and, at the same time, improve some beneficial adaptations to exercise.

Given the hormetic benefits of certain mild pro-oxidant stresses, such as green tea and physical activity, the oversimplistic narrative of "antioxidants good, free radicals bad"[1640] must be revised.[1641] Perhaps nowhere is this more apparent than in the case of broccoli.

KALE FLIPS THE SWITCH

The dietary antioxidants we co-opt from plants represent only our second line of defense against free radicals.[1642] Our frontline defenders are our own antioxidant enzymes. The human body naturally produces 100,000,000,000,000,000,000,000 free radicals an hour.[1643] This is why we make enzymes like catalase, the fastest-reacting enzyme in our body, able to detoxify literally millions of molecules of hydrogen peroxide into water and oxygen each second.[1644] (You know that fizzing that occurs when you pour hydrogen peroxide on a wound? That's from the oxygen bubbles formed by the catalase enzyme.) Is there any way to boost this first line of antioxidant defense?

In the 1980s, scientists first began discovering a specific genetic sequence in the promoter regions of dozens[1645] and then hundreds of "cytoprotective" (cell-protecting) genes.[1646] It was found promoting genes that code for antioxidant enzymes that quench free radicals directly, like catalase,[1647] enzymes that make antioxidants like glutathione,[1648] and even genes for DNA repair enzymes[1649] and detoxification enzymes in our liver.[1650] Whatever bound to these so-called antioxidant response elements could activate our global antioxidant defense system all at once.

In the 1990s, this trigger was discovered—Nrf2, a protein floating in the cell's cytoplasm that is normally bound to a suppressor protein.[1651] But, when that suppressor protein gets oxidized, it releases Nrf2, which is then able to dive into the cell's nucleus to bind to the antioxidant response elements and activate the powerful battery of antioxidant protections.[1652] The entire process can be completed within fifteen minutes.[1653] Nrf2 is considered the "master regulator of the environmental stress response"[1654] and is expressed universally in all cells,[1655] just waiting to be freed to hit the panic button and rally cellular defenses.

Nrf2 is also called a "guardian of healthspan and gatekeeper of species longevity."[1656] Boosting Nrf2 signaling causes significant increases in longevity in *C. elegans*[1657] and fruit flies,[1658] and correlates with maximum lifespan potential across ten different species of rodents.[1659] For example, the Nrf2 gene is overexpressed sixfold in long-lived naked mole rats compared to mice,[1660] combined with lower suppressor protein expression.[1661] That may not only help explain why they live eight times longer[1662] but also why it takes up to a hundred times the concentration of toxins like heavy metals and chemotherapy drugs to kill the same percentage of skin cells taken from naked mole rats compared to mice.[1663] They are little nude detoxification machines.

Unfortunately, Nrf2 levels[1664] and signaling tend to decrease with age.[1665] Thirty minutes of cycling can boost them,[1666] for example, but the most potent natural Nrf2 inducer on the planet may be sulforaphane,[1667] the compound formed when we bite into cruciferous vegetables, such as broccoli, kale, collards, cabbage, and cauliflower. Sulforaphane, like the active components of green tea and turmeric, frees Nrf2 by oxidizing its suppressor protein, resulting in a rejuvenating effect on aged mice.[1668] Older mice fed sulforaphane actually had superior grip strength compared to younger mice and performed just as well on a treadmill.[1669] Nrf2 activation led to decreased DNA damage and muscle loss, and improved heart function and lifespan.

What about us? Sulforaphane can also restore Nrf2 activity in our aging tissues,[1670] which may explain why sulforaphane can delay the senescence of human stem cells.[1671] Just one stalk of broccoli a day can significantly reduce the DNA damage from cigarette smoke,[1672] and two daily cups of brussels sprouts can minimize the DNA damage from a type of cooked meat carcinogen (a heterocyclic amine).[1673] About a third of a cup a day of broccoli sprouts can help our body clear benzene from air pollution.[1674] One study found that sulforaphane could tamp down the inflammation from diesel exhaust that was squirted into subjects' noses at levels simulating hours of rush-hour exposure on a Los Angeles freeway.[1675]

Cruciferous vegetables so boost our detoxification pathways that heavy broccoli eaters might need to drink more coffee to get the same buzz, as the drug-metabolizing pathway that clears caffeine can get so revved up.[1676] The protection veggies from the cabbage family give us can even be

demonstrated topically. Rubbing a broccoli extract on your skin before spending time in the sun can decrease the redness of a sunburn by 35 percent by reducing the tissue damage caused by UV rays through Nrf2 activation.[1677]

The discovery that sulforaphane can switch on Nrf2 arguably heralds a "new paradigm in nutrition science."[1678] No wonder cruciferous vegetable intake is associated with decreased risk of cardiovascular disease, cancer, and mortality from all causes put together.[1679] Even those who average just a single floret's worth of broccoli a day have lower mortality rates than those who eat little or none.[1680] However, the life-extending benefits of broccoli may extend even beyond sulforaphane. Animals fed 1 percent broccoli diets lived longer, but those given just the amount of sulforaphane found in that much broccoli (the compound without the broccoli itself) did not. Sulforaphane salads trump sulforaphane supplements.[1681]

Enhancing Sulforaphane Formation

Acidifying raw cruciferous vegetables can boost sulforaphane formation. Adding lemon juice to a shredded cabbage salad, for instance, may help a little, but adding vinegar is even better, presumably because of its higher acid content. However, the opposite may be true when cooking cabbage. Boiled red cabbage should be kept blue, not pink, indicating a more alkaline environment that helps keep the critical cruciferous components from degrading.[1682] (See see.nf/cabbageph.) The most critical factor when it comes to cooking, though, is pausing between chopping and heating, my "hack and hold" strategy detailed in my Cruciferous Vegetables chapter in *How Not to Die* and in my video see.nf/hackandhold.

FAT REACTOR

We know that some foods have antioxidant qualities, while others act, on balance, as pro-oxidants. Just as the Dietary Inflammatory Index was designed to weigh the balance of anti- and pro-inflammatory foods, more than twenty oxidative balance scoring systems have been developed. In general, the more the scale tips toward the pro-oxidant side, the higher the risk of heart disease, kidney disease, and getting and dying from cancer and all causes put together. Although all the different scoring systems have a different complement of components, they all agree that exercise, cruciferous vegetables, and certain constituents of whole plant foods, such as fiber and carotenoid phytonutrients, are net antioxidant, squelching free radicals, whereas meat, alcohol, fat, and activities like smoking are pro-oxidant, generating free radicals. Of all the dietary pro-oxidants, saturated fat is considered the worst.[1683]

Heterocyclic amines, the carcinogenic compounds formed when meat is cooked or tobacco is smoked,[1684] can induce free radical formation,[1685] but that's not the only reason meat and meat products contribute to oxidative stress.[1686] Our stomach acts as a "bioreactor"[1687] in which the heme proteins in blood and muscle oxidize the fat in the acid bath of our stomach. It turns out that during slaughter, chickens, for example, are bled of only about half their blood,[1688] and the remaining residual can be such a powerful promoter of fat oxidation that some within the industry are advocating for an additional decapitation step during the slaughter process.[1689]

When we consume the oxidized (rancid) fat, it can then make it into our LDL cholesterol particles that accelerate atherosclerosis, the hardening of arteries that, ultimately, is our leading cause of death.[1690] Oxidized fat levels in circulating LDL can double within four days of eating grilled turkey cutlets every day.[1691] (Damaging effects can be mediated by eating berries with meaty meals, though. See the Berries chapter.) This may help explain why vegetarians appear protected from cardiovascular disease,[1692] but oxidized fats are also created when vegetable oils are heated.[1693] It's no surprise then that the consumption of more ultraprocessed junk food is associated with higher rates of DNA damage compared to those eating less.[1694] However, the oxidation of animal fats may be even worse because of the "dreaded oxysterols."[1695]

Antioxidant Status of Vegetarians

Both systematic[1696] and nonsystematic[1697] reviews have concluded that plant-based diets protect against free radical damage, which "may explain why vegetarians live longer."[1698] Most studies show that vegetarians, for example, suffer lower levels of oxidative stress,[1699,1700,1701,1702,1703,1704,1705,1706] but some show no significant difference compared to meat eaters[1707,1708] or fish eaters,[1709] or even higher levels in the vegetarians.[1710,1711] As I detail in see.nf/antioxveg, the discrepant results may be due to vitamin B_{12} inadequacy among vegetarians and vegans who don't supplement their diet with B_{12} or B_{12}-fortified foods,[1712] as even subclinical (asymptomatic) B_{12} deficiency is associated with increased oxidative stress.[1713] A regular reliable source of vitamin B_{12} is critically important to take advantage of the full spectrum of benefits to plant-based eating.[1714]

DIRTY COPs

Too much cholesterol in the blood has long been considered to be a primary risk factor for developing Alzheimer's disease.[1715] Cholesterol cannot directly get across the blood-brain barrier,[1716] though, but cholesterol oxidation products (COPs) can. Also known as *oxysterols*, oxidized cholesterol present in the bloodstream accumulates in the brain,[1717] where it's considered to be a driving force behind the development of Alzheimer's disease.[1718] I present the chain of evidence in my video see.nf/copdementia.

COPs can be up to a hundred times more toxic than unoxidized cholesterol.[1719] They may contribute to a wide range of age-related diseases, including atherosclerosis,[1720] cataracts,[1721] kidney failure,[1722] osteoporosis,[1723] and cancer.[1724] This may explain why egg consumption[1725] and dietary cholesterol in general are associated with an increased risk of breast cancer.[1726] The main cholesterol oxidation by-product in the blood, known

as *27-hydroxycholesterol*,[1727] is estrogenic and increases the proliferation of most breast cancer cells[1728]—sometimes even in the context of estrogen-blocking drugs.[1729]

How can we cut down on the amount of oxidized cholesterol in our blood? Since oxidized cholesterol in the diet is a source of oxidized cholesterol in our bloodstream, one way is by not eating it.[1730] Levels of oxidized cholesterol rise in the blood within hours of consumption[1731] and circulate for more than six and even eight hours after a meal.[1732] Oxidized cholesterol is found in milk powders, meat and meat products (including fish), cheese, and eggs and egg products,[1733] such as powdered eggs, which are found in a lot of processed foods.[1734] Fresh, raw meat may start out with zero oxidized cholesterol, but cooking or storage can cause a dramatic increase in levels.[1735] All forms of cooking can do it, since maximum cholesterol oxidation can be achieved at only about 300°F (149°C), but some types of cooking are worse than others.[1736] See details in my video see.nf/stopcops.

In general, the cholesterol in white meat is more susceptible to oxidation than the cholesterol in red meat, due to white meat's higher polyunsaturated fat content. Fish tends to be the worst, followed by poultry, pork, then beef.[1737] Chicken has about twice the oxidized cholesterol of beef, even before it's irradiated.[1738] When chicken meat is irradiated to improve its food safety from an infectious disease standpoint, it may diminish food safety from a chronic disease standpoint, due to extra cholesterol oxidation.[1739]

Exposure to cholesterol oxidation products is said to be "unavoidable,"[1740] but let's take a step back. Only foods that start out with cholesterol can end up with *oxidized* cholesterol.[1741] So, the primary method to reduce dietary intake may be to reduce the total cholesterol content of the diet by centering one's diet around unprocessed plant foods, which don't have any cholesterol to get oxidized in the first place.

Clarifying a Mystery

Until relatively recently, our understanding of dietary oxidized cholesterol has been limited by the lack of testing

methods and procedures to accurately analyze the amount in various foods.[1742] Though oxidized cholesterol products have been found throughout animal products, the levels in canned tuna are surprisingly high, fifteen times higher than in beef or pork chops, for example, but ghee takes the cake.[1743]

Ghee, clarified butter, is commonly used in Indian cooking.[1744] Boiling, the method of preparation, appears to multiply oxidized cholesterol levels tenfold. This dietary exposure to oxidized cholesterol may help explain why the subcontinent of India is ravaged by heart disease even though a significant proportion of the population eschews meat and eggs.[1745] A number of Indian dairy-based desserts are also made in a similar way.[1746]

SUPPLEMENTS

I had known antioxidant supplements had grown into a multibillion-dollar business, but I was surprised to learn that Big Pharma had turned it into "the biggest, most elaborate, longest lasting, and most harmful of the international cartels discovered by the U.S. Department of Justice (DOJ) [in] the 1990s," according to a textbook on global price fixing. Before being busted with dozens of criminal convictions and record-setting fines, drug companies had conspired in a complex, illegal, monopolistic price-fixing scheme to overcharge for vitamin supplements by the billions.[1747] To make matters even more egregious, people were cheated for nothing—or worse. No antioxidant supplement has ever been shown to reduce mortality, and supplemental beta-carotene, vitamin E, and higher doses of vitamin A may even cut people's lives short.[1748] This parallels many animal studies that found either no effect at all or significant lifespan shortening.[1749]

There are countless antioxidant supplements on the market, many of which make "strongly exaggerated and … flawed" claims.[1750] Here's a short rundown of some of the lesser-known ones.

ALPHA-LIPOIC ACID

Alpha-lipoic acid is an antioxidant our body manufactures internally.[1751] Is there any advantage to taking extra in supplement form? I discuss the pros and cons in see.nf/lipoic. Bottom line? I would exercise caution until we have a better idea of its dosing safety window.

COENZYME Q_{10}

Coenzyme Q_{10}, more commonly known as CoQ_{10}, is the only fat-soluble antioxidant produced by the human body.[1752] Because we synthesize it from scratch, there's no need to consume any,[1753] yet it's one of the most popular dietary supplements.[1754] Centenarians have low levels compared to seventy-six-year-old controls,[1755] but this fact can be used to argue two diametrically opposed positions: Some posit that CoQ_{10} levels decrease with age so we should supplement to regain youthful levels, while others maintain that low levels may be beneficial to achieving such remarkable longevity.

Animal studies echo this ambiguity. Indeed, both added CoQ_{10}[1756] and subtracted CoQ_{10} (by repressing synthesis) have been found to extend lifespan in *C. elegans*[1757] but mostly have no effect on rats and mice.[1758] In people, CoQ_{10} supplementation reduces markers of inflammation[1759] and oxidative stress[1760] and may benefit patients with heart failure[1761] and migraines, reducing headache frequency and duration but not severity.[1762] Those who choose to take it need to keep it in a cool, dark, airtight container since it's sensitive to heat, light, and oxidation.[1763] I prefer to regenerate it naturally using the technique I described in my Greens chapter in *How Not to Die*. It involves eating a chlorophyll-rich diet,[1764] which may be especially important for those on cholesterol-lowering statin drugs, as these medications can interfere with CoQ_{10} production.[1765]

GINSENG

Ginseng root is a popular herbal medicine.[1766] Like the word "panacea," ginseng's Latin name, *Panax*, is derived from the Greek roots *pan* and *akos* for "cure-all." However, although there have been more than a hundred clinical trials on various ginseng formulations,[1767] to date, the results for even one of its most promising usages (blood sugar regulation)[1768] have been less than impressive.[1769]

From an oxidative stress standpoint, American (*Panax quinquefolius*),[1770] Chinese (*Panax notoginseng*),[1771] and Korean (*Panax ginseng*) ginseng[1772] have all been shown to acutely protect against free radical–induced DNA damage within hours of consumption, but one longer-term trial raised red flags. Although four weeks of consuming Korean ginseng reduced levels of oxidative stress,[1773] four months of consuming American ginseng caused an uptick in DNA damage from less than a quarter teaspoon a day of whole root powder.[1774] Until it can be shown that the chronic intake of other ginsengs isn't also DNA-damaging, I'd recommend steering clear.

N-ACETYLCYSTEINE

N-acetylcysteine (NAc) increases the lifespan of male mice, but not female mice, and only because it apparently led to reduced food and water consumption.[1775] In *C. elegans*[1776] and fruit flies, lifespan was extended at one dose but, at a higher dose, was dramatically cut short by up to 70 percent, raising a "serious concern" for taking NAc supplements.[1777] More details in see.nf/nacse.

SELENIUM

Selenium, a critical component of key antioxidant enzymes, is considered an essential trace mineral,[1778] though, given its narrow safety margin, it's also been termed an "essential poison."[1779] Indeed, the consumption of just a single high-selenium Brazil nut a day was found to have pro-inflammatory effects.[1780] I also cover selenium in see.nf/nacse, but basically, both low[1781] and high[1782] blood levels are associated with dying prematurely, and certain doses of selenium supplements may shorten your life,[1783] as well as worsen blood sugar control in diabetics[1784] and increase the risk of developing diabetes in the first place.[1785]

What About Vitamin C?

Vitamin C is likely the most abundant antioxidant in the body,[1786] but levels decline with age. Vitamin C levels in the

blood cells of those aged eighty-five and older may be only half that compared to those at age sixty.[1787] Vitamin C levels in the brain seem to drop about 40 percent (comparing those sixty and older to those fifty-nine and younger).[1788] Might restoring youthful levels be beneficial? It's been tried and flopped. Vitamin C supplements fail to extend life, improve quality of life or cognitive performance, or prevent eye diseases, infections, cardiovascular diseases, or cancer.[1789]

There is insufficient evidence to even claim vitamin C supplements are effective in preventing DNA oxidation[1790] and, at higher doses (about 900 mg plus NAc), may actually cause *more* oxidative damage.[1791] This Janus-faced nature of vitamin C has similarly been demonstrated in animal models: an antioxidant at lower doses but a pro-oxidant at higher doses.[1792] This may help explain why animal studies have shown that vitamin C treatments are all over the map, resulting in increased, decreased, and neutral effects on longevity.[1793]

Although high-dose vitamin C supplementation may result in oxidative DNA damage, so can slipping below the recommended dietary allowance (RDA). Over the last twenty years, vitamin C consumption has declined in the United States by more than 20 percent, due largely to the decrease in fruit juice consumption without a compensatory increase in whole fruit intake. It's gotten to the point that nearly half of all Americans now fall below the estimated average requirement.[1794] What's the optimal intake? See see.nf/vitaminc for details, but the magic number appears to be about 200 mg a day. Since a single serving of fruits and vegetables may have about 50 mg of vitamin C, just four or five servings of fruits and veggies a day should get you up to ideal blood levels.

Another reason to avoid megadoses of vitamin C is the risk of kidney stones, at least in men.[1795] Those taking 1,000 mg or so of vitamin C a day may as much as double their risk, from having a one-in-six-hundred chance of getting a

kidney stone every year to a one-in-three-hundred chance.[1796] We don't yet know if women are similarly at risk.

Food for Thought

The mitochondrial theory of aging explains why animals with the lowest rate of free radical production live the longest. We can slow this rate through exercise training and methionine restriction, which can be achieved with a predominantly whole food, plant-based diet.[1797] Such an eating pattern would also cut down on pro-oxidant foods rich in cholesterol, salt, saturated fat, and sugar, while boosting the intake of plant foods that have the dual benefit of enhancing our primary oxidant defense via Nrf2 activation and our second line of radical resistance, the symphony of natural antioxidant compounds that can work in concert in a way in which antioxidant supplements have failed.

To help slow this aging pathway, on a daily basis, consider:

- exercising
- restricting methionine intake by choosing plant-based protein sources and reducing overall protein intake to recommended levels
- activating Nrf2 defenses by eating green (cruciferous vegetables) and drinking green (tea)
- eating berries and other naturally vibrantly colored foods
- using herbs and spices, such as cinnamon, cloves, garlic, ginger, and marjoram
- avoiding added salt, sugar, and saturated fat– and cholesterol-rich foods

SIRTUINS

Each of us contains tens of billions of miles of DNA—enough for 100,000 trips to the moon and back if each strand were uncoiled and placed end to end.[1798] How does our body prevent these precious ribbons of information from getting all twisted and tangled? Enzymes known as *sirtuins* keep our DNA neatly and nicely wrapped around spool-like proteins and, by doing so, silence whatever genes are in that stretch of DNA. The name *SIR*tuins stands for Silencing Information Regulator.[1799]

THE GUARDIANS OF HEALTHSPAN

Since this seminal discovery, myriad other functions of sirtuins have been discovered, including their ability to activate or deactivate more than fifty other proteins.[1800] What most excited the scientific community about these regulatory enzymes is that boosting their activity could extend yeast lifespans by as much as 70 percent.[1801,1802] Boosting sirtuins also boosts the lifespans of other model organisms—worms and flies—leading to great hopes that it could do the same in mammals.[1803]

In a few mouse models, sirtuin upregulation was found to extend life,[1804,1805] but most mice studies just showed healthier lives, rather than longer ones,[1806] thereby earning sirtuins the title of "guardians of mammalian healthspan."[1807] In addition to preserving DNA integrity,[1808] sirtuin activation improves DNA repair,[1809] downregulates inflammation,[1810] and contributes to telomere maintenance,[1811] which I discuss in the next chapter. This translates into better blood sugars and bone mass, and less DNA damage and cancer.[1812] So, in the few cases in which lifespan was extended, it may have been more a matter of suppressing age-related diseases than slowing the rate of aging per se.[1813] Regardless, these effects were found in mice and have yet to be confirmed in humans. We do know, however, that there doesn't seem to be an association between exceptional longevity in people bearing any of the different variants of at least one of the sirtuin genes.[1814] As one reviewer mused, sirtuins may have lost their "Methuselah" image but may still be a helpful metabolic "Samaritan."[1815]

As you'll recall, the fuel gauge enzyme that I discussed in the AMPK chapter boosts sirtuin activity.[1816] So, activating AMPK via metformin,[1817]

caloric restriction,[1818] or exercise[1819] can lead to sirtuin activation. However, since the sirtuin boost is an indirect effect caused by AMPK, chugging sugar water before a sprint, for example, a sports or energy drink, blunts the sirtuin response to exercise.[1820] While mild caloric restriction—by about 15 percent, roughly 350 calories a day—had no effect on sirtuin activity,[1821] a 30 percent reduction in calories for eight weeks did,[1822] but not for just five days.[1823] However, Buchinger fasting (consuming only a limited selection of juices and vegetable broth) can boost sirtuin activity within five days,[1824] as can alternate-day fasting for three weeks,[1825] dropping down to 1,000 calories a day for a month,[1826] or six months of 25 percent calorie restriction.[1827]

The way AMPK enhances sirtuin activity is by increasing levels of cellular nicotinamide adenine dinucleotide (NAD^+).[1828] NAD^+ is a critical cofactor necessary for sirtuin activity. Alternate means of boosting NAD^+ levels include taking a variety of NAD^+ precursors,[1829] as I'll discuss in the Anti-Aging Eight section. Raising NAD^+ levels is one of two basic approaches to sirtuin stimulation.[1830] The other is via STACs, sirtuin-activating compounds, the most widely known of which is resveratrol,[1831] a natural compound concentrated in the skin of grapes.

RESVERATROL

Resveratrol, the "red wine molecule,"[1832] became a household word[1833] in 1991 when a scientist from Bordeaux University[1834] appeared on the popular TV show *60 Minutes* and attributed the so-called French Paradox to the French habit of drinking red wine.[1835] As you can see in see.nf/resveratrol, the "paradox" was effectively debunked,[1836] but not before resveratrol research had already taken root, culminating in more than 15,000 scientific publications to date.[1837,1838]

As I show in the video, animal data are mixed. For example, resveratrol extends the lives of worms[1839] and bees,[1840] but not flies[1841] or fleas.[1842] Unfortunately, most studies on mammals (mostly mice) failed to show a lifespan benefit.[1843] Even its purported sirtuin activity has been called into question.[1844] Commentaries with titles like "Is Resveratrol an Imposter?"[1845] and "Promising Therapeutic or Hopeless Illusion?"[1846] were published, suggesting that seeming sirtuin activity was probably the result of

experimental artifact.[1847] It didn't help matters when a leading resveratrol researcher was found guilty of 145 counts of fabrication and falsification of data, throwing the whole field into turmoil.[1848]

In a 2014 medical journal editorial titled "The Resveratrol Fiasco," the editor in chief summarized the state of the science: "The conclusions are quite clear-cut: after more than 20 years of well-funded research, resveratrol has no proven human activity."[1849] However, since that publication, more than 150 human clinical trials have been published.[1850] I present the update in see.nf/resveratrolhealth. No impact on inflammation, cancer, cardiovascular disease, long-term frailty,[1851] or death[1852] has been found epidemiologically for dietary resveratrol exposure, and meta-analyses of randomized controlled trials of resveratrol supplements failed to find clinically[1853] or even statistically[1854] significant effects on systemic markers of oxidative stress, helping to explain the lack of apparent DNA protection.[1855]

For almost all outcomes measured in randomized controlled trials of type 2 diabetes, metabolic syndrome, or nonalcoholic fatty liver disease, the effects of resveratrol were trivial at best,[1856] but a meta-analysis found that doses ranging from 5 to 500 mg twice a day resulted in an average twenty-point drop in fasting blood sugars.[1857] There was also a significant benefit for longer-term (HbA1c) blood sugar control, though this only appeared to be the case in shorter-term studies.[1858] What's the point of better longer-term control if resveratrol only works in studies lasting less than three months? Well, there was a study suggesting accelerated healing of diabetic foot ulcers,[1859] a leading cause of lower-limb amputations.[1860]

In see.nf/resveratrolclinical, I run through what else resveratrol supplementation might be able to do clinically. In rats[1861] and mice,[1862] resveratrol can help ameliorate the effects of experimentally induced periodontitis, the inflammatory gum disease. It appeared to have no effect, however, on the progression of chronic periodontitis in human sufferers.[1863] Resveratrol may help with the inflammatory bowel disease ulcerative colitis[1864,1865] and knee osteoarthritis,[1866] though.

Resveratrol has some estrogenic activity,[1867] and, although it doesn't appear to help with hormonal migraines,[1868] it does appear to help with a few symptoms of polycystic ovary syndrome (PCOS)[1869] and menopause.[1870] Unfortunately, a meta-analysis of studies on resveratrol supplementation to

improve bone quality found no significant effect on bone health markers or bone mineral density of the spine, hip, or overall skeleton.[1871] The same was true for cognitive effects, leading one systematic review to suggest resveratrol may be a "cognitive enhancer for mice only."[1872] The largest trial of resveratrol for Alzheimer's disease even found a tripling of brain shrinkage in those randomized to the resveratrol group compared to placebo.[1873]

Negative or null findings are often marginalized by the resveratrol research community.[1874] As I review in see.nf/resveratrolsafety, there are no long-term safety data,[1875] but even supplementation purported to be "safe"[1876] (150 mg to 250 mg a day) found that resveratrol may blunt some of the positive effects of exercise training, undercutting physical fitness in both the young[1877] and the old.[1878]

A recent review overreacted to these data by suggesting that "foods containing resveratrol should not be consumed during exercise,"[1879] but to reach even the lower dose of 150 mg, you'd have to eat more than a hundred pounds of grapes.[1880] The exercise impairment with supplemental resveratrol does make sense, though, given its purported mechanism. Sirtuin activation by resveratrol is thought to occur via the activation of the body's fuel gauge AMPK by impairing energy production in our cells' mitochondria.[1881] Mouse cells react by increasing mitochondria to compensate,[1882] but human cells apparently do not,[1883] so the energy-dimming effect of resveratrol may explain why the effects of exercise are impaired.

The hype surrounding resveratrol, concluded one review, may "turn out to be nothing more than a slight-of-hand [*sic*] marketing device using peer-reviewed, published, non-human research as a cover."[1884] The fitness-blunting exercise study of older adults was supported in part by a manufacturer of resveratrol supplements. To their credit, however, the researchers responded to an angry letter by a supplement company consultant that "it is our opinion that we, as scientists, have a responsibility to report what we find, and not to twist our findings to fit the commercial interests."[1885]

HOW ABOUT THEM APPLES?

Resveratrol may be the most familiar STAC, but thousands of others have been discovered.[1886] In vitro, apple extracts have been shown to activate sirtuins, as well as AMPK and autophagy, while suppressing mTOR signaling.[1887] It's perhaps unsurprising, then, that a meta-analysis of population studies found that those who ate more apples had a 15 percent lower risk of premature death.[1888] How many apples is "more"? The "high" category of apple consumption averaged only about a quarter of an apple a day. The one study that looked at the greatest apple intake—half an apple a day compared to less than one apple in an entire month—found a 35 percent lower risk of dying early.[1889] Over a lifetime, that could translate into around four more years of life.[1890] Forget just the doctor. An apple a day may keep the mortician away, too.

A single apple phytonutrient, *phloridzin*, was found to boost sirtuin expression and extend the lifespan of yeast, though it also increases levels of the antioxidant enzyme superoxide dismutase, so it's not clear what role the sirtuin played.[1891] In fruit flies, at least, the increase in average lifespan from an apple extract requires intact antioxidant enzymes, suggesting it may be more of an antioxidant effect.[1892] Even just straight apple fiber (pectin) had a lifespan-extending effect, and this wasn't solely due to caloric dilution (dietary restriction achieved through bulking the diet with fiber). The pectin group actually ate more food yet lived longer.[1893] The whole apple, however, may be better than the sum of its parts.

Adding the flesh of an apple to a prematurely aging mutant yeast that normally only lives about ten days bumped up its lifespan to eleven days, whereas adding the skin of an apple extended its life up to fourteen days. Seems like most of the good stuff is in the peel, right? What do you predict would happen if you add both the flesh and the skin? I would have guessed the whole apple would extend the lifespan somewhere between eleven and fourteen days since the components of the peel would get diluted, but I would have been wrong. The *whole* apple more than *doubled* lifespan, taking it to twenty-one days.[1894]

Similarly in *C. elegans*, whole apple extracts increased average lifespan up to 39 percent, which is more than three times the 12 percent achieved with a subfraction of purified apple compounds (though the studies also

used different apples, Red Delicious[1895] and Fuji, respectively). In *C. elegans*, at least, sirtuin dependency of the longevity benefit was confirmed.[1896]

If the components of apple peel and pulp can synergize, providing benefits greater than the sum of the parts, what about combining apples and blueberries? In *C. elegans*, both apple and blueberry extracts extend life, but using half of each extended life significantly more than either could alone.[1897] Results like these buttress the commonsense notion that, whenever possible, we should strive to acquire our nutrition from combinations of whole foods rather than isolated components in pill form.

THE QUEEN OF SPICES

Are there any other "sirtfoods," foods with sirtuin-activating properties?[1898] Numerous food components boost sirtuin activity in cells in a petri dish, but very few have been put to the test in people.[1899] Two hundred daily micrograms of selenium for ten weeks can upregulate sirtuin expression,[1900] but, as I note in see.nf/nacse, that dose used long-term has been shown to increase diabetes risk.[1901] Curcumin, the pigment that makes turmeric yellow, works in vitro[1902] and in an animal model[1903] but flops when it comes to significantly changing sirtuin gene expression in humans, even after taking the equivalent of about a quarter cup of turmeric every day for months.[1904] One spice that might work, though, is cardamom.

A member of the ginger family, green cardamom (*Elettaria cardamomum*) is known as "the queen of spices."[1905] In a trial of patients with fatty liver disease, those randomized to a half teaspoon of cardamom three times a day with meals for three months not only had improvements in liver function and markers of systemic inflammation but they also saw a significant increase in sirtuin levels in their bloodstream.[1906] Now, we aren't exactly sure about the origin or implication of sirtuins in the blood. It's not like a hormone. Each cell appears to make and use its own sirtuins internally. However, blood levels do decline with age,[1907] and accelerated decline in sirtuins is associated with age-related impairments such as frailty,[1908] cognitive decline, and Alzheimer's disease,[1909] suggesting it may be a biomarker of aging.[1910]

As a bonus, the same cardamom dose over two to three months can significantly improve markers of inflammation and oxidative stress,[1911] and be a safe, cheap, convenient way to decrease the level of triglycerides in the blood by about twenty points (mg/dL).[1912] I enjoy it in my chai tea and like adding it to cocoa powder any time I'm chocolating anything up. No significant adverse side effects have been reported from taking such doses, though there are no long-term data available at this time.[1913]

AGEs SUPPRESS SIRTUINS

Is there anything we need to avoid to preserve sirtuin function? Smokers have diminished sirtuin levels in their lungs,[1914] and in vitro, cigarette smoke extracts actively decrease sirtuin levels and activity in lung cells, helping to establish cause and effect.[1915] The advanced glycation end products (AGEs) in smoke may be contributing, since AGEs alone suppress sirtuin expression in vitro and feeding AGEs to mice causes a sirtuin brain deficiency, along with an impairment of learning and memory.[1916] Unfortunately, as we learned in the Glycation chapter, people are also exposed to dietary AGEs.

Increasingly, sirtuin activity is being seen as playing a significant role in protecting against Alzheimer's dementia.[1917] The fact that dietary AGE intake is linked to lower sirtuin expression may help explain why high blood, brain, and dietary AGE exposure is associated with cognitive decline in elderly adults. Researchers have concluded that human sirtuin deficiency is "both preventable and reversible by AGE reduction," suggesting that avoiding high-AGE foods may offer a new strategy to combat the Alzheimer's epidemic.[1918] However, dietary AGEs are unlikely to pose a central role in sirtuin regulation, as no differences have been found in sirtuin expression or activity in a cross-sectional comparison of healthy omnivores, vegetarians, and vegans.[1919]

Food for Thought

Sirtuins are a class of protein regulators that appear to play a key role in protecting us against a variety of age-related

diseases, though their role in longevity is questionable.[1920] Dependent on a molecule called NAD^+, sirtuins can be upregulated by anything that increases NAD^+ levels, including AMPK activation. Certain foods and supplements may also be able to activate sirtuins in other ways, but research on resveratrol has been largely disappointing and raised certain safety concerns.

To help boost this anti-aging pathway, on a daily basis, consider:

- elevating cellular NAD^+ levels (see the NAD^+ chapter)
- following the recommendations on AMPK activation (see the AMPK chapter)
- snacking on apples and experimenting with adding cardamom to meals
- not smoking
- avoiding foods high in AGEs (see the Glycation chapter)

TELOMERES

In each of our cells, we have forty-six strands of DNA coiled into chromosomes. At the tip of each chromosome is a protective cap called a *telomere*, which keeps our DNA from fraying or fusing with other chromosomes,[1921] analogous to how the plastic tips on the ends of our shoelaces keep them from unraveling. ("Telomere" comes from the Greek words *telos* for "end" and *meros* for "part."[1922]) Each time our cells divide, however, a bit of that cap is lost. When telomeres become critically short, the exposed ends of our chromosomes appear like double-stranded DNA breaks, an emergency signal that sends the damaged cells into senescence, or death.[1923] Our body does this on purpose, it is thought, to protect us from cancer.[1924]

ON A SHORT FUSE

Remember the "Hayflick limit" from the Cellular Senescence chapter? Telomere shortening is the mechanism by which many cells are restricted from dividing more than about fifty times.[1925] This cap on cellular immortality may limit our lifespan potential, but it may also protect us from tumor formation. This may explain, for example, why those of European ancestry tend to have shorter telomeres than those from sub-Saharan Africa.[1926] The Europeans' lighter skin tones made them more susceptible to melanoma skin cancer, so their cells were presumably forced to adapt. This may be another example of antagonistic pleiotropy.[1927] What may have been helpful in letting us reach reproductive age so we could pass along our genes (not dying from a childhood cancer) may not bode well for successful aging and longevity (the littering of our tissues of zombified senescent cells from critical telomere shortening).[1928]

At birth, our telomeres start out at maximum length, but then they tend to get progressively eroded year after year as we age.[1929] That's why telomeres are often thought of as a "life clock."[1930] Based on how much the length of your telomeres changes every year, you can approximate the rate of biological aging. Two people can have the same chronological age but suffer more, or less, effective cellular aging. If you smoke a pack of cigarettes a day for a decade, your cells may age about three years faster, for example, and drinking just 8 oz of sugar-sweetened soda every day is associated with nearly two years of additional aging.[1931]

Our telomeres can start shortening as soon as we are born, and when they're gone, we are, too. Though a gross oversimplification, they're kind of like life's fuse. Accelerated telomere shortening has been identified as a key biomarker for accelerated aging, disease, and diminished longevity,[1932] and shortened telomeres have been associated with arthritis, diabetes, heart disease, kidney failure, liver failure, lung disease, osteoporosis, stroke, and vision loss.[1933] Telomere length is also tied to a reduction of muscle mass and performance (measured in grip strength),[1934] as well as reduced immune function. When the common cold virus is dripped into people's noses, those with shorter telomeres in key immune cells are significantly more likely to get sick.[1935] Alzheimer's disease, though not necessarily cognitive decline in

general,[1936] is one of the age-related diseases most strongly linked to short telomeres.[1937] Shorter ends may also lead to a faster end.

LOOKS CAN BE PERCEPTIVE

Large-scale studies have found that research subjects with the shortest telomeres had a 17 to 66 percent increase in mortality risk when compared to subjects with the longest ones.[1938] In other words, longer telomeres may mean a longer life. Studies of hundreds of twins, for example, found that the twin with shorter telomeres was more likely to die at an earlier age.[1939] And, not only did the twin with the longer telomeres live longer, but they looked younger, too.[1940]

Looking "old for your age" is actually an indicator of poor health and a strong predictor of mortality, independent of physical and mental functioning. When geriatric nurses were given high-quality photographs of hundreds of pairs of twins, they were able to pick out who was more likely to die first—just based on which twin looked older. Perceived age is linked to telomere length, too.[1941] Even those born with a genetic predisposition to longer telomeres grow up to experience less facial aging, suggesting the relationship is cause and effect[1942] rather than due to some third variable, like smoking, that may concurrently age your appearance and snip away at your telomeres.[1943]

As one might expect, women tend to have longer telomeres than men and a presumed slower telomere erosion rate, consistent with the fact that women typically live longer.[1944] The telomere shortening rate is a powerful predictor of lifespan across species,[1945] as well as within them. For example, telomere length is a strong predictor of average lifespan among fifteen different breeds of dogs, who sadly lose their telomeres at approximately ten times the rate of humans and have about tenfold shorter lives.[1946]

ON THE CLOCK

Is telomere length a cause of aging or merely a consequence? Mice manipulated to start out with longer telomeres at birth do live longer and healthier lives.[1947] The case for causation in humans is buttressed by rare genetic disorders of telomere maintenance that manifest as accelerated

aging, from premature hair graying and skin pigmentation to untimely heart attacks.[1948] Telomere shortening is thought to actively drive aging through cellular senescence and the ensuing constellation of SASP inflammation.[1949] (See the Cellular Senescence chapter.)

The concept of telomeres as a constantly ticking biological clock is not quite accurate.[1950] By taking DNA from a blood stain, forensic scientists may be able to roughly estimate a person's age simply based on the length of the blood cell's telomeres,[1951] but the shortening rate and baseline length vary widely between individuals.[1952] The fuse burns faster in some people than in others. On average, across an adult population, there appears to be a constant, inexorable yearly loss in length, but the individual data are scattered such that it's not uncommon to run across an eighty-year-old whose telomeres are as long as those of a thirty-year-old.[1953]

In addition to this, there is variability within the same person—and also within the same cell within the same person. Each cell has ninety-two telomeres capping off either end of our forty-six chromosomes.[1954] All it takes is a single critically short telomere to send the entire cell into a spiral of senescence or death.[1955] Most studies track the average telomere length of individuals, usually from their blood cells for convenience's sake; however, the length of our *shortest* telomeres may provide a better predictor of remaining healthy years of life.[1956] Thankfully, there's a way not only to slow down the rate of telomere attrition but to build back up our shortest telomeres.

BUILD BACK BETTER

The answer lies in an enzyme found in Methuselah. That's the name given to a bristlecone pine tree growing in California's White Mountains. When it was named, the tree was the oldest recorded living being. Today, it's nearing its 4,800th birthday. For context, Methuselah had already been alive for centuries before construction of the Egyptian pyramids had even begun. An enzyme found in the roots of bristlecone pines appears to peak a few thousand years into the trees' lifespan and actually rebuilds telomeres.[1957] Scientists named the enzyme *telomerase*. Once they knew what to look for, they found that the enzyme is present in our cells, too.

It makes sense that such an enzyme exists. If we didn't have a telomere-maintaining mechanism in our testicles and ovaries so our sperm and eggs could start out with fully intact telomeres, every generation would begin with at least a puberty's worth of telomere loss.[1958] And, how could we explain cancer? The vast majority of cancer cells crank up telomerase activity to obtain effective immortality.[1959] In most cells, though, telomerase becomes relatively inactive after birth, so our telomeres usually lose ground year after year[1960]—but not every year and not in everyone.

Longitudinal studies that tracked telomere length in the same people over time unexpectedly found that 1.5 to 25 percent of individuals experienced an elongation in their telomeres.[1961] In the Bogalusa Heart Study, for example, 16 percent of all participants showed telomere lengthening over a period of seven years, but, by year twelve, that figure decreased to 1.5 percent.[1962] So, eventually, time may win out, but from one year to the next, we may be able to keep telomere shrinkage at bay, thanks to telomerase activation.

Your trajectory of telomere length over time may have serious health consequences. In the MacArthur Study of Successful Aging, for example, elderly men whose telomeres shortened over a two-and-a-half-year period had a threefold higher chance of death from cardiovascular disease over the subsequent decade compared with participants whose telomere length was lengthened or even just maintained.[1963] Centenarians appear to be particularly good at maintaining their telomeres,[1964] especially those who successfully escape the major age-related diseases.[1965] So, is telomerase the "fountain of youth," as it's been described?[1966] An "anti-aging molecular switch"?[1967]

Mice engineered to be deficient in telomerase suffer critical telomere shortening and experience premature aging and death, which can be prevented by reinstating telomerase.[1968] Conversely, when mice were engineered to express even more of the enzyme, there was a striking 40 percent extension of average mouse lifespans.[1969] Further demonstrating its anti-aging activity, telomerase activation in various mouse models has also been shown to lead to a reduction in age-related osteoporosis[1970] and improvements in heart,[1971] liver,[1972] and kidney function,[1973] as well as coordination, balance,[1974] and movement.[1975] Telomerase may even have additional beneficial "non-canonical" activities, such as DNA repair.[1976]

What About Cancer?

Since telomerase can be hijacked by cancer cells, should we be concerned that boosting its activity would increase our cancer risk? Drug companies have been trying to come up with anti-telomerase chemotherapy in an effort to stop cancer, but they haven't been successful. Not only are there toxic effects on stem cells that rely on telomerase, but cancer can't be stopped in time. Even if telomerase were completely blocked and cancer cell telomeres began getting ratcheted down, we could be dead long before the Hayflick limit was reached. (The amount of cancer produced during fifty doublings is more than enough to kill us.[1977])

Ramping up telomerase activity does not, however, seem to be a problem. Telomerase is a permissive, but not sufficient, cause of cancer, meaning the enzyme can be used by cancer cells but does not itself cause it.[1978] Skin cells (taken from circumcised foreskins) in a petri dish "immortalized"[1979] with telomerase activation, for example, were not transformed into skin cancer cells.[1980] Similarly, in mice, telomerase activation delays aging and increases lifespan without increasing cancer risk.[1981] Since we're left with apparently all upsides, we should try to boost activity of the age-defying enzyme.

DIETARY TELOMERE PROTECTION

Approximately 30 percent of the difference in telomere-shortening rates between people is genetically determined, but the majority of influence over whether our telomeres lengthen or shorten and at what rate is determined by external factors, such as environment, lifestyle, and diet.[1982] This helps explain the correlation of telomere length shared by spouses,[1983] for example, but it doesn't necessarily mean we have control over that full 70 percent of our telomeric destiny. For instance, we can suffer telomere loss before we're even born due to prenatal exposure to alcohol,[1984] smoking,[1985]

or air pollution.[1986] But, the choices we make every day—or three times a day—can make a difference.

The main drivers of accelerated telomere loss may be oxidative stress and inflammation.[1987] (For an explanation why, watch see.nf/ttaggg.) No surprise, then, that a systematic review on the role of nutrition concluded that longer telomeres were associated with the intake of vegetables, fruits, legumes, nuts, and other foods high in fiber and antioxidants. In contrast, the consumption of processed meats, alcohol, soda, and other foods and beverages rich in saturated fat and sugar was linked to shorter telomeres.[1988] So, a whole food, plant-based diet was put to the test.

HOW TO WIND BACK THE CLOCK

Research pioneer Dean Ornish was the first to show, in a randomized controlled trial, that a whole food, plant-based lifestyle could reverse the progression of heart disease.[1989] He then showed that the same dietary changes could also help reverse the trajectory of early-stage prostate cancer,[1990] and he is currently pitting plants against dementia in an attempt to reverse the course of early-stage Alzheimer's disease.[1991] In a study partially funded by the U.S. Department of Defense to see what a healthy diet and lifestyle could do for cellular aging, Ornish teamed up with Dr. Elizabeth Blackburn, who was awarded the Nobel Prize in medicine for her role in the very discovery of telomerase.[1992]

Thirty men aged forty-nine to eighty were encouraged to eat a low-fat diet centered around whole plant foods—fruits, vegetables, whole grains, and beans—as well as walk for exercise and practice stress management. Within three months, their telomerase activity jumped by nearly 30 percent. This was the first ever intervention that showed significant boosting of the telomerase enzyme. The study was published in one of the world's leading medical journals,[1993] and the accompanying editorial concluded that the landmark findings "should encourage people to adopt a healthy lifestyle in order to avoid or combat cancer and age-related diseases."[1994]

In the five-year follow-up study, the researchers measured the lengths of the subjects' telomeres to determine if the telomerase boost actually translated into a slowing of telomere loss. For similarly aged men in the control group who maintained their regular diets, their telomeres

predictably shrank with age. In the healthy-living group, however, the subjects' telomeres didn't just shrink less or hold steady—they *grew*. Five years after that first intervention, their telomeres were even longer on average than when they had started participating in the study, suggesting for the first time ever that a healthy plant-based diet and lifestyle can boost telomerase enzyme activity and effectively reverse cellular aging.[1995] But, was it the diet, the exercise, or the stress management?

CAN WE DE-STRESS OUR TELOMERES?

In the Hollywood blockbuster *The Holiday*, Cameron Diaz's character announces, "Severe stress … causes the DNA in our cells to shrink until they can no longer replicate."[1996] Did Tinseltown get that right? As I review in see.nf/destress, the data on stress and telomeres are conflicting, finding, for example, decreased telomerase activity among one set of dementia caregivers[1997] and increased telomerase activity among another.[1998] In the video, you'll see the data are also mixed on the role of meditation.[1999] Regardless, there appears to be more to the remarkable Ornish results than just the stress reduction component. What about the exercise and weight loss?

TELOMERE LENGTH IN THE LONG RUN

We can't always change our station in life, but we can always go out for a walk. A study of thousands of twins found that those who exercised more appeared to pump up their telomeres along with their muscles.[2000] Although some findings suggest that walking as little as 150 minutes a week is associated with longer telomeres[2001] and, on average, those who exercise tend to have longer telomeres than those who don't,[2002] the majority of studies on physical activity and telomere length actually came up short, finding no significant association.[2003] "[I]t is not clear," concluded one review, "whether P[hysical]A[ctivity] is protective for the shortening of telomere DNA."

The data are more consistent with elite athletes. Those taking part in national or international competitions[2004] and master athletes competing in professional sports tend to have longer telomeres than age-matched non-

athletes.[2005] Ultramarathoners,[2006] marathoners, and triathletes running fifty miles a week for thirty-five years[2007] may have longer telomeres, but what about those of us who haven't run the equivalent of three times around the Earth's equator?

Of the five randomized controlled trials that have actually put exercise to the test, only one found a significant difference in changes in telomere length.[2008,2009,2010,2011] Six months of aerobic endurance training (running) or high-intensity interval training (HIIT) increased telomerase activity and telomere length, whereas resistance training for the same period did not.[2012] But none of the other interventional trials found any significant effect regardless of the regimen, calling any telomere effects of exercise into question, at least in the short term.[2013]

WAS IT THE MENU OR THE MOVEMENT?

To tease out the critical Ornish study question—*Was it the plant-based nature of the diet, the exercise, or the weight loss?*—ideally a study would randomize people into at least three groups: a control group who did nothing (sedentary on a typical diet), a group who just exercised, and a group who lost weight eating pretty much the same diet but in smaller portions. And just such a study was published by a team of American and Canadian researchers.[2014]

About four hundred postmenopausal women were randomized into one of four groups for a year: a control group, an exercise group, a portion-controlled diet group, and an exercise *and* portion-controlled diet group. As expected, after twelve months of doing nothing, there was little change in the control group. What about after a year of exercise? They did no better, and this study's exercise group did more than just walk for half an hour like those in the Ornish study; they were tasked with forty-five minutes of moderate-to-vigorous exercise, like jogging. And the portion-controlled diet group? The weight loss had no effect, nor was there a significant change in telomere length in the combined exercise and weight-loss group. This is on par with inconsistent findings across the board with weight-loss interventions attempting to restore telomere integrity.[2015]

So, as long as we're eating the same diet, it may not matter how small our portions are, how much weight we lose, or how much we exercise; after

a year, the subjects saw no benefit. In contrast, the individuals in the Ornish study on a whole food, plant-based diet who exercised only half as much and enjoyed the same amount of weight loss after just three months[2016] appeared to acquire significant telomere protection.[2017] In other words, neither the weight loss nor the exercise reversed cell aging by rebuilding telomeres. It was the food—and not just any diet. A similar study across a similar time frame—four and a half years of more moderate nutritional advice, such as choosing low-fat dairy and skinless chicken breast, along with more fruits, vegetables, and whole grains[2018]—failed to significantly affect telomere length.[2019]

FOODS TO AVOID

Not all plant foods are good for you. For example, eating french fries is associated with shorter telomeres.[2020] Yes, vegetable intake goes hand in hand with longer telomeres, but that may be trumped by a deep fryer.[2021] Refined carbs, like cookies and crackers, may also snip at your telomeres.[2022] So, part of the benefit of centering one's diet around *whole* plant foods may be from cutting out junk. Those eating the most ultraprocessed foods have nearly twice the odds of having shorter telomeres,[2023] not to mention a higher risk of obesity,[2024] depression, heart disease, stroke, and premature death in general.[2025]

Alcohol is another processed plant product. Researchers followed a cohort of Helsinki businessmen for nearly thirty years and found that those who drank the most ended up with an extra decade of telomere aging. Although they also found that even minor alcohol consumption during middle age might result in shortened telomeres,[2026] a systematic review of evidence published in 2021 concluded that any negative effects of alcohol on telomeres appeared to be limited to heavier drinkers with alcohol dependence.[2027]

In addition to eschewing alcohol, the Ornish study participants were asked to cut out processed meat. Consumption of foods like bacon, ham, hot dogs, lunch meat, and sausage has been associated with both cancer[2028] and shorter telomeres, although unprocessed red meat—a steak, for example—does not appear to be similarly associated with telomere length.[2029] There have been studies implicating meat, including wild game, poultry,[2030] and

fish,[2031] but, more broadly, it appears to be more of an issue with processed meat.[2032]

Long-chain omega-3 fats in fish and fish oil were presumed to benefit telomeres because they score as anti-inflammatory in the Dietary Inflammatory Index.[2033] A 2010 population study correlated higher baseline blood levels of omega-3 fatty acids with less telomere shortening over a five-year period, which launched a series of randomized controlled trials.[2034] Though a secondary analysis of a clinical trial on schizophrenics found an increase in telomerase activity,[2035] unfortunately, not a single one of the randomized controlled trials putting fish oil supplementation to the test could demonstrate a significant effect on telomere length.[2036,2037,2038,2039]

The most pro-inflammatory food component is saturated fat.[2040] Figuring it's never too early to start eating more healthfully, researchers randomized more than a thousand infants to a diet low in saturated fat or a control group for their first twenty years of life. This remarkable Finnish study found that, compared to those growing up in the healthier diet group, subjects in the control group suffered twice the annual rate of telomere loss. However, this may be more than an effect of saturated fat reduction. Although that was the main focus of the study, those in the intervention group were also encouraged to reduce their salt intake and eat more fruits, vegetables, and whole grains, making it impossible to pinpoint the decisive factor.[2041]

On the other end of the research spectrum is a series of randomized controlled dietary trials that only lasted four weeks but had an innovative study design. Cells from umbilical cords (a convenient source of human tissue) were cultured in the blood of elderly subjects after a month of eating a diet high in butter versus a similar diet high in olive oil. A greater percentage of cells bathed in the buttery blood had shortened telomeres.[2042] A Mediterranean-style diet, which is typically higher in olive oil and lower in dairy, may be insufficient, though. Although cross-sectional studies have found that higher adherence to a more Mediterranean diet correlated with longer telomeres, the only longitudinal and controlled trials found telomere lengths to be the same or even shorter.[2043]

The adverse effects of saturated butterfat may help explain the association between increased biological aging and the consumption of high-fat milk in a national survey of thousands of Americans. Even increasing milk fat by just 1 percent—for example, going from 1% low-fat

milk to 2% reduced-fat milk—correlated with the equivalent of more than four years of telomere loss, presumed to be due to the inflammatory response and oxidative stress triggered by the saturated fat.[2044]

TELOMERE-FRIENDLY FOODS

The most anti-inflammatory food component is fiber.[2045] The same representative sampling of thousands of U.S. adults found that the more fiber people consumed, the longer their telomeres tended to be. Since there appeared to be a straight-line increase, researchers could do the math. It seems that just a 10 g increase in fiber per 1,000 calories equates to four fewer years of telomere aging.[2046] That's comparable in magnitude to the additional years of aging associated with consumption of processed meat (4.0 extra aging years),[2047] drinking 20 oz of soda a day (4.6 more years),[2048] or smoking (also 4.6 extra aging years).[2049]

Fiber intake may just be a marker for the consumption of plant foods, since, by definition, they are the only place fiber is found.[2050] So, the apparent link between fiber consumption and telomere length may have nothing at all to do with fiber; it could be related to some other protective component or components of plant foods. It's like the studies showing longer telomeres in people with higher dietary intakes[2051] or blood levels[2052] of carotenoids, plant pigments like beta-carotene. Again, that could just be a proxy for the intake of plants. Also associated with longer telomeres is consumption of coffee,[2053] and that has neither fiber nor carotenoids. Interestingly, while coffee intake is linked to longer telomeres, *caffeine* intake seems to be coupled with shorter telomeres,[2054] presumably because so much caffeine intake these days is from sodas and sugary energy drinks.[2055]

Green tea consumption has been associated with longer telomeres in elderly men[2056] and shown to protect telomeres in rats,[2057] but it wasn't put to the test clinically in an interventional trial until 2016. It's hard to make a convincing placebo tea, so researchers used green tea extract capsules. In my video see.nf/nutsandtea, I show how those randomized to the equivalent of about four cups[2058] of green tea a day for five months experienced a significant boost in telomere length in the green tea group over placebo.[2059] (It is unclear if nuts help our telomeres or not.)

Green tea is essentially a green leafy vegetable dipped in hot water. What about *eating* green leafy veggies? In the video, I profile a dietary intervention that showed that eating the equivalent of one and a quarter daily cups of kale—cooked, not raw—boosted telomerase activity in as little as five days. The study provided, for the first time, evidence that telomerase activity can respond in a matter of days to a food intervention. Not just any food, though, but the healthiest food out there—cruciferous, dark green leafy vegetables. Within sixteen days of stopping the kale, however, telomerase activity was back to baseline.[2060] So, as I recommend in my Daily Dozen, try to fit cruciferous veggies into your regular dietary routine.

SUPPLEMENTS

One of the reasons I don't recommend taking green tea extract supplements is the risk of liver toxicity. We used to think such reactions were rare, on the order of one in a hundred thousand.[2061] But, now that there are large studies like the Minnesota Green Tea Trial, we realize it may be more like one in twenty.[2062] (In contrast, not a single liver problem has been reported in any of the trials that used green tea in regular beverage form.[2063]) Are there any other supplements that aren't as risky yet may protect our telomeres?

VITAMIN D

Nearly every supplement study to date has failed to find benefits for our telomeres. None of the fish oil trials successfully delayed telomere shortening,[2064,2065,2066,2067] nor did extra-virgin olive oil,[2068] B vitamins,[2069] or zinc supplements.[2070] Of the ten studies on vitamin D and telomeres, only two were double-blind, randomized, placebo-controlled trials,[2071] but they both showed benefits (at 60,000 IU once a month[2072] and 800 IU once a day[2073]). Details in see.nf/dtelomeres.

ASTRAGALUS

Astragalus root is one of the most popular herbs in traditional Chinese medicine,[2074] widely marketed for millennia as a "life-prolonging" tonic.[2075] A compound in the root called *cycloastragenol* (branded as "TA-65")

appeared to moderately enhance telomerase activation in vitro,[2076] but the only study suggesting clinical benefit was funded by the company that sells it[2077] for $600 a bottle online. It grossed more than $50 million before being charged with false and deceptive claims and practices by the Federal Trade Commission.[2078] For those interested in learning more, I explore the pros and cons in see.nf/astragalus.

GOTU KOLA

In 2019, the most powerful telomerase activator to date was discovered in *Centella asiatica*, also known as *gotu kola*. It was found to cause a nearly ninefold increase in telomerase activity, four times that of TA-65.[2079] Widely used in both Ayurvedic and traditional Chinese medicines,[2080] gotu kola is a green leafy vegetable, commonly eaten fresh in salads or cooked in soups in Malaysia and Indonesia or juiced or brewed as tea in India and Thailand. In India, it is primarily considered a "brain food"[2081] and has been found to enhance cognitive function in mice,[2082] but a meta-analysis of the handful of studies done to date with people found no significant effect on human cognition.[2083] Should clinical benefits be discovered, gotu kola tea can be purchased online for only about a nickel per cup.

Food for Thought

Telomeres are one of the aging pathways that have crept into the public consciousness. Increasing telomere length to slow or even prevent aging is a popular idea, though, as I've addressed, the science is controversial.[2084] Telomere elongation is possible through activation of the telomerase enzyme, but there is a constant battle between the forces hacking away at our telomeres, such as aging, oxidative stress, and inflammation, and the lifestyle decisions that can help build them back up.[2085]

Some people have expressed concern that boosting telomerase activity could theoretically increase cancer risk,[2086] since tumors have been known to hijack the telomerase enzyme and use it to ensure their own immortality,[2087] but the same lifestyle changes that Dr. Ornish used to protect

telomeres appeared to slow, stop, or even *reverse* tumor progression of cancer in a randomized controlled diet and lifestyle program of early-stage prostate cancer.[2088]

In response to Ornish's work showing that telomerase may be boosted and telomeres elongated with a plant-based diet and lifestyle, an accompanying editorial suggested that such studies might uncover mechanisms that can be exploited by Big Pharma since "adopting a healthy lifestyle is not always possible in today's world.…"[2089] Hopefully, if you're reading this book, you're motivated to take at least a step or two toward living more healthfully, which, in the case of telomere protection, may involve quitting smoking[2090] and reducing your intake of refined grains,[2091] soda,[2092] processed meat,[2093] and dairy,[2094] while increasing consumption of fruits,[2095] vegetables,[2096] and other antioxidant-rich foods.[2097]

To help boost this anti-aging pathway, on a daily basis, consider:

- following the recommendations in the Inflammation and Oxidation chapters
- eating a high-fiber diet centered around whole plant foods
- choosing to drink tea or coffee over soda or milk
- eating cruciferous vegetables
- supplementing with 800 to 2,000 IU of vitamin D_3 a day if your vitamin D blood level is under 20 ng/mL (50 nmol/L)

CONCLUSION

Most of the major advances made in our understanding of these aging pathways have occurred in the last twenty years, after I had already graduated from medical school; hence, much of the research I uncovered while working on this book has been eye-opening to me, too. The more we

learn about them, the more we discover their interconnectedness. Rather than existing as distinct entities, the aging pathways are intertwined in a complex circuitry: A boost in AMPK downregulates mTOR while upregulating autophagy and NAD^+ levels, which in turn raise the sirtuin activity that then lowers IGF-1 and feeds back on AMPK.[2098] It is therefore no surprise that they share many common triggers.

Here is a chart of interventions that may help slow aging by hacking each of the eleven aging pathways:

Interventions to Regulate the Eleven Aging Pathways

	Exercise	Smoking Cessation	Caloric Restriction	Protein Restriction	Decrease in Certain Animal Foods	Decrease in Certain Processed Foods	Increase in Certain Plant Foods
AMPK	✓		✓	✓	✓	✓	✓
Autophagy	✓		✓	✓	✓	✓	✓
Cellular Senescence	✓	✓	✓	✓		✓	✓
Epigenetics	✓	✓	✓	✓	✓		✓
Glycation	✓	✓	✓	✓	✓	✓	✓
IGF-1				✓	✓		
Inflammation	✓	✓	✓	✓	✓	✓	✓
mTOR		✓	✓	✓	✓		✓
Oxidation	✓	✓	✓	✓	✓	✓	✓
Sirtuins	✓	✓	✓	✓	✓	✓	✓
Telomeres	✓	✓		✓	✓	✓	✓

It is remarkable that, just since the turn of the century, research has uncovered a half dozen single compounds that can significantly extend the lifespan of mammals. Though there is elaborate cross-talk between many of the aging pathways, the drugs or supplements that extend life primarily target only one or another. Metformin, for example, can extend the lifespan of mice by boosting AMPK, and rapamycin by suppressing mTOR.[2099] When they're taken together, they appear to work synergistically—not only better than each taken alone but better than just adding together each of their independent effects.[2100] This may be a major advantage of diet and lifestyle approaches, as they can target multiple aging pathways at the same time.

II. The Optimal Anti-Aging Regimen

DIET

Worldwide each year, physical inactivity has potentially accounted for more than ten million years of healthy life lost, but what we eat may account for nearly twenty times that amount.[2101] According to the Global Burden of Disease Study, the most comprehensive and systematic analysis ever undertaken of the causes of death,[2102] the number one killer in the United States[2103] and on planet Earth is a bad diet.[2104] Unhealthy diets shave hundreds of millions of disability-free years off people's lives annually.[2105] That is why I've dedicated my life to the study of nutrition.

THE BEST FOODS

Funded by the Bill & Melinda Gates Foundation, the Global Burden of Disease Study pulled together nearly five hundred researchers from more than three hundred institutions in fifty countries and examined almost 100,000 data sources.[2106] Among the findings, they determined that the number one killer of Americans is the American diet, bumping tobacco down to number two. Smoking now only kills an estimated half million Americans every year, whereas our diet appears to kill many more.[2107]

Diet is considered to be the most important modifiable lifestyle factor when it comes to aging, healthspan, and lifespan.[2108] When studies find that "optimal nutrition," "healthy dietary patterns," or "higher diet quality" are associated with increased life expectancy, lower risk of all types of chronic disease,[2109] a higher quality of life,[2110] or more successful aging, what do they mean by *healthy diet*?[2111]

Tallying higher on each of the four major dietary quality scoring systems has been associated with an extended lifespan and lowering of heart disease and cancer mortality,[2112] and they share only four fundamental elements: more fruits, more vegetables, more whole grains, and more nuts and beans.[2113] They are all built on a common core of a plant-rich diet, whereas food patterns that are rich in refined and animal foods and poor in plant foods, referred to as the Western diet or westernized diets, are associated with higher risks.[2114]

In the Global Burden of Disease Study, four of the top five dietary risk factors for death were foods of which we're not eating enough. Eating more vegetables could potentially save about one and a half million lives around the world every year. Eating more nuts and seeds? Two million lives. More fruits? Close to two and a half million lives. And inadequate intake of whole grains may be responsible for the loss of three million lives annually. Salvation for millions may lie not in some new medicine or vaccine but in eating more whole, healthy plant foods.[2115] (Note that pickled vegetables, with added salt, and canned fruit, with added sugar, may do more harm than good.[2116])

THE WORST FOODS

When making critical life-or-death decisions, like what is best to feed ourselves and our families, how should we evaluate our choices? "Best available balance of evidence" is a phrase I often use, but what does it mean? What a single study says matters less than what the totality of peer-reviewed science has to say.

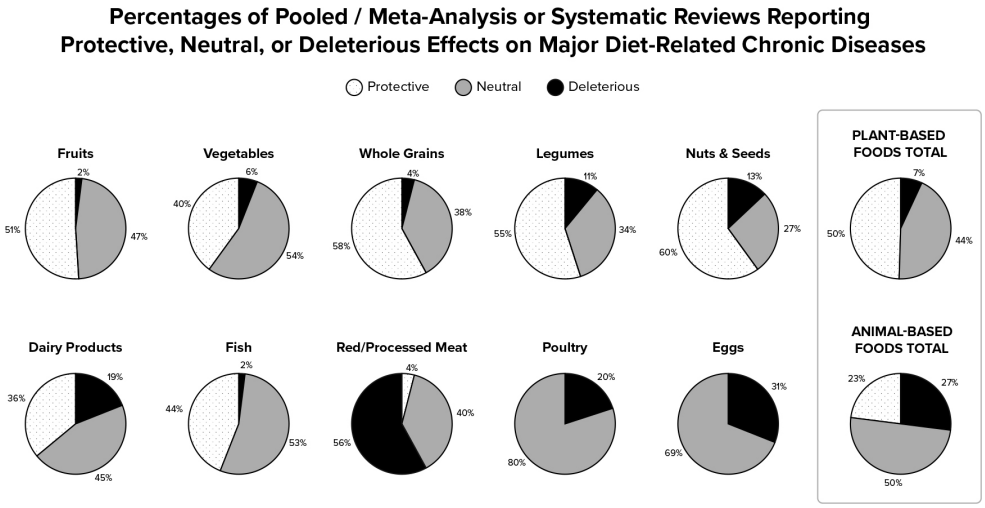
Individual studies can lead to headlines like this one from *Forbes*: "Study Finds No Link Between Secondhand Smoke and Cancer."[2117] To know if there's *really* no link between secondhand smoke and lung cancer, it would be better to look at a review or meta-analysis that compiles multiple studies together. The problem is that even these collated findings can sometimes contradict each other. For instance, some reviews say that breathing secondhand tobacco smoke is a cause of lung cancer,[2118] while others not only say that the effects are insignificant, and such talk may "foster irrational fears," but claim that you can even *directly* smoke four to

five cigarettes a day and not worry about it.[2119] (You can imagine who funded that one.)

Why do review articles on the health effects of passive smoking reach different conclusions? It may not surprise you that about 90 percent of reviews written by researchers affiliated with the tobacco industry said it was not harmful, while about 90 percent of independent reviews concluded that it was. In fact, reviews written by industry-affiliated authors had eighty-eight times the odds of concluding that secondhand smoke was harmless.[2120] It was all part of a deliberate corporate strategy to discredit the science by, in the words of the US Tobacco Institute's market research advisers, "developing and widely publicising … medical evidence that passive smoke is not harmful to the nonsmoker's health."[2121]

In that case, can't we just stick to independent reviews? If only we could figure out which are truly impartial. Industry-funded researchers have all sorts of sneaky ways of getting out of declaring conflicts of interest, so it's hard to follow the money. Regardless, even without knowing who funded what, the majority of reviews still concluded that secondhand smoke is harmful. So, just as a single study may not be as helpful as a compilation of studies, a single review may not be as useful as a compilation of reviews. Looking at a review of reviews can provide a better sense of where the best available balance of evidence may lie. For secondhand smoke, with 63 percent of reviews concluding that it is deleterious for your health, 37 percent concluding it's neutral, and none suggesting protective benefits, it's probably best not to inhale.[2122]

If only there were a review of reviews for different foods. There is! An exhaustive review of meta-analyses and systematic reviews on the associations between food and beverage groups and major diet-related chronic diseases was finally published. To offer the broadest takeaway, the researchers first split the food groups into plant-based and animal-based. The vast majority (94 percent) of reviews on whole plant foods show either protective or, at the very least, neutral effects, whereas most (77 percent) reviews of animal-based foods identified deleterious health effects or, at best, neutral ones.[2123] (Note that due to rounding of percentages, not all totals equal 100.)



The plant-based category was broken up into five groups—fruits, vegetables, whole grains, legumes, and nuts and seeds—and each consistently rated well, between 87 and 98 percent protective or at least neutral. The five groups of animal foods, however, varied considerably. As you can see in the figure, if it weren't for dairy and fish, the animal foods total would be rated almost entirely (98.7 percent) neutral or negative.[2124]

In the Beverages chapter, I'll talk in detail about the impacts of dairy industry funding, as well as substitution effects. For example, those who drink milk may be less likely to drink soda, a beverage even more universally condemned, so any protective benefits may be relative, arising not necessarily from what is consumed but rather from what is avoided. This may help explain the fish findings, too. After all, the prototypical choice is between chicken and fish, not chicken and chickpeas. Not a single review found a single protective effect of poultry consumption. As you will see in the figure here, even the soda industry received 14 percent protective effects, but chicken and eggs got big fat goose eggs—and that's even in spite of all the funding supplied by the National Chicken Council and the American Egg Board. Like the secondhand smoke reviews, perhaps a whitewash is sometimes all the best money can buy.

Like the calcium in dairy, there are some healthy components of fish, namely the long-chain omega-3 fatty acids EPA and DHA. Not necessarily for heart health, though. In the most extensive systematic assessment to date of effects of omega-3 fats on cardiovascular health, increasing intake of the fish oil fats has little or no effect on cardiovascular health. In fact, if

anything, only the *plant*-based omega-3s found in flaxseeds and walnuts might be protective.[2125] The long-chain omega-3s are important for brain health, though. Thankfully, just like there are best-of-both-worlds nondairy sources of calcium,[2126] there are pollutant-free (algae-based) sources of EPA and DHA.[2127]

The bottom line is that when it comes to the diet-related diseases the researchers considered, such as obesity, type 2 diabetes, mental health, bone health, cardiovascular disease, and cancers, even if you lump all the animal foods together, ignore any industry-funding effects, and simply take the existing body of evidence at face value, nine out of ten study compilations show that whole plant foods are, in the very least, *not bad*, whereas about eight out of ten of the reviews on animal products show them to be *not good*.[2128]

COMPARING BUTTS TO BURGERS

How not good are we talking? Meat consumption is associated with increased risk of more than twenty different diseases, but by how much?[2129] To compare different chronic risks to one another, researchers came up with the concept of a "microlife," defined as thirty minutes of your life expectancy. Someone in their twenties may have about fifty-seven years left of life on average. That's about 20,000 days, a half-million hours, or one million half hours. A microlife is one of the million half hours we may have left. Smoking two cigarettes or drinking two pints of beer, on average, would cost a thirty-year-old man one microlife, as would each day he is eleven pounds overweight.[2130] See how helpful this can be in terms of comparing risks? Drinking a pint of strong beer, for example, cuts your life expectancy as much as smoking one cigarette does. If it's unthinkable for you to have so little respect for your own health that you'd light up twice a day, then it should be just as unthinkable to be eleven pounds overweight.

Alternately, you can compare life-extending behaviors. For instance, eating at least five daily servings of fruits and veggies may add an average of four years onto your lifespan. That's about twice as beneficial as the estimate for exercising every day. But, even exercising for twenty minutes may add an hour (two microlives) to your life. So, for everyone who says they don't have time to work out, exercising potentially gives a three-to-one

return on investment. Give twenty minutes of your life to theoretically get sixty minutes of life. Beyond that, there's a bit of diminishing returns, but exercise an hour a day and you still may get back more time than you put in.[2131]

What about meat? A single burger is associated with losing a microlife. Is eating a burger worth thirty minutes of your life?[2132] So, in terms of lifespan, one burger appears to equal two cigarettes. If you wouldn't light up before and after lunch, maybe you should consider a bean burrito instead.

An egg salad sandwich wouldn't be a great choice either. In 2021, the largest prospective study ever done on eggs and mortality was published, the NIH-AARP Diet and Health Study, sponsored by the National Institutes of Health and the American Association of Retired Persons, which followed more than half a million people for an average of sixteen years. Each half-an-egg-a-day was associated with a 7 percent increase in all-cause mortality,[2133] which would make one egg on par with one burger for reducing lifespan.[2134]

BACON CAUSES CANCER

Processed meat is even worse. Imagine two people who are identical in every way, except one consumes around 50 g of processed meat a day—about one large sausage or hot dog, or a few strips of bacon—and the other doesn't have any. Eating just that single daily serving of processed meat is expected to take off around two years of life.[2135]

Alternately, you can frame it as a daily loss. Eating a sandwich with just two slices of deli meat like baloney or ham is expected to take off around one hour of your life.[2136] Do you ever feel like there are never enough hours in the day? Well, you may have effectively one less hour depending on what you pack for lunch.

Processed meat—bacon, deli meats, hot dogs, and the like—causes cancer. In 2015, the most prestigious cancer research institution in the world classified processed meat as a group 1 carcinogen—a substance known to cause cancer.[2137] Critics questioned putting processed meat in the same carcinogenic classification as asbestos, tobacco,[2138] and mustard gas,[2139] but the classifications relate to the strength of evidence that the agent causes

cancer or not, not how *much* cancer.[2140] All substances with group 1 classification are not equally dangerous.[2141] Even though they are both group 1 carcinogens, it's safer to eat a sandwich filled with pastrami than plutonium.

Just how dangerous is processed meat? The elevated risk of colorectal cancer is 18 percent for every 50 g of processed meat consumed a day, so if you have a sandwich with two small slices of baloney every day for lunch, you would increase your colorectal cancer risk by 18 percent. A half-pound pastrami on rye could bump it up by more like 80 percent.[2142] How does "18% increased cancer risk" compare to other risky behavior? When I testified before the 2020–2025 U.S. Dietary Guidelines Scientific Committee, I said, "We try not to smoke around our kids, so why would we send them to school with a baloney sandwich?" That may sound like a hyperbolic metaphor, but it isn't an exaggeration. According to the surgeon general, living with a smoker increases your risk of lung cancer by 15 percent.[2143] So, breathing in secondhand smoke day in and day out increases your risk of lung cancer almost to the same extent that eating a single daily serving of processed meat increases your risk of colorectal cancer.

Colorectal cancer is the second leading cause of cancer death, after lung cancer.[2144] So, if you don't smoke, colon and rectal cancer may be your greatest cancer nemesis. But, you can drop that risk by nearly a fifth just by cutting a serving of processed meat out of your daily diet.

BACK TO NATURE

Given that the healthiest foods tend to come from plants, it should come as no surprise that healthy plant-based diets are associated with a lower risk of premature death in the general population[2145] and, specifically, among older adults.[2146] For healthy aging,[2147] longevity,[2148] and delaying age-related diseases,[2149] recommended diets center around whole plant foods. Such a diet may cut the risk of Alzheimer's disease by more than half, for instance, and could save billions in healthcare costs.[2150] Just one additional serving of fruits or vegetables a day could potentially slash $5 billion off U.S. medical expenditures each year.[2151]

The benefits of plant-based eating likely derive from the dual action of increasing protective dietary factors like fiber while decreasing intake of

pathogenic (disease-causing) dietary factors like saturated fat.[2152] For eighteen years, the Baltimore Longitudinal Study of Aging followed individuals who had started out at an average age of around sixty. Researchers found that more fruits and vegetables, as well as less saturated fat, were associated with a lower likelihood of dying from heart disease within that period, but only the *combination* of elevated produce consumption and decreased saturated fat intake significantly reduced the risk of dying from all causes put together.[2153] This kind of diet is in line with what's natural based on our ancestral history.

For the millions of years before we began to mill grains, sharpen spears, or boil sugarcane, our entire physiology is presumed to have evolved in the context of eating what our great ape cousins did—leaves, stems, and shoots (that is, vegetables), seeds, nuts, and fruits.[2154] We started using tools during the Paleolithic period, which only goes back about two million years, but we and other great apes have been evolving since the Miocene era, which goes back about *twenty* million years.[2155] So, our body evolved on mostly plants for the first 90 percent of our hominoid existence.[2156] We were built to have nutrition from wild plant foods—especially fruits[2157]—continuously flowing throughout our system,[2158] with extremely low intake of cholesterol and saturated fat.[2159] Perhaps it's no wonder that our body thrives best on the diet we were designed to eat. Maybe we should get back to our (edible) roots.

NOT WORTH YOUR SALT

The skyrocketing intake of salt has been one of our most dramatic dietary changes. For most of human existence, we only got the pinch of salt that's naturally found in whole foods.[2160] Today, due primarily to processed foods, we're exposed to ten times more than our body was meant to handle,[2161] and it's having devastating health consequences.[2162]

I've mentioned four of the five deadliest dietary traps defined in the Global Burden of Disease Study—not eating enough whole grains, fruits, nuts and seeds, and vegetables—but the most fatal flaw about humanity's diet is not what we're getting too little of but what we're getting too much of. Excess sodium appears to be humanity's number one dietary risk factor for death.[2163]

Please see my High Blood Pressure chapter in *How Not to Die* for an in-depth review. The evidence that sodium raises blood pressure is clear, including double-blind, randomized trials dating back decades.[2164] Even just a single meal can do it. When subjects with normal blood pressure were given a bowl of soup containing the amount of salt typically found in an average American meal,[2165] their blood pressure climbed up over the next three hours compared to those who ate the same soup without any added salt.[2166] Having a "normal" salt intake can lead to a "normal" blood pressure, which can contribute to us dying from "normal" causes like heart attacks and strokes.

In the United States, most adults aged forty-five and older have high blood pressure, including nearly nine out of ten after age seventy-four,[2167] whereas there is no rise in blood pressure with age in no-salt cultures like the Amazon Yanomami, who eat a normal-for-the-human-species sodium intake. Not a single case of high blood pressure was found. Their average pressures start out about where all human infants do,[2168] at about 100 over 60, and stay that way throughout life.[2169]

A number of simple strategies can help you shake your salt habit.[2170] Don't cook with salt or add it to food. The food may taste a little bland when you first start skipping the salt, but, within just two to four weeks, the salt-taste receptors in your mouth become much more sensitive so the flavor of your food improves. After two weeks, you may actually *prefer* the taste of less salty food.[2171] Play around with pepper, lime, onions, basil, garlic, tomatoes, thyme, sweet peppers, parsley, celery, chili powder, lemon, rosemary, smoked paprika, curry, and coriander to find new, deeper flavors to enjoy.[2172] An editorial in the prestigious *New England Journal of Medicine* argued that "the individual approach is probably impractical" since 75 percent or so of salt exposure comes from manufactured foods,[2173] but that perversely presumes that processed foods are somehow preordained. We have control over the foods we buy, though some high-sodium foods may come as a surprise.

For example, the greatest contributor of sodium to the diet of twenty- to fifty-year-olds is chicken.[2174] The poultry industry routinely injects chicken carcasses with salt water to artificially inflate their weight, yet they can still be labeled as "100 percent natural." *Consumer Reports* found some chickens in grocery stores so pumped full of salt that they had a whopping

840 mg of sodium per serving. That could be more than a full day's worth of sodium in just a single chicken breast.[2175]

The now defunct Salt Institute reliably railed against public health recommendations to reduce sodium intake. In testimony before a congressional dietary guidelines committee, the presumption that healthier diets would cut healthcare costs was challenged. "Indeed," one processed food industry defender testified, "healthcare expenditures *increase* if the lifespan is prolonged." If people live longer because they eat more healthfully, it could be *more* expensive, it was argued, noting that "[i]f tobacco were banned the increase in the expected lifespan would simultaneously increase the cost of care of old people.…."[2176]

Tongue Scraping

As we age, our sense of taste may decline. As a consequence, older adults often oversalt their foods.[2177] An innovative way to counter this loss in salt sensitivity is cleaning the whitish-gray coating off your tongue that can block your taste pores.[2178] Check out my video see.nf/tonguecleaning on how tongue brushing or scraping has been shown to improve the ability to taste saltiness in both younger[2179] and older adults,[2180] effectively decreasing your taste for death.[2181]

POTASSIUM-BASED SALT SUBSTITUTES

Hypertension, or high blood pressure, is called the "silent and invisible killer" because it rarely causes symptoms but is one of the most powerful independent predictors of some of our leading causes of death.[2182] The American Heart Association's recommended limit is 1,500 mg of sodium a day.[2183] Care to guess what percentage of Americans exceed that? An incredible 99.4 percent.[2184] The overwhelmingly vast majority of U.S. adults consume too much sodium and, at the same time, too little potassium, a mineral that lowers blood pressure. (Less than 2 percent of U.S. adults

consume the recommended daily minimum intake of potassium.)[2185] This is even more striking when we compare our current intake with that of our ancestors, who consumed huge amounts of dietary potassium.[2186] We likely evolved getting more than 10,000 mg a day.[2187] The recommended daily minimum is to only get about half of that, yet most of us don't come anywhere close.

Put the two guidelines together, and sodium and potassium goals are currently met by less than 0.015 percent of the U.S. population.[2188] Close to 99.99 percent noncompliance, with only one in about seven thousand Americans meeting even the minimal recommendations. What about using potassium-based salt substitutes? Instead of flavoring our food with sodium chloride (salt), why not shake on some *potassium* chloride? A naturally occurring mineral salt, potassium chloride is obtained in the same way as regular sodium salt.[2189] Randomized controlled trials have found that simply swapping in some potassium chloride for regular salt can not only lead to significant reductions in blood pressure[2190] but can prevent hypertension in the first place and, most important, save lives. Even just switching to half potassium salt appeared to effectively make people more than a decade younger when it came to the risk of death.[2191] I review the studies in my video see.nf/ksalt.

It seems a little too good to be true. Why haven't more people embraced this salt substitute if it works so well and can taste just as good?[2192] Potassium chloride is "generally regarded as safe" by the Food and Drug Administration (FDA).[2193] The reason healthy people don't have to worry about getting too much potassium is that our kidneys just pee out the excess.[2194] However, people with known kidney disease, diabetes (since diabetes can lead to kidney damage), severe heart failure, or adrenal insufficiency, and those on medications that impair potassium excretion need to be careful.[2195] Older adults should ask their doctor to get their kidney function tested before starting salt substitutes. For more details on this, go to see.nf/ksaltsafety.

The only downside for healthy individuals is the taste. If you go 100 percent sodium-free and use straight potassium chloride, you may find that it has a bit of a bitter or metallic taste.[2196] Personally, I've found it depends on what I'm putting it on. Potassium chloride works perfectly on some foods, but, for me, makes others inedible. When I learned about the sodium

science and threw out my salt shakers for good, my palate totally changed within a few weeks and everything tasted fine without salt—except pesto. For some reason, pesto without any salt just never tasted like it used to, so I tried the potassium chloride salt substitute and it worked fabulously. I couldn't tell the difference at all, so I got the best of both worlds. Enthused, I decided to re-create a childhood favorite. I used to put a tiny sprinkle of salt on watermelon to make it even sweeter, a traditional southern culinary trick, but when I tried it with the potassium salt, I almost gagged!

WE ARE WHAT WE EAT

Not only is the American diet the leading killer of Americans, but, thanks in part to the obesity epidemic, our diet is also the leading cause of disability in the United States.[2197] So, what we eat is the number one determinant of how long we live and what most determines whether we will become disabled or not.

If our diet is the number one cause of death and disability,[2198] and if most deaths are preventable and related to nutrition,[2199] then, obviously, nutrition is the number one subject taught in medical school, right? It's the number one thing your doctor discusses with you at every single visit, right?

How can there be such a disconnect between the science and the practice of medicine?

Unfortunately, doctors suffer from a severe nutrition deficiency—in education. Most medical students are never taught about the impact that healthy nutrition can have on the course of illness, so they graduate without this powerful arsenal of knowledge.[2200] There are also institutional barriers, such as time constraints and lack of reimbursement. In general, doctors aren't paid for counseling their patients on how to better care for themselves.[2201] Of course, the drug companies also play a role in influencing medical education and practice. The director of the Institute for the Medical Humanities concluded an ethics journal article on Big Pharma's influence on medical education with these words: "I am not sure which is the more severe condemnation of our professionalism—our willingness to be bought; or our willingness to rationalize and deny, to make it seem as if we are not being bought."[2202] Ask your physician when they were last wined and dined by Big Broccoli.

It's like smoking in the 1950s. Even then, we already had decades of science linking cigarettes with cancer, but it was largely ignored in part because smoking was *normal*.[2203] The average per capita cigarette consumption was 4,000 cigarettes a year[2204]—meaning the average American smoked half a pack a day. Back then, the American Medical Association reassured everyone that "smoking in moderation" was just fine.[2205] After all, most doctors themselves smoked cigarettes.[2206] There was the same disconnect between the science and medical practice: overwhelming evidence versus the inertia of personal habit.

It took more than twenty-five years,[2207] 7,000 studies, and the deaths of countless smokers before the first surgeon general's report against smoking was published in the 1960s.[2208] You'd think maybe after the first *6,000* studies they could have given people a little heads-up or something, but no. Big Tobacco was a powerful industry, and today's alcohol, meat, sugar, dairy, salt, egg, and processed food industries are using the same tobacco industry tactics to try to twist the science and confuse the public.[2209]

Big Food is a trillion-dollar industry with thousands of trade associations spending hundreds of millions of dollars on lobbying our legislative leaders. After the processed food sector, which is led by PepsiCo, the next top three food lobbies are sugar, meat, and dairy.[2210] (Dairy is the only food trade group with a budget exceeding $100 million.[2211]) This tells us a lot about the American diet. *Cui bono?* Follow the money.

Today, only 1 to 2 percent of doctors smoke,[2212,2213] but most continue to eat foods that are contributing to our epidemics of dietary disease.[2214] Until the system changes, we have to take personal responsibility for our own health and our family's. We can't wait until society catches up to the science again, because it's a matter of life and death.

Master of Your Own Destiny

Longevity experts consider nutrition likely "the most important intervention for the promotion of health and the prevention of the great majority of age-associated chronic diseases."[2215] Changing from a typical diet to a more optimized one starting at age twenty would be expected to

increase the lifespan of women by about eleven years and men by thirteen. The largest lifespan gains would be made by eating more legumes, then whole grains and nuts, and cutting down on meat, then sugary beverages like soda. And it's never too late. At age sixty, starting to eat more healthfully could mean eight or nine more years of life. Even starting as late as age eighty could add years to your life.[2216] Changing your health destiny can start with your very next meal.

BEVERAGES

You may have heard that the human body is 70 percent water. That's true of newborn babies, but as Aristotle said, "Old age is dry and cold." Older individuals may only be about 50 percent water.[2217] With smaller fluid reserves, a diminished sensation of thirst,[2218] and waning ability of the kidneys to concentrate urine, the elderly are particularly susceptible to dehydration,[2219] especially when taking laxatives or diuretic drugs.[2220] What's the best way to remain hydrated?

CONSENSUS PANEL RECOMMENDATIONS

There are scads of dietary guidelines for what we should eat, but what about for what we should drink? A Beverage Guidance Panel was assembled to bring together leading health experts like Dr. Walter Willett, then chair of the Harvard University School of Public Health's nutrition department. The panel's task was to provide recommendations on the nutritional risks and benefits, as well as the relative healthfulness, of different beverage categories, ranked on a six-tier scale from best to worst.

Unsurprisingly, soda came in last. Beer and whole milk were grouped together as two other beverages to be avoided. They cited concerns about the association between milk and prostate cancer and aggressive ovarian cancer, arising from well-documented effects on circulating levels of insulin-like growth factor 1, which I covered in the IGF-1 chapter. Tied as

the second *healthiest* beverages were tea and coffee, preferably without sweetener or creamer. And the top-ranked drink? Water.[2221]

HELL OR HIGH WATER?

In the *How Not to Die* beverages chapter, I trace the origins and bust the myth of the "drink at least eight glasses of water a day" recommendation, as well as discuss the difficulty of establishing cause and effect in the multitude of studies correlating low water intake with a wide range of diseases.[2222] I review all the studies on water consumption and mortality in see.nf/h2olongevity. Basically, three studies showed a mortality benefit,[2223,2224,2225] whereas four did not,[2226,2227,2228,2229] so the connection remains murky.

SO HOW MUCH WATER SHOULD YOU DRINK?

Based on snapshot-in-time blood sampling, between 20 to 30 percent of older adults are dehydrated at any one time.[2230] Such individuals are at increased risk for heart attacks, pneumonia, and blood clots, which results in a doubling of the odds of becoming disabled over the subsequent four years.[2231] How do you know if you're dehydrated? Younger folks can just check the color of their urine. The gold standard for hydration—or rather, the *pale* gold standard—is the color of straw, a light yellow. A darker yellow, amber, or brownish coloring has been validated as a way to detect dehydration in athletes,[2232] pregnant and lactating women,[2233] and the broader general population,[2234] but it does not appear to work in older adults.[2235] Not one of sixty-seven different assessments for dehydration—including urine color or volume, or having a dry mouth or feeling thirsty—appeared consistently useful in determining hydration status for adults older than sixty-five. Only the combination of experiencing fatigue and missing some drinks between meals appeared predictive for impending dehydration in older men and women.[2236]

Based on the best evidence to date, authorities from the World Health Organization and the U.S. Institute of Medicine recommend eight to eleven cups of water a day for women and ten to fifteen daily cups for men.[2237] This includes water from all sources, though, not only beverages. We get

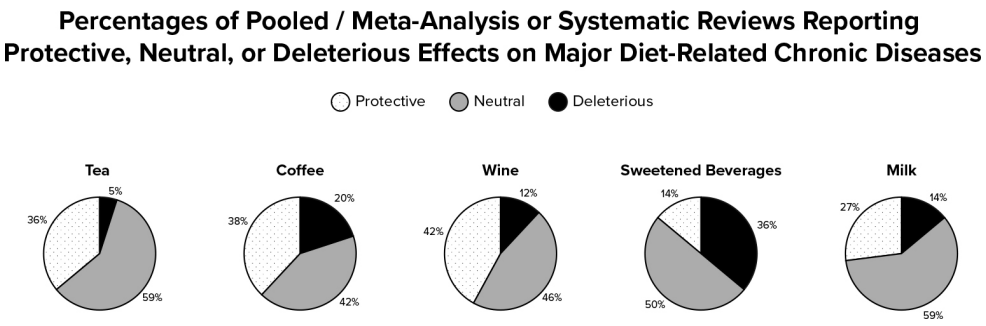
about four cups of water from the food we eat and what our body produces on its own[2238] (for example, when our body burns fat), so the guidelines translate roughly into a daily recommendation for drinking four to seven cups of water for women and six to eleven cups for men, assuming moderate physical activity at moderate ambient temperatures.[2239] The kidney capacity of older individuals tends to be limited to approximately three to four cups per hour, though, so under normal circumstances, avoid exceeding that limit.[2240] Drinking more than the recommended amount could critically dilute the electrolytes in your brain.[2241]

What Kind of Water Should We Drink?

Many are distrustful of the safety of tap water,[2242] but bottled water may not be any cleaner than water right out of the faucet.[2243] How much is that saying, though? Drinking water safety isn't only about preventing waterborne diseases. In fact, our fight against microbial contaminants introduced a new kind of contamination in our water—in the form of disinfection by-products caused by the chlorination of drinking water. In my video see.nf/water, I quantify the potential bladder cancer risks and review the efficacy of two fridge filters (Whirlpool and GE) and three pour-through pitchers (Brita, PUR, and ZeroWater) to remove contaminants.

BEVERAGES RANKED FROM BEST TO WORST

Other than water, what are the best beverages? Below is another graphic from the exhaustive study that encompassed hundreds of pooled meta-analyses and systematic reviews cataloging protective, neutral, or deleterious associations with diet-related chronic diseases.[2244]



As expected, sweetened drinks like soda ranked most deleterious, but 14 percent of reviews reported *protective* effects of soft drinks. How is that possible? Most were references to cross-sectional studies like one that found that eighth-grade girls who drank more soda were skinnier than girls who drank less.[2245] That was just a snapshot in time, though. What do you think is more likely? Heavier girls weighed more because they drank less soda, or they drank less sugary soda because they were heavier? Soda abstention may be a *consequence* of obesity rather than a cause, yet it gets marked down as protective because less of the beverage was associated with less of the disease.

Study design flaws may also account for findings about wine. The review of reviews was published in 2014, before the revolution in our understanding that the purported health benefits from "moderate" alcohol intake may have just been a mirage.[2246] (See here for a discussion of the systematic error of misclassifying former drinkers as if they had been lifelong abstainers.[2247]) Sometimes, however, there are unexplainable associations. For instance, one of the soft drink studies found that increased soda consumption was associated with *lower* risk of certain types of esophageal cancers. Let me guess. Was the review funded by Coca-Cola? Yes, the review was funded by Coca-Cola.[2248] Do similar conflicts of interest help explain the "protective" milk studies? Were those funded by the National Dairy Council? In fact, even *more* conflicts of interest have been found among milk studies than soda studies, and exclusively industry-funded studies of all such beverages are four to eight times more likely to be favorable to the financial interests of the sponsor.[2249]

Funding bias aside, though, there could be legitimate reasons for the protective effects associated with dairy milk consumption. After all, those who drink more milk may drink less soda, which is an even more

deleterious beverage, so the milk drinkers may come out ahead. But it may be more than just relative benefits. Even something as universally condemned as tobacco isn't universally bad. More than forty studies have consistently found a protective association with Parkinson's, thanks to the effects of nicotine on the brain.[2250] Even secondhand smoke may be protective.[2251] Of course, you'd still want to avoid it. Tobacco may decrease the risk of Parkinson's, but its use increases the risk of stroke, an even deadlier brain disease, not to mention lung cancer and heart disease, which have killed millions of Americans since the first surgeon general's report against smoking was released.[2252]

Thankfully, by eating certain nicotine-containing vegetables, we may be able to get some of the benefits without the risks[2253] (see.nf/nightshades), and the same concept may be true of dairy. The consumption of milk is associated with increased risk of prostate cancer,[2254] which has led to recommendations suggesting that men may want to cut down or minimize their intake,[2255] but dairy consumption is also associated with *decreased* colorectal cancer risk.[2256] This protection appears to be a calcium effect.[2257] Thankfully, we may be able to get the best of both worlds by eating high-calcium plant foods, such as greens and beans.[2258]

I explored dairy in greater detail (see here) and covered the benefits of coffee (see here). However, based on the bird's-eye view provided in the figure here, every cup of coffee may be a lost opportunity to drink something even healthier, like a cup of tea.

The Healthiest Type of Milk

There is a constellation of new choices in the dairy case these days, with milks made from everything from almonds to oats,[2259] so much so that major dairy corporations are going out of business.[2260] Of all the options, soymilk is probably the healthiest. See here and watch my video see.nf/milks. All plant-based milks lack lactose, which is a benefit worthy of emphasis.[2261]

The majority of adult humans are lactose intolerant, meaning they have trouble digesting dairy milk. Throughout

childhood, the enzyme we have that breaks down the milk sugar lactose begins to decline in most of us around the world, which makes sense since milk is for babies.[2262] Why would we need to be able to digest it after we've weaned from the breast? So, when drinking milk, most people on the planet can experience symptoms like bloating, abdominal pain, intestinal gas, and watery stool, or even nausea and vomiting.[2263]

The estimated global prevalence of lactose malabsorption is more than two out of three people. In the United States, it's more like one out of three,[2264] but 95 percent of Asians, 60 to 80 percent of African Americans and Ashkenazi Jews, 80 to 100 percent of American Indians, and 50 to 80 percent of Hispanics have trouble digesting milk. It's those of northern European origin who are more likely able to handle it throughout adulthood.[2265] So, saying that everyone should drink milk seems like an example of racial bias in federal nutrition policy.[2266] Spoiler alert: Not everyone in the United States is of northern European descent.

For reasons like these, Canada removed dairy as a separate food group in its national dietary guidance. After a thorough review, the Canadian dietary guidelines and food guide were updated and rereleased in 2019. Emphasis was placed on the importance of consuming more plant-based foods.[2267] The reduced emphasis on dairy products and the increased focus on plant-based foods were based in part on the removal of industry-funded studies from consideration by the Canadian experts.[2268] What a concept! Many leading medical journals already refuse to accept papers funded by Big Tobacco.[2269] It's time to consider extending this to all commercial entities intent on skewing the science to place profits over public health.

GREEN AND BLACK TEAS

Around the world, we consume literally billions of cups of tea every day.[2270] Even just the purified green tea compound EGCG (epigallocatechin gallate), purported to be the main active ingredient, can extend the lifespan of *C. elegans* under stressful conditions,[2271] as well as delay the deaths of rats by eight to twelve weeks (extending average lifespan by about 14 percent).[2272] Although we are still waiting for long-term randomized controlled clinical trials, an umbrella review of ninety-six meta-analyses of observational studies found that increasing tea consumption by three cups a day may decrease the risk of premature death from all causes put together by 24 percent,[2273] which is the equivalent of adding about two years onto your lifespan.[2274] This applies to both green tea and black tea, though green tea may have a slight edge.[2275] (Details in see.nf/greenblack, where I also review some rather disappointing data on the use of matcha to treat Alzheimer's disease.)

Don't Add Milk

The apparent mortality benefit of tea is thought to derive largely from cardiovascular protection, as both green and black tea consumption can significantly improve arterial function within hours of ingestion.[2276] This may only work, however, if you skip the milk. In 2007, we first learned that the addition of dairy milk "completely blunted the effects of tea" when it came to improving artery function.[2277] In 2018, we then learned it was even worse than that. Men and women were randomized to a month of drinking their black tea black, a month of drinking black tea with milk, or a month just drinking plain hot water. The straight black tea group experienced a significant improvement in artery function, as expected. The tea-with-milk group, however, not only did worse than the plain tea group but they had significantly impaired artery function compared to the plain hot water group. So, the milk didn't just neutralize the

beneficial effects; drinking tea with milk was worse than not drinking any tea at all.[2278] Milk also appears to undercut the benefits of berries,[2279] chocolate,[2280] and coffee.[2281] (See here.)

RED TEA

Black, green, and white teas all come from the same evergreen plant (*Camellia sinensis*), whereas herbal tea involves pouring water over any plant other than the tea plant. I covered hibiscus tea in the AMPK chapter and chamomile in the Glycation and Inflammation chapters. Rooibos, also known as red tea or redbush tea, is another notable herbal tea that may have anti-aging properties. It has been shown to increase the lifespan of *C. elegans* by as much as 23 percent under conditions of oxidative stress, presumed to be due to its antioxidant properties.[2282] In a head-to-head comparison of fifteen herbal teas, rooibos came in second (after dandelion) in a measure of in vitro antioxidant power.[2283]

I review optimal tea brewing techniques in see.nf/red. Red tea should ideally be simmered[2284] for at least five minutes.[2285] Brew black tea for four minutes,[2286] green tea for three minutes at 85°C (185°F),[2287] and white tea for seven minutes at 98°C (208°F).[2288] Surprisingly, bags are better than bulk, because the leaves in tea bags are much more finely chopped, allowing for greater extraction.[2289]

SODA

Now that we've covered some of the best beverages, what about some of the worst?

A typical can of soda contains about nine spoonsful of sugar. Given that sugar-sweetened beverages are the single largest source of added sugar in the American diet,[2290] it should come as no surprise that their consumption is associated with dying prematurely. Each additional daily can of soda's worth of sugar appears to increase all-cause mortality by about 8 percent,[2291] likely due to associated increased risks of heart disease[2292] and diabetes.[2293]

Diet soda is still associated with increased mortality risk, but at an 8 percent elevated risk from *two* servings a day, it's only half as bad as

regular soda.[2294] Now, those who drink a lot of artificially sweetened soda also tend to be more likely to be overweight or obese. Rather than diet soda leading to health problems, maybe health problems led people to drink diet drinks—so-called reverse causation. However, all the analyses took weight into account and the mortality risk remained significant. This was the case even when studies didn't count the first few years of follow-up in order to eliminate those who may have switched to diet soda to address health problems right before their deaths. An editorial accompanying a Women's Health Initiative study linking diet soda and stroke risk summed it up in its title: "Artificial Sweeteners, Real Risks."[2295] Read my Not Sweet Nothings section in *How Not to Die* for details on how artificial sweeteners may mess with our microbiomes and metabolism.

ALCOHOL

When I sat down to research this section, I was surprised to find a paper titled "Tequila … Extends Life Span in *Drosophila melanogaster*"—fruit flies.[2296] I imagined hordes of buzzed little flies buzzing around, but, alas, no. "Tequila" is just the name a creative fly geneticist gave to some fruit fly gene.[2297] So, tequila (the spirit) may not help fruit flies live longer, but what about us?

Alcohol use appears to be the seventh leading risk factor for death globally, leading to millions of people dying annually[2298] and resulting in three times more healthy years of life lost than all illicit drug use combined.[2299] About half of all alcohol-related deaths may be due to sudden causes, such as vehicular accidents; the other half are slower, with alcoholic liver disease the leading cause.[2300] Over the last twenty or so years in the United States, there has been about a 50 percent increase in alcoholism rates, annual alcohol-related emergency room visits,[2301] and alcohol-related death rates.[2302]

There is agreement that binge drinking, drinking during pregnancy, and heavy drinking are bad for you, but what about "moderate" drinking? In terms of aging pathways, even one to two drinks' worth of alcohol[2303] can decrease NAD^+ levels and sirtuin activity in human brain cells in vitro.[2304] On the other hand, alcohol is detoxified in our body into acetic acid,[2305] which activates AMPK.[2306] Unfortunately, before alcohol is fully converted

into acetic acid, a toxic intermediate, *acetaldehyde*, is formed, and it's a known carcinogen. This may be the reason alcohol is believed to increase the risk of several different cancers,[2307] including breast and colorectal—even among light drinkers who only have up to one alcoholic beverage a day.[2308]

Yes, alcohol may be an addictive, intoxicating carcinogen that can cause birth defects,[2309] but what role might it play when it comes to our heart? Could it help reduce heart disease risk, particularly since alcohol consumption has clearly been shown to raise HDL, the supposed "good" cholesterol?[2310] Sadly, HDL is no longer considered to be protective, based in part on Mendelian randomization studies that found that having a high HDL throughout your entire life doesn't appear to help lower heart disease risk[2311] (whereas a lifelong reduction of bad LDL cholesterol, thanks to nothing more than luck-of-the-draw genetics, does indeed decrease risk).[2312]

So, the boost alcohol gives our HDL may not matter, and if you look at early signs of atherosclerosis, like the thickening of the wall of the carotid arteries in your neck, those who completely abstain from alcohol seem to be at the lowest risk.[2313] We see the same with coronary calcium scores, where, in general, the lower the alcohol consumption, the lower the risk.[2314] Alcohol bumps up our blood pressure a bit, too, which would be expected to raise, not lower, our cardiac risk.[2315] So, where did we get this idea that moderate alcohol consumption was good for us? From the famous *J curve*.[2316]

WHAT HAPPENED TO THE J CURVE?

In large populations followed over time, in general, the more people drink, the higher their risk of dying prematurely. However, those with the lowest risk, those who tend to live the longest, are not the abstainers who drink zero alcohol but those who imbibe a few drinks a week.[2317] The mortality-versus-drinking curve, therefore, resembles the letter *J* rather than being a straight diagonal line up like a slash.

I describe our evolution in understanding in my video see.nf/jcurve, but, long story short, this appears to be an artifact of the "sick quitter effect" arising from the systematic misclassification of former drinkers as lifelong abstainers.[2318] It's the same reason studies can find higher mortality rates

among those who quit smoking compared to those who continue to smoke. It's not that abstention led to poor health but rather that poor health led to abstention.[2319]

When researchers went back and controlled for the error of misclassifying former drinkers as if they were lifelong abstainers, the J-shaped curve disappeared. In other words, the death-versus-alcohol relationship became more consistent with a linear dose response, meaning more alcohol, more death, with no protection at low levels of consumption.[2320]

MENDELIAN RANDOMIZATION

Confusing nondrinkers with those who quit drinking alcohol in response to ill health raises the issue of reverse causation. We've also seen this with studies that purport to show that those who tend to sit around and watch more TV have worse health. Is more TV leading to illness, or is illness leading to more TV?[2321] That's one of the reasons why, if you look at the "hierarchy of evidence," interventional trials with control groups tend to offer better evidence than observational studies of populations, which can suffer from both reverse causation[2322] and confounding factors. For example, as a group, light drinkers may be more likely to sip their glass of wine with a salad than a cheeseburger, so maybe that's why the wine appeared protective.[2323] Moderate alcohol intake is also strongly linked to higher socioeconomic status, which itself is a predictor of a longer life.[2324] But sometimes it's hard to do randomized controlled trials. It would be impractical—not to mention unethical—to randomize people to smoke a pack a day for a few decades, for instance, so you sometimes have to base public health decisions on observational data.[2325] We now have an extra tool, though: "nature's clinical trial," Mendelian randomization.[2326,2327]

In cases where randomized controlled trials are not feasible or practical, Mendelian randomization can provide reliable cause-and-effect evidence.[2328] As I mentioned, the unraveling of HDL as a protective factor was based in part on Mendelian randomization studies, where people who were randomly assigned higher lifelong HDL levels genetically from birth didn't go on to suffer less heart disease.[2329] Instead of researchers doing it, the randomization was accomplished through chance meeting of that exact

sperm and egg. Is there any way to study people who were randomly assigned since conception to not drink as much? Remarkably, yes.[2330]

Alcohol is detoxified in the liver to carbon dioxide and water by two enzymes, but, in the process, acetaldehyde is produced, the toxic intermediate metabolite I mentioned earlier, which can cause unpleasant nausea and flushing sensations. So, if you are born with either a slow variant of acetaldehyde-removing enzyme or a superfast variant of the acetaldehyde-forming enzyme, acetaldehyde can build up, making drinking alcohol a relatively unpleasant experience throughout your life. In this way, some people are born less likely to drink. Do they have an *increased* risk of heart disease like the original J-curve observational studies would suggest? No, they have a *reduced* risk of heart disease. This suggests that even light to moderate drinkers may benefit from reducing their consumption.[2331]

ACTUAL RANDOMIZATION

Some observational studies continue to find a J-shaped curve even after controlling for confounding factors and reverse causation,[2332] and it's possible that the genetic variants related to reduced alcohol intake have independent protective effects, which would undermine the strength of the Mendelian randomization data.[2333] We are left with a raging, bitter controversy in the medical literature,[2334] with some scientists continuing to push the J-shaped curve narrative[2335] (particularly those who've received industry funding[2336]) and others dismissing any purported benefits as outdated wishful thinking[2337] or alcohol industry spin-doctoring.[2338] What we need, concluded the National Institutes of Health (NIH), is a randomized controlled trial to put the question to rest once and for all. Enter the Moderate Alcohol and Cardiovascular Health Trial.[2339]

Thousands of volunteers aged fifty and older at high risk for cardiovascular disease were to be recruited. Half would be randomized to abstain from alcohol for the next six years, and the other half told to drink one serving of alcohol every day. Which group would suffer more heart attacks, strokes, diabetes, or death?[2340] There was a problem, though. NIH researchers, in violation of federal policy,[2341] solicited the likes of Anheuser-Busch and Heineken to pick up most of the $100 million tab for the study. The lead investigator and NIH officials swore that the industry funders

would play no role in influencing the study design, but, predictably, we learned otherwise from an exposé published in *The New York Times* based in part on emails obtained through the Freedom of Information Act.[2342] Critics questioned, for example, why study endpoints didn't include cancer and heart failure, known alcohol-associated harms.[2343] The trial was summarily canceled after an internal investigation revealed, in the words of the then NIH director, that "[s]o many lines have been crossed that people were frankly shocked."[2344] The Moderate Alcohol and Cardiovascular Health Trial was no more.

Even if unbiased funders could be found, at this point it may not be ethical to randomize people to drink alcohol.[2345] Soon after the original trial was conceived, the Global Burden of Disease Study published the most comprehensive estimate on the overall effect of alcohol use,[2346] summarizing evidence from nearly seven hundred data sources.[2347] The conclusion, echoed by the World Health Organization[2348] and the World Heart Federation,[2349] was clear and unambiguous: "The safest level of drinking is none."[2350]

WINE

Even wine? A twenty-year study of older adults found that any apparent mortality benefit of moderate wine drinking seemed to disappear when variables such as sociodemographic differences were taken into account.[2351] I cover the not-so-paradoxical French Paradox in see.nf/resveratrol. The grape polyphenols in red wine have antioxidant properties when tested in isolation,[2352] but alcohol acts as a pro-oxidant, increasing markers of oxidative damage within hours of consumption.[2353] So, which wins out when you drink them together in wine? In the short term, the antioxidant power of red wine is enough to counteract the LDL oxidation of a bacon cheeseburger from McDonald's,[2354] but, over a period of weeks, consumption of wine, whether white or red, does not reduce markers of oxidative damage—unless the alcohol is removed.[2355] Even when sugar is added to the de-alcoholized wine to make the calorie count similar to regular red wine, a month of red wine consumption results in significantly more oxidative damage compared to consumption of the same wine with the alcohol removed.[2356] A comparable benefit-blunting effect was found

with blood pressure: Nonalcoholic red wine lowers blood pressure, but regular red wine does not.[2357] So, might de-alcoholized wine offer the best of both worlds?

If you eat cheese and crackers with red wine, you can end up with five times more triglycerides (fat) in your blood six hours later than if you had drunk water with them instead. We know it's the alcohol, because the same wine with the alcohol removed doesn't cause the same spilling of fat into the bloodstream.[2358] Red wine and white wine also cause inflammation—a 56 percent (red) or 62 percent (white) rise in IL-6 levels over the six hours after consumption, which is significantly higher than drinking a sugary beverage (11 percent).[2359] Although the effects of wine on artery function are mixed,[2360,2361,2362,2363] the fatty, inflammatory reaction could explain the results of the largest such study that showed that de-alcoholized wine improved artery function, while regular red wine made things worse.[2364]

FRUIT JUICE

What about just drinking grape juice? Rats given access to Concord (purple) grape juice improved their cognitive performance compared to sugar water[2365] and white grape juice,[2366] but what about people? For a review of the available data, see my video see.nf/grapejuice. The bottom line is that the evidence is underwhelming, despite the spin Welch's-funded researchers tried to put on it.[2367]

My first instinct was to unreservedly recommend whole fruit over juice, given that fruit consumption is associated with living longer while fruit *juice* consumption is not,[2368] but the Kame Project study I profile in see.nf/juicybrain inspired me to dig a little deeper. It was a cohort study in which those drinking fruit or vegetable juice three or more times a week seemed significantly less likely to develop Alzheimer's disease compared to less than once a week.[2369] It's possible that the high-pressure extraction methods used to make commercial juices draw out more brain-protecting polyphenols from the pulp, peel, or seeds,[2370] but as I document in the video, the interventional studies to assess at least short-term cognitive effects are largely disappointing.

In see.nf/juicyarteries, I review studies on fruit juice and cardiometabolic health. The bottom line: If you are going to drink juice,

cloudy apple juice is preferable to clear,[2371] red (blood) orange juice is preferable to regular,[2372] and drink juice with meals rather than between them.[2373] Pomegranate juice got its own video for its disappointing data (see.nf/pomjuice). Salt-free tomato may be the healthiest juice. Tomato juice can lower LDL cholesterol[2374] and improve artery function,[2375] helping to explain why higher tomato product intake has been associated with a significantly lower risk of premature death, even after controlling for other diet and lifestyle factors.[2376]

Fruit juice can carry a similar load of sugar to soft drinks but, unlike soda, is not associated with a shortened lifespan.[2377] This is presumed to be because of the presence of polyphenols,[2378] natural compounds in fruit thought to account for many of the benefits associated with fruit consumption. Fruit juice may be better than soda, but it is not as good as whole fruit for living to a ripe old age. Consumption of whole fruit is associated with significantly lower risk of premature death—11 percent lower risk with just a single serving a day compared to none.[2379]

WHAT DO CENTENARIANS EAT?

To study the lifestyle habits of our eldest elders, you first have to establish how old people really are. Centenarian science has long been plagued by rampant age exaggeration.[2380] According to an editor of *The Guinness Book of World Records*, "No single subject is more obscured by vanity, deceit, falsehood and deliberate fraud than the extremes of human longevity."[2381] It's a tale as old as time, dating back at least to biblical times with boasts of patriarch Methuselah living to 969.[2382]

One of the most famous blows to the credibility of studies of long-lived individuals was a 1973 cover story in *National Geographic*. It fascinated readers with its description of extraordinary rates of centenarians in the Caucasus region of the former Soviet Union, the Hunza Valley in Pakistan, and the village of Vilcabamba in Ecuador. Upon closer inspection, however, not only had none of the "centenarians" actually reached a hundred years of age, but none of the "nonagenarians" had even made it to ninety. Given the age exaggeration, whether for social status or to promote local tourism, the

average "100-year-old" turned out to be eighty-four.[2383] The debacle was eventually recognized and acknowledged by the physician-author,[2384] but not before casting a shadow over the entire field.[2385]

Despite this inauspicious start, there are now more than a dozen major ongoing studies of actual centenarians that can offer insight into their exceptional longevity.[2386]

BLUE ZONES FOOD GUIDELINES

Careful checks have systematically invalidated nearly all claims of allegedly long-living populations as being inflated or undocumented, so we're left with five authenticated "blue zones"[2387]—longevity hot spots named for the color a demographer used in a global "heat map" of mortality.[2388] The five generally accepted blue zones are the Nicoya Peninsula in Costa Rica, the island of Sardinia in Italy, Ikaria in Greece, Okinawa in Japan, and Loma Linda, California, in the United States.[2389] These are the regions with high concentrations (up to ten times the U.S. average) of centenarians[2390] and other seniors who have reached old age in good health and remain active members of the community.[2391]

They share a number of lifestyle characteristics, including low smoking rates, daily moderate physical activity, and social engagement, and, nutrition-wise, they all center their diets around whole plant foods.[2392] Dan Buettner, the founder of the Blue Zones organization, along with a team of researchers, distilled findings from more than 150 dietary surveys from the world's longest-living people to create a set of ten food guidelines. The foundation of the Blue Zones Food Guidelines is "See that your diet is 95%–100% plant-based." Vegetables are emphasized (especially leafy greens), along with fruits, whole grains, and legumes. The list ends with "Retreat from meat," noting that blue zones centenarians only eat about 2 oz or less of meat about five times per month.[2393] Traditionally, people of the blue zones eat at least 90 percent plant-based.[2394] And the population with perhaps the highest life expectancy in the world, the Loma Linda Adventist vegetarians, don't eat any meat at all.[2395]

The Blue Zones Food Guidelines

To follow in the footsteps of people with the longest lifespans and healthspans, consider following the official Blue Zones Food Guidelines[2396]:

1. "95–100% plant-based"
2. "Go wholly whole" (reduce intake of processed foods)
3. "Daily dose of beans" (one to two servings of beans, chickpeas, lentils, or split peas)
4. "Drink mostly water"
5. "Snack on nuts"
6. "Go easy on fish"
7. "Eliminate eggs"
8. "Slash sugar"
9. "Reduce dairy"
10. "Retreat from meat"

LEGUME LONGEVITY

The emphasis on minimally processed plant foods is consistent with studies on long-lived persons that date back more than a century,[2397] including ones on modern-day centenarians.[2398,2399,2400,2401] Of all plants, beans appear most often as the dietary cornerstones for centenarians, as well as for individuals throughout each of the blue zones.[2402,2403]

A paper titled "Legumes: The Most Important Dietary Predictor of Survival in Older People of Different Ethnicities" detailed a study in which researchers looked at five cohorts in Australia, Greece, Japan, and Sweden. Of the food factors investigated, the only one found to have a consistent and significant association with a longer lifespan across the board was intake of legumes, whether it was Swedes eating their brown beans and peas, Japanese eating their soy, or Greeks eating their lentils, chickpeas, and white beans. The researchers identified an 8 percent reduction in risk of death for every 20 g increase in legumes consumed each day,[2404] which is just about two tablespoons' worth.[2405] This is consistent with data from the

Global Burden of Disease Study that found that of all foods considered, the largest lifespan gains would be expected from eating more legumes.[2406]

In the United States, for more than a decade now, the federal government has aimed to encourage Americans to build healthy meals with its MyPlate campaign using the visual guide of a dinner plate. Vegetables and whole grains should fill most of it, and fruits and proteins should take up the remaining space. Legumes are given special treatment, straddling both the protein and vegetable groups.[2407]

Legumes are loaded with protein, zinc, and iron, as you'd expect from other protein sources like meat, while being naturally low in sodium and saturated fat, and they have zero cholesterol. But they are also chock-full of nutrients concentrated in the vegetable kingdom, like fiber, potassium, and folate, making beans among the best bargains for nutrition density per dollar.[2408]

In Costa Rica, researchers found that those who ate beans every day had a 38 percent lower risk of heart attack compared to non-bean-eaters, and this was after controlling for saturated fat and cholesterol, so it apparently wasn't just because they were eating beans instead of beef.[2409] Randomized controlled trials dating back as far as sixty years[2410] have proven that cardiovascular risk factors, such as cholesterol levels, blood pressure, and markers of inflammation, can be lowered simply by eating legumes, typically about a cup a day for four to eight weeks.[2411] One study found that two daily servings of beans, chickpeas, lentils, and split peas cut cholesterol levels so much that many participants, aged fifty and older, fell out of the range that typically results in the prescribing of cholesterol-lowering statin drugs.[2412] Dozens of randomized controlled trials have found that soy can lower cholesterol[2413] and blood pressure,[2414] but compilations of more than sixty randomized controlled trials have found that other beans also lower cholesterol,[2415] as well as benefit blood sugars and lower insulin levels.[2416] Despite this overwhelming evidence, surveys suggest that most American consumers are unaware of these benefits.[2417] They don't know beans!

In some of the studies, beans replaced meat, which makes it impossible to tease out the effects of boosting beans versus moderating meat.[2418,2419] Nevertheless, even interventional studies that pit beans, chickpeas, or lentils head-to-head against other healthy foods, like whole grains, show benefits in terms of cholesterol, blood pressure, and weight loss.[2420] One particularly

instructive study added chickpeas to the diet for five months, which resulted in average total cholesterol dropping from levels typical in the Western world (around 206 mg/dL) down to about 160,[2421] which is close to the target of under 150.[2422] Interestingly, the study was performed in northern India, so the participants' cholesterol levels actually started out at an average of 123. Only after packing their diets with saturated fat were they able to *raise* their cholesterol to typical American levels in order to test out the effects of chickpeas. So, while it would be better to just eat healthier in the first place, why not eat healthier with hummus—a diet low in saturated fat with lots of legumes?

REVERSING ARTERIAL DISEASE WITH BEANS

Legumes are not interchangeable, though. A Venn diagram of the phytochemicals found in lentils, beans, soybeans, and chickpeas shared only a 7 percent overlap, so we should strive for variety.[2423] That's easier than ever before given the variety of ways to enjoy them. Have you had pasta made from legumes? Substituting just 40 percent of the semolina flour in pasta for sprouted chickpea flour can significantly improve artery function within hours of consumption, compared to regular pasta.[2424]

Are the improvements we get from eating legumes enough to actually reverse arterial disease? Researchers looked at legumes and peripheral artery disease, which results from the buildup of atherosclerotic plaque that causes decreased blood flow down to the legs. The way the disease is diagnosed and monitored is with the ankle-brachial index—the ratio of blood pressure at the ankle compared to the arm. If the index falls below 0.9, it indicates a clog in the flow of blood to your lower body. Researchers had twenty-six individuals with peripheral artery disease eat a half serving of beans, split peas, chickpeas, and lentils every day for a week, followed by one full daily serving for the next seven weeks. After just two months of eating beans, the ankle-brachial index of four participants jumped up into the normal range. The researchers concluded that "a legume-rich diet can elicit major improvements in arterial function."[2425] The study didn't have a control group, but peripheral artery disease patients tend to get worse, not better.

If you know my personal story, you may remember that my grandmother suffered from this disease. It was one of the reasons she was confined in a wheelchair waiting to die—until her life was saved by evidence-based nutrition. That's what inspired me to dedicate my life to do for everyone's family what Nathan Pritikin did for mine.

SLOW YOUR BEATING HEART

In chemistry and physics, there are constants—physical quantities thought to be both universal and unchanging. Biology, though, was considered too complex and too messy to be governed by simple, natural laws. In 1997, however, a theoretical high-energy physicist from Los Alamos joined two biologists to describe universal scaling laws that appear to apply across the board.[2426] For example, the number of heartbeats per lifetime is remarkably similar whether you're a hamster or a whale. Mice, who typically live for less than two years, have a heart rate of about five hundred to six hundred beats a minute—up to ten beats a second. In contrast, the heart of a Galápagos tortoise beats a hundred times more slowly, but they live about a hundred times longer.[2427]

There's such a remarkable consistency in the number of heartbeats mammals get in their lifetimes that a group of researchers started to ask a provocative question: *Can human life be extended by reducing the average heart rate?* For further exploration, see my video see.nf/pulse, but the bottom line does seem to be that a faster heart rate may lead to a faster death rate.[2428] We should shoot for an average resting heart rate of no more than sixty-five beats per minute, so a goal of about one heartbeat per second to beat the clock.[2429] Every ten-beats-per-minute increase in resting heart rate above about sixty-five beats per minute is associated with a 10 to 20 percent increase in the risk of premature death.[2430] Men with no apparent evidence of heart disease who have a pulse of ninety beats per minute had five times higher risk of sudden cardiac death compared to those in the apparent safety zone of less than sixty beats per minute.[2431] Resting heart rates around ninety beats per minute increase heart disease risk at a level similar to smoking.[2432] Thankfully, as I explore in my follow-up video see.nf/heartrate, we can slow our pulse with pulses.

Diabetics randomized to eat around a cup of beans, chickpeas, or lentils each day for three months not only experienced a significant improvement in blood sugar control but a drop of three beats per minute in average resting heart rate[2433]—as much as a twelve-week aerobic conditioning program of cycling, stair-climbing, and running on a treadmill.[2434]

All these short-term bean benefits appear to translate out in population studies to a decreased risk of heart disease, high blood pressure, obesity,[2435] and, most important, premature death.[2436] A single daily serving of beans, chickpeas, or lentils may be associated with a 10 percent decrease in all-cause mortality risk.[2437] The fact that the lowered risk was found even in studies that controlled for meat consumption suggests it's not just a substitution effect.[2438]

Beans, Beans, They're Good for Your Heart

Sadly, only one in twenty-five Americans approaches even a single serving of legumes a day.[2439] Why aren't more people clamoring for beans? For some, it's fear of flatulence.[2440] Beans have been christened the musical fruit, but could that just be a lot of hot air? A randomized controlled crossover study put it to the test, and the researchers concluded that "[p]eople's concerns about excessive flatulence from eating beans may be exaggerated."[2441]

Study participants were randomized in separate trials to eat pinto beans, black-eyed peas, or vegetarian baked (navy) beans. During the first week, 35 percent reported increased flatulence, but that fell to 15 percent by week three, 5 percent by week five, and only 3 percent by week eight.[2442] It turns out that much of beans' bad rap may have grown out of short-term studies in the 1960s that did not account for our body's ability to adapt.[2443]

In the long term, most people bulking up on high-fiber foods do not appear to have significantly increased problems with gas.[2444] When we first start incorporating more beans and foods higher in fiber in our diet, though,

"[a] little bit of extra flatulence," reads the *Harvard Health Letter*, "could be an indication that you're eating the way you should!"[2445] The indigestible sugars in beans that make it down to our colon may even function as prebiotics to feed our good bacteria and make for a healthier colon.[2446]

Some of it may also just be in our heads. Preconceived notions about beans may be so strong that just the *expectation* of flatulence from eating them may influence our perceptions of having gas.[2447] Studies show that when we eat a product that's labeled as having an ingredient that may cause intestinal distress, it causes more intestinal distress—whether or not it actually contains that ingredient.[2448] In other words, the mere belief that we're eating something that causes us to pass more gas can cause us to perceive that we're passing more gas. Don't let the fartcebo effect prevent you from eating more healthfully.

THE HISPANIC PARADOX

The benefits of beans may help explain the so-called Hispanic Paradox. Hispanic Americans—despite socioeconomic patterns that generally lead to worse health outcomes like disparities in education and healthcare, as well as higher rates of poverty[2449]—tend to live longer than other ethnic groups in the United States.[2450] With lower risks of nine out of the top fifteen causes of death, notably including less heart disease and cancer, Hispanics have a 24 percent lower risk of premature death.[2451] For more on this topic, check out my video see.nf/hispanic.

In a study of Mexican Americans, researchers found that, compared with other groups, they not only eat more beans but also more fruits and vegetables,[2452] including tomatoes and corn.[2453] (These healthy dietary patterns extend down to Central America, too. After rice and beans, corn tortillas are the most commonly eaten food in the Costa Rican blue zone.[2454]) They also eat more chili peppers.[2455] Can chilies spice up longevity?

PEPPER UPPER

The spicy compound in hot chilis can extend the lifespan of fruit flies,[2456] but what about us? See my twin videos see.nf/spicy and see.nf/peppers for details, but basically, four out of four studies on spicy food and mortality found a significant decrease in death risk from any cause in people who ate more spicy chilis.[2457,2458,2459,2460] I wrote an entire section on chili peppers in my Fat Burners chapter in *How Not to Diet*, detailing how cayenne pepper can counteract the metabolic slowing that accompanies weight loss and, as a bonus, accelerate fat burning,[2461] but the apparent longevity benefits of chili pepper consumption remain after controlling for body mass index.[2462]

There are at least a half dozen no-salt-added hot sauces on the market. Even Tabasco is pretty low in sodium, though only the original flavor. (Spin-off flavors have up to five times more salt.) You can also add straight powdered chilis. I have different ones in shaker bottles for every occasion, including powdered adobo chilis, chipotle peppers, and crushed Thai bird's eye chilis for when I really want to kick up the heat.

THE MEDITERRANEAN DIET

Two of the world's blue zones, Ikaria and Sardinia, are located in the Mediterranean, home to the Mediterranean diet, about which the "father of preventive cardiology,"[2463] Jeremiah Stamler, once wrote, "Uncritical laudatory coverage is the common parlance."[2464] Does it live up to the hype?

CLUB MED

More than a dozen countries border the Mediterranean Sea. The Mediterranean diet refers to what was being eaten on the Greek isle of Crete more than a half century ago. After World War II, the government of Greece asked the Rockefeller Foundation to come in and assess postwar conditions.[2465] Impressed by the low rates of heart disease in the region, nutrition scientist Ancel Keys—after whom "K" rations, the prepackaged daily rations for American soldiers, were named—initiated his famous Seven Countries Study, the longitudinal study of diet and cardiovascular

disease in men in seven regions of the world. The researchers, led by Keys, found that the rate of fatal heart disease in men on Crete was twenty times lower than in the United States and they also had the lowest cancer rates and fewest deaths overall.[2466] What were they eating? Their diets were more than 90 percent plant-based, which may explain why coronary heart disease was such a rarity there.[2467] A rarity, that is, except in a small class of wealthy residents whose diet differed from that of the general population—they ate meat every day instead of once every week or two.[2468]

The main characteristic of the Mediterranean diet is that it is mainly plant-based,[2469] low in the meat and dairy Dr. Keys considered to be the "major villains in the diet" due to their saturated fat content. Unfortunately, few really eat the traditional Mediterranean diet anymore, even in the Mediterranean. The prevalence of coronary heart disease skyrocketed by an order of magnitude within a few decades in Crete, blamed on the increased consumption of meat and cheese at the expense of plant foods.[2470]

So, even though many talk about the Mediterranean diet, few actually follow it.[2471] People often think of pizza or spaghetti with meatballs when they think of Italian food. While "Italian restaurants brag about the healthy Mediterranean diet," Dr. Keys wrote, "they serve a travesty of it."[2472] If no one's really eating this way anymore, how do you study it?

Researchers came up with a variety of scoring systems to assess adherence to the Mediterranean diet to see if people who are eating more Mediterranean-ish do better. You get higher points the more plant foods you eat, and, effectively, points are deducted with just a single daily serving of meat or dairy. So, it's no surprise those with relatively higher scores on the scale have a lower risk of heart disease, cancer, and death overall.[2473] The Mediterranean diet is protective compared to the standard American diet—no question—but any diet rich in whole plant foods and low in animal-fat consumption could be expected to confer protection against many of our leading killers.[2474]

Based on dozens of prospective cohort studies, the more adherent people are to a Mediterranean-style diet, the lower their risk of premature death.[2475] The difference in average age at death between those eating the least and the most Mediterranean may be on the order of two years.[2476] Mediterranean diet adherence is also associated with healthier aging[2477] and a lower risk of frailty.[2478] What about the diet is particularly protective?

A meta-analysis of studies on the most protective components of the Mediterranean diet found that, food-wise, the mortality benefit appeared to be derived from greater fruit and vegetable intake and reduced meat consumption. In contrast, eating fish, the only animal-based food promoted in the Mediterranean diet, did not seem to matter.[2479]

Criticism of Dr. Keys has become sort of a cottage industry as of late[2480] by "bloggers, commercial book writers or journalists in quest of sensationalism or financial gain," but the scientific record is clear that such invective constitutes "either investigative incompetence or plain dishonesty at the edge of scientific fraud."[2481] Ever the consummate scientist, Dr. Keys, when asked on his hundredth birthday whether he thought his diet contributed to his long life, answered, "Very likely, but no proof."[2482]

Dr. Stamler said as much about the Mediterranean diet on the occasion of *his* hundredth birthday.[2483] The centenarian remained committed to his pioneering research[2484] even after turning one hundred. We lost him on January 26, 2022, at the age of 102.[2485]

OLIVE OIL

Olive oil is commonly used in the Mediterranean to dress vegetables and salads, beans and other legumes, so its consumption can be an indicator of a more traditional, healthier diet.[2486] To better tease out the effects of the olive oil itself, then, it would be more instructive to study olive oil consumption in a non-Mediterranean country. Harvard researchers took up the mantle and dug through decades of data from nearly 100,000 women and men in the Nurses' Health Study and the Health Professionals Follow-Up Study. They found that replacing about a teaspoon of butter, mayonnaise, margarine, or dairy fat with about a teaspoon of olive oil every day would be expected to lower heart disease risk by 5 to 7 percent. So, olive oil is better than butterfat, but no significant difference was found between olive oil and other oils.[2487]

What about the study often cited by advocates of low-fat eating that implicated not only saturated fat but also monounsaturated and polyunsaturated fats in the appearance of new atherosclerotic lesions in coronary arteries?[2488] I discuss the critical flaw in their reasoning in my video see.nf/mediterranean. The fact is that olive oil is better for us than

butter when it comes to LDL cholesterol level[2489] or artery function,[2490] though olive oil[2491]—even extra-virgin olive oil—can still acutely impair our arterial function,[2492] even to an extent similar to fast food and cheesecake.[2493]

Palm oil, soybean oil,[2494] and sunflower oil[2495] can also impede our arteries' ability to relax and dilate normally, which does not occur after we eat Green Light sources of fat, like nuts[2496] or avocados.[2497] (In *How Not to Die*, I defined Green Light fare as foods of plant origin to which nothing bad has been added and from which nothing good has been taken away.) Whole plant foods may even be able to mediate oil's ill effects. Consuming that extra-virgin olive oil with a salad, for example, as part of a balsamic vinaigrette, was shown to neutralize the artery-impairing effects of the oil. Unfortunately, because of the typical brining process, the whole-food source of olive oil—olives—is too high in sodium for regular consumption. Just twelve jumbo olives could take up nearly half of your recommended sodium limit for a whole day.[2498]

How might we see if major sources of plant fats, like olive oil or nuts, help or hurt in terms of hard endpoints, such as diagnosed disease? Ideally, we would run a multiyear, randomized study with thousands of participants and have one-third eat more nuts, another third eat more olive oil, and the final third essentially do nothing, then see who does better. And that's exactly what researchers ended up doing.

PREDIMED

In the PREDIMED study, from the Spanish *PREvención con DIeta MEDiterránea*, an impressive 7,447 people at high risk for heart attack were randomized into three groups.[2499] For all the nitty-gritty, watch my video see.nf/predimed, but basically, though it wasn't the researchers' original intention, it turned out that the participants were effectively randomized for about four years to either (1) switch from consuming about three tablespoons of half-virgin olive oil a day to four tablespoons of all-virgin olive oil, (2) go from eating about half an ounce of nuts a day to a whole ounce, or (3) pretty much continue their regular diet.[2500] The results were published in *The New England Journal of Medicine*.[2501]

Wasn't PREDIMED Retracted?

The PREDIMED trial is one of the most influential randomized dietary studies ever performed,[2502] yet, in 2018, the original paper was withdrawn due to irregularities in randomization procedures at two of the eleven sites where the study had been run.[2503] Household members were invited to participate and were allocated to the same diet. This makes sense to avoid assigning different diets to people in the same household, but the whole point of *randomized* controlled trials is to assign diets *randomly*. Thankfully, this only applied to about 6 percent of study participants. And, when the data were corrected, reanalyzed, and republished, the original results and conclusions remained the same.[2504,2505]

What happened to the amount of plaque in the arteries of the PREDIMED subjects over time? There was significant worsening of carotid artery thickening and plaque in the essentially-no-dietary-changes control group, and no significant changes in the olive oil group, but those in the added-nuts group showed a significant reversal in thickening and an arrest in plaque progression. The researchers concluded that nuts may not only be a preferable source of fat compared to olive oil but they may "delay the progression of atherosclerosis, the harbinger of future cardiovascular events," such as having a stroke.[2506] And that's exactly what seemed to happen. Those who switched to extra-virgin olive oil had about one-third fewer strokes, and those who added more nuts to their daily regimen cut their stroke risk nearly in half, dropping their ten-year risk of stroke from about 6 percent down to 3 percent.[2507] If nuts worked as well in the general population, that would mean the potential for preventing more than 85,000 strokes a year in the United States alone.[2508] Imagine that: About ten strokes an hour around the clock potentially prevented simply by adding about five almonds, walnuts, and hazelnuts to one's daily diet.

With no significant differences in meat and dairy intake across the study groups, there were no significant differences in saturated fat or cholesterol intake, so no surprise that there were no significant differences in their blood cholesterol levels or the number of subsequent heart attacks.[2509] In the five or so years the study ran, there were thirty-seven heart attacks in the olive oil group, thirty-one in the nut group, and thirty-eight in the essentially-no-dietary-changes control group. Similarly, there weren't significant differences among the three groups in the number of subjects dying from a heart attack, stroke, or from any cause. Those in the olive oil group and especially the nut group, however, did have significantly fewer strokes.

Regardless of which group the PREDIMED participants were in, those consuming a greater amount of nuts each day had a significantly lower overall risk of dying prematurely.[2510] Those consuming more olive oil or extra-virgin olive oil, what I consider Red and Yellow Light sources of fat, respectively, failed to get any survival benefit.[2511] This is consistent with Ancel Keys's take on olive oil. The so-called father of the Mediterranean diet considered its benefit to be more as a means of replacing animal fats like lard and butter.[2512]

VIRGIN TERRITORY

PREDIMED's bottom line for olive oil is that if you are going to use it, use extra-virgin. Extra-virgin olive oil is produced by simply pressing the oil out of olive paste, whereas "pure," "regular," and "light" olive oils are further refined, which results in a greater loss of the original olive phytonutrients. Those randomized to swap out their refined olive oil for extra-virgin not only had fewer strokes but they ended up with better global cognition[2513] and significantly less atrial fibrillation,[2514] peripheral artery disease,[2515] diabetes,[2516] diabetic vision loss,[2517] mild cognitive impairment,[2518] and breast cancer.[2519] This may be because extra-virgin olive oil doesn't appear to induce the same spike in inflammatory markers that regular (refined) olive oil does[2520] and may also be better at reducing oxidative stress,[2521] presumably due to the greater extraction of anti-inflammatory and antioxidant olive compounds.[2522] There are also

potentially toxic chemical contaminants formed when refined oils are deodorized, such as 3-MCPD (3-monochloropropane-1,2-diol).[2523]

Regular olive oil has up to twenty-five times the 3-MCPD levels as extra-virgin olive oil.[2524] In fact, that's how you can discriminate among the various processing grades of olive oil. If a bottle of oil is labeled as "extra-virgin olive oil" but it contains a lot of 3-MCPD, then it must have been diluted with some refined olive oil. The ease of adulteration, the difficulty of detection, the economic drivers, and the lack of control measures all contribute to the susceptibility of extra-virgin olive oil to fraud.[2525] How widespread is the problem?

Of eighty-eight bottles of olive oil purchased in California that were *labeled* as extra-virgin, only thirty-three were found to be authentic when tested.[2526] Does it make a difference if you stick to the top-selling imported brands, such as Colavita, Star, Bertolli, Filippo Berio, and Pompeian? No. A whopping 73 percent of those extra-virgin olive oil samples failed. Only about one in four appeared to be entirely genuine, and not a single top-selling brand had even half of their samples pass the test.[2527] So, even if you want to switch to extra-virgin olive oil, it may not be so easy.

THE LYON DIET HEART STUDY

Our understanding of the Mediterranean diet, in general, is limited by the quantity and quality of the existing body of scientific research. Ironically, there may be more meta-analyses or systematic reviews of Mediterranean diet studies for cardiovascular health than there are actual original studies.[2528] And, most such reviews have been found to be faulty, using inappropriate statistical methods to combine study findings.[2529]

It also doesn't help that different studies used up to thirty-four different Mediterranean diet scoring systems.[2530] For example, some gave points for eating potatoes or subtracted them for consuming eggs, while others did neither.[2531] Most scored olive oil and nuts as characteristic components of a Mediterranean diet, which led to accusations that the research was in some way a conspiracy of vested Big Fat commercial interests; however, the vast majority of studies on the Mediterranean diet have been publicly, not privately, funded.[2532] That doesn't prevent questionable work from being published, of course. Consider the "Indo-Mediterranean Trial," which has

been largely discredited as being, at the very least, "severely flawed"[2533] due to evidence that the researcher had "either fabricated or falsified data."[2534] When challenged to produce the original research records, he declined, responding they had been "eaten by termites."[2535]

One famous Mediterranean diet trial that has stood the test of time is the Lyon Diet Heart Study.[2536] About six hundred individuals who had each already had a heart attack were randomized into two groups. The control group received no dietary advice, apart from whatever their doctors had told them, while the experimental group was instructed to eat more of a Mediterranean-type diet, supplemented with a canola oil–based spread that would give them the plant-based omega-3s they would have normally gotten from foods like walnuts if they had actually lived on a Greek isle in the 1950s.[2537] Canola oil also lowers LDL cholesterol better than olive oil does,[2538] and, unlike olive oil, canola has been shown not to acutely impair artery function.[2539]

The Mediterranean group did end up taking some of the dietary advice to heart. They ate more breads and fruits, and less butter, cream, processed meat, and meat in general. Other than that, though, no significant changes in diet were reported in terms of wine, olive oil, or fish consumption. So, they ate less saturated fat and cholesterol and increased their intake of plant-based omega-3s, but otherwise didn't make any other great changes.[2540] Even so, at the end of about four years, forty-four individuals from the control group had a second heart attack, some fatal, but only fourteen suffered another attack in the group that had changed their diet.[2541] The Mediterranean diet group went from having a 4 percent chance of having a heart attack each year down to just 1 percent.

A cynic might say that while there was less death and disease, the Mediterranean diet continued to feed their heart disease, so much so that fourteen of them suffered new heart attacks while on the diet. There was a remarkable drop in heart attack rates, but, yes, ideally we would want a diet that could stop or even reverse heart disease.

Dr. Caldwell Esselstyn and his colleagues at the Cleveland Clinic published a case series of 198 consecutive patients with serious cardiovascular disease who had been counseled to switch to a diet composed entirely of whole plant foods.[2542] Of the 198 participants, 177 stuck to the diet, whereas the other 21 fell off the wagon. This set up a

natural experiment. What happened to the noncompliant 21? In about the next four years, more than half suffered a fatal heart attack or needed angioplasty or a heart transplant. In contrast, of the 177 participants who stuck to the plant-based diet over the same time period, just a single patient had a major event as a result of worsening cardiovascular disease—0.6 percent versus 62 percent in the noncompliant group, an apparent hundredfold drop in risk.

Dr. Esselstyn's was not a randomized trial, so it can't be directly compared to the Lyon study. It also included very determined patients. Not everyone is willing to dramatically change their diets, even if it may literally be a matter of life and death. In that case, rather than doing nothing, eating a more Mediterranean-type diet may cut the risk of subsequent heart attacks by about two-thirds. Cutting 99 percent of risk would be better if Esselstyn's results were replicated in a controlled trial, but even a 70 percent drop in risk could save countless lives every year. "Although the results may seem simply too good to be true," wrote the director of the Harvard Program in Cardiovascular Epidemiology, "given the 20-fold or more differences in coronary rates across countries, such results for dietary change are entirely plausible."[2543]

THE OKINAWAN DIET

The U.S. Dietary Guidelines recommend that we choose meals or snacks that are high in nutrients but lower in calories to reduce the risk of chronic disease.[2544] By this measure, the healthiest foods on the planet—that is, the most nutrient dense—are vegetables, which contain the most nutrient bang for our caloric buck. What would happen if a population centered their entire diet around vegetables, like the Okinawa Japanese did traditionally? They would end up having among the longest lives in the world.[2545] (And yes, a validation study did confirm true centenarian prevalence.[2546])

The traditional Okinawan diet revolved around steamed sweet potatoes, simmered or steamed leafy greens and other vegetables, and soy, mostly in the form of tofu and miso soup.[2547] There's a common misconception that their traditional diet included a substantial contribution from fish or other

meat,[2548] but if you look at their actual dietary intake, that doesn't seem to be the case. The United States occupied the island of Okinawa from 1945 until 1972, when it was returned to Japan's control, so we have data on what Okinawans were eating in the U.S. National Archives.[2549]

How did the traditional diets of more than 2,000 Okinawans break down? Only 1 percent of their diet was fish, less than 1 percent was other meats, and less than 1 percent was dairy and eggs, so it was more than 96 percent plants, with few processed foods.[2550]

A greater than 90 percent whole food, plant-based diet would be highly anti-inflammatory and highly antioxidant.[2551] When the level of oxidized fat was measured within centenarian Okinawans' systems, there was compelling evidence of less free radical damage,[2552] despite similar antioxidant enzyme activity.[2553] What may be making the difference are all the extra antioxidants they were getting from their mostly vegetable diet. Okinawa has had six to twelve times fewer heart disease deaths per capita than the United States, two to three times fewer colon cancer deaths, seven times fewer prostate cancer deaths, and five and a half times lower risk of dying from breast cancer.[2554]

Their traditional cuisine was not only whole food, plant-based and not only centered around vegetables, but one vegetable in particular, purple and orange sweet potatoes.[2555]

SWEET SPOT

Sweet potatoes have formed the bulk of the traditional Okinawan diet since the 1600s, accounting for 69 percent of daily caloric intake.[2556] This may be one of the secrets to Okinawan longevity. A study in China of 14,000 men and women followed for an average of fourteen years found that those who ate sweet potatoes had a significantly lower chance of dying prematurely (by 18 percent), even after controlling for a wide range of dietary, lifestyle, and socioeconomic factors.[2557] And no wonder. The Center for Science in the Public Interest ranked sweet potatoes as one of the healthiest foods on the planet[2558]—and, one day, perhaps even off the planet, as NASA has chosen the sweet potato for space missions.[2559]

Sweet potatoes are also a nutritional bang-for-your-buck bargain. A study of dozens of different vegetables found that some of the healthiest

foods, like dark green leafy vegetables, may also be the most affordable, with the single highest nutrient-rich food score per dollar going to sweet potatoes.[2560] And purple sweet potatoes may be the best of the best.

Anthocyanins are a class of natural purple, red, and blue pigments in such plants as berries, grapes, plums, red cabbage, and red onions. The anthocyanins in red rice, black rice, and purple wheat have been shown to have anti-aging and/or life-extending properties in model organisms such as yeast, worms,[2561,2562] flies,[2563] and mice.[2564] Of all the plant pigments tested in a head-to-head comparison, the purple in purple sweet potato beat out the pigments in grape skins, elderberry, red cabbage, and purple corn for antioxidant activity.[2565]

Even regular sweet potatoes have been shown to exert both acute and chronic anti-inflammatory effects in rats,[2566] but the purple sweet potato pigment goes above and beyond with its ability to reverse or repair the damage resulting from inflammatory[2567] or oxidative[2568] insults to the brain in mice. From an anti-aging perspective, the color compounds in purple sweet potatoes also reduce inflammation, amplify autophagy, and delay senescence in human blood vessel cells in a petri dish,[2569] as well as activate sirtuin activity by boosting levels of NAD^+ in mice.[2570]

The autophagy activation is thought to underlie the 15 percent life extension in fruit flies fed a purple sweet potato extract, which is accompanied by a decrease in age-related gut leakiness, suggesting a healthspan benefit as well. Researchers fed fruit flies blue food coloring, which stains the digestive tract of young flies but seeps out of the leaky intestines in older flies, turning their entire bodies blue. It's called—no joke—the "Smurf assay." The number of "Smurf flies" was significantly lower in the purple sweet potato extract group.[2571]

Have any of these benefits been validated in clinical studies? Purple sweet potato anthocyanins have been shown to have prebiotic effects in human fecal culture studies, enhancing the proliferation of the good bacteria *Bifidobacterium* and *Lactobacillus*, along with a boost in protective short-chain fatty acids.[2572] That may help explain the anti-inflammatory effects found in the only double-blind placebo-controlled study I could locate. Men with inflamed livers were randomized to drink a cup a day of a purple sweet potato smoothie and experienced a significant improvement in their liver

function tests within eight weeks, compared to those given a placebo beverage with a similar look and taste.[2573]

SOY SALUBRITY

The primary source of concentrated protein in the traditional Okinawan diet is soy. Eating an average of 3 oz of soy products a day—as mentioned, mostly in the form of tofu and miso—they had among the highest soy intake in the world.[2574] Might this also play a role in their longevity? How well does the science support the old Chinese saying "vegetables and tofu keep you healthy"?[2575]

For more than two decades, soy's ability to protect against heart disease has been recognized as one of the rare "FDA-approved" food-label health claims. Randomized controlled trials have shown that soy consumption can result in small decreases in cardiovascular risk factors, such as blood pressure[2576] and cholesterol.[2577] A billion-dollar industry, Big Soy has a lot of money to fund research touting the benefits of its bean. But, is soy really the top bean or are other legumes just as powerful? It turns out that *non*-soy beans, including lentils, lima beans, navy beans, and pinto beans, can drop bad cholesterol levels as effectively as soy protein—an eight-point drop in LDL cholesterol,[2578] compared to five (mg/dL) for soy.[2579] But, if you separate out the studies, natural soy products, such as soymilk and soybeans, really do seem to pull ahead, leading to an average eleven-point drop in LDL versus three points for highly processed soy extracts.[2580]

This appears to translate into reduced risk of heart disease and stroke,[2581] along with lower risk of death from both cancer and cardiovascular diseases. However, a significant reduction in all-cause mortality was only apparent in higher-quality studies, such as those with at least 10,000 participants. Compared to the lowest category of intake, the highest intake of isoflavones (the natural phytoestrogens in soy) was associated with a lower risk of premature death across the board. "Our findings," conclude the meta-analysis researchers, "may support the current recommendations to increase intake of soy for greater longevity."[2582]

What About the Sodium in Miso?

The process of producing miso involves adding a lot of salt, so it was always something I avoided—until I actually looked into it. Read my Beans chapter in *How Not to Die* for the details, but it turns out miso is not associated with the stomach cancer risk attributed to the salt in other fermented foods, like kimchi,[2583] nor the risk of developing high blood pressure.[2584] But what if you are already hypertensive?

Men and women with stage 1 or 2 hypertension (blood pressures ranging from 130 to 159 over 85 to 99) were randomized to eat either two bowls a day of miso soup, which alone exceeded the recommended daily sodium limit, or soybeans with no added salt for two months. Surprisingly, the miso group ended up with *lower* nighttime blood pressures than the soybean control group. The mechanism is unclear.[2585] Given a slight drop in body weight in the miso group, the miso may have a diuretic effect by increasing sodium excretion through the kidneys, a phenomenon that has been demonstrated in rats.[2586,2587] Regardless, miso is now a staple of my kitchen and cookbooks.

WAKAME THIS WAY

Sea vegetables are another important component of the Okinawan diet.[2588] Sea veggies have been associated with significantly lower all-cause mortality among those in Japan eating seaweed five or more times a week compared to fewer than three times.[2589] In addition to being an excellent source of trace minerals, sea vegetables have multiple unique components, including the olive-brown carotenoid *fucoxanthin*[2590] and a type of fiber called *porphyran* found to have lifespan-extending effects in model organisms.[2591]

One way seaweed could contribute to longevity is by lowering high blood pressure. With seaweed consumption associated with better blood pressure control in both children[2592] and adults,[2593] researchers decided to

put it to the test and found significantly lower blood pressures from 6 (but not 4) g a day for a month of dried wakame (the sea vegetable in seaweed salad). A nice thing about whole food, plant-based interventions is that you sometimes get *good* side effects. In this study, one participant who had been suffering from gastritis saw their stomach inflammation resolved, and another's chronic headaches disappeared.[2594] Seaweed salad may also boost immune function, as I note in the Preserving Your Immune System chapter.

The Healthiest Source of Iodine

One advantage of cow milk over plant milk is iodine,[2595] a mineral essential for thyroid function. Dairy milk supplies about a quarter to one half of the daily iodine requirement in the United States, though, ironically, milk itself has little native iodine. The iodine residues in dairy appear to originate mainly from the contamination of the surface of the cow's udders from iodine-containing teat disinfectants that leach into their milk.[2596]

For a comparison of the healthiest iodine sources, see my video see.nf/iodine. In short, I recommend the dark-green leafies of the sea. The recommended daily intake can be had in about two sheets of nori,[2597] the seaweed used for sushi. I just nibble on them as snacks. A teaspoon of mild seaweed, like dulse or arame, or a tablespoon of seaweed salad would also fulfill your iodine needs for the day. You can sprinkle dulse, sold as pretty purple flakes, onto just about anything, and arame is one of my favorite ingredients to add to soups. Given that iodine is extensively stored in the thyroid, it can safely be consumed intermittently, meaning you don't have to get it every day.[2598] For more on safe sources, see my Supplements chapter at the end of *How Not to Die*.

ERGOTHIONEINE: THE "LONGEVITY VITAMIN"

Another component that may contribute to successful aging in Okinawa is mushroom consumption.[2599] Fruit flies fed a diet of 1 percent oyster mushrooms showed a slight but significant survival advantage,[2600] perhaps because oyster mushrooms are one of the most concentrated sources of ergothioneine.[2601]

To describe nutrients that may not necessarily be essential for life but may be required for long-term health,[2602] famed biochemist Professor Emeritus Bruce Ames coined the term "longevity vitamin" and identified ergothioneine as a likely candidate.[2603] Of more than a hundred compounds measured in the bloodstreams of thousands of individuals, the one most associated with the lowest rates of disease and death was ergothioneine,[2604] thought to function as a potent intramitochondrial antioxidant.[2605] I review what it can do and the best way to get it in see.nf/ergo.

In short, mushrooms and tempeh—a fungi-fermented soybean cake—are the only concentrated dietary sources.[2606] Porcinis lead the pack, with about three times more ergothioneine than oyster and shiitake mushrooms, which in turn have about three times more than the typical white, cremini, or portobello varieties.[2607] Ergothioneine may explain why mushroom consumption is associated with a lower risk of dying prematurely from all causes put together.[2608]

Interestingly, blood ergothioneine levels in the brain appear to decline after age sixty and this reduction is tied to both cognitive decline[2609] and frailty,[2610] and does not appear to be due to decreasing mushroom intake.[2611] Perhaps the function of the ergothioneine transporter at the blood-brain barrier declines with age, potentially making mushroom intake all the more beneficial as we grow older.

Mushroom Monition

Morel,[2612] shiitake,[2613] and *Agaricus* mushrooms, like white, cremini, and portobello, should be cooked before eaten. Oyster mushrooms can be safely consumed raw.[2614] For the

reasons why and other potential provisos, go to see.nf/caveats.

THE "MUSHROOM OF IMMORTALITY"

Can mushrooms be medicinal? Mushroom-based products make up a sizable chunk of the $50 billion supplement market. As a senior editor of the journal *Fungal Biology* wrote, "This profitable industry provides a powerful incentive for companies to test the credulity of their customers and unsupported assertions have come to define the medicinal mushroom business," recalling the quackery of patented "medicines" with names like the very real "Dr. Bonker's Celebrated Egyptian Oil."[2615]

Now, it wouldn't be surprising if mushrooms had some potent properties. After all, a lot of drugs have been developed from fungi, not the least of which is penicillin, but also the cholesterol-lowering statin lovastatin and the powerful immunosuppressant drug cyclosporin.[2616] Still don't think a humble little mushroom can have pharmacological effects? Don't forget that they can also produce some of our most powerful poisons.[2617] Some look the part, like the polka-dotted fly agaric toadstool popularized by *Super Mario Bros.*, but others have a much more innocent look,[2618] like the mushroom actually named the "destroying angel." As little as one teaspoon of it can cause "a painful, lingering death."[2619]

I discuss the immune-boosting properties of mushrooms in the Preserving Your Immune System chapter. One of the most popular so-called medicinal mushrooms is called *reishi* in Japan (*lingzhi* in China), and it's revered as "the mushroom of immortality."[2620] It's a white-rot fungus that grows off decaying wood.[2621] It isn't edible in the culinary sense, as it's corky and bitter, but it's traditionally been revered in some Asian countries as an herbal concoction for longevity.[2622] Is it worthy of such reverence? Well, it works for wee worms, significantly prolonging the lifespan of *C. elegans*,[2623] and a related mushroom species has been shown to have anti-aging properties when injected into the abdomens of mice.[2624] Unfortunately, nearly every human clinical trial of reishi mushrooms over the last few decades for a variety of conditions has failed.[2625] The area

where it may hold the most promise is cancer. For details, check out my video see.nf/reishi.

Of course, to be effective, a reishi mushroom supplement presumably needs to actually contain reishi mushrooms. No thanks to the 1994 Dietary Supplement Health and Education Act, the supplement manufacturers themselves—as opposed to the FDA—are responsible for the safety and integrity of their own products.[2626] You can imagine how well that has gone. Out of nineteen reishi supplements tested, none contained actual reishi.[2627]

GARLIC FOR ARTERY HEALTH

I've covered sweet potatoes, soy, sea vegetables, and mushrooms. What about the foods that have spiced up the traditional Okinawan diet—garlic, ginger, and turmeric?

In ancient Greece, the art of medicine was divided into three areas: cures through diet, cures through drugs, and cures through surgery. Garlic, Hippocrates wrote, was one such medicinal food—but it was used to treat a nonexistent entity called displacement of the womb, so ancient wisdom only goes so far.[2628]

Over a thirteen-year period, about 9,500 octogenarians, 9,500 nonagenarians, and 8,500 centenarians were recruited from twenty-three provinces in China to study the effect of garlic consumption on the eldest elderly. Compared to those who rarely ate garlic, those who ate garlic at least five times a week had about a 10 percent lower mortality rate, which translated into them living about a year longer.[2629] The investigators suspect that a reduction in cardiovascular disease may have played a role. Those who eat the equivalent of at least one large clove of garlic a day do seem to have better artery function than those who eat less,[2630] but you don't know if it's cause and effect until you put it to the test.

Check out see.nf/garlic for a remarkable series of interventional trials showing that, compared to placebo, a quarter teaspoon of garlic powder can dramatically improve artery function[2631] and slow the progression of atherosclerosis.[2632] Garlic can also significantly lower cholesterol[2633] and blood pressure.[2634] If plain old garlic powder can do that, what about those fancy Kyolic aged garlic extract supplements? They're up to thirty times more expensive and don't seem to work at all.[2635]

As I explored in *How Not to Diet*, a quarter teaspoon of garlic powder can also cause overweight men and women to lose nearly six pounds of straight body fat in fifteen weeks, compared to placebo.[2636] In the Preserving Your Immune System chapter, I'll talk about its immune-boosting effects. A systematic review concluded that plant-based medicine can provide beneficial effects, with little or no side effects, and "compared to other medicine are relatively cost effective."[2637] I'd say so, at as little as one or two pennies a day.

Garlic for Those Who Vant to Suck Your Blood

No data yet on its efficacy against vampires, but eating garlic can protect against other bloodsuckers. Check out see.nf/repellent, but basically, eating garlic has been shown to be useless against mosquitoes[2638] but to successfully reduce tick bites[2639] (though not as much as permethrin clothing treatments[2640]).

GINGER

For thousands of years, ginger has been used to treat disease in China and India.[2641] In India, in fact, it's known as *maha-aushadhi*, "the great medicine." Of course, Indian and Chinese systems of medicine have both also prescribed mercury,[2642] so there are limits to what we can glean from "traditional use." That's why we have science.

More than a hundred randomized controlled trials of ginger have been published.[2643] The most well established use of ginger is the alleviation of nausea and vomiting. It was first shown to beat out Dramamine in a head-to-head test forty years ago in which volunteers were blindfolded and spun around and around in a tilted, rotating chair.[2644,2645] Today, ginger is considered to be a nontoxic, broad-spectrum antiemetic (antivomiting) agent, effective in countering nausea induced by motion sickness, nausea during pregnancy, nausea after chemotherapy and radiation, and nausea

after surgery.[2646] Even just inhaling ginger essence has been shown to help.[2647]

Randomized, double-blind, placebo-controlled trials have also found ginger to be effective for treating osteoarthritis,[2648] premenstrual syndrome,[2649] and menstrual pain;[2650] preventing[2651] and treating migraine headaches;[2652] and reducing cholesterol, triglycerides,[2653] blood sugars,[2654] blood pressure,[2655] excess body weight,[2656] and signs of oxidative stress[2657] and inflammation[2658]—typically for just pennies a day using the type of ground ginger you'd find at any grocery store. When ginger is dried, fresh ginger's main pungent compound *6-gingerol* is converted into *6-shogaol*[2659] (from the Japanese word for ginger), which may be even more potent.[2660]

Okinawans have traditionally eaten shell ginger, which is a species in the same family but separate from common ginger.[2661] Extracts of shell ginger leaves have been shown to increase the lifespan of *C. elegans*, but who eats ginger leaves?[2662] We technically don't eat the root either, but rather the ginger rhizome, which is an underground part of the stem.[2663] Thankfully, 6-shogaol, the dehydration product found in common ground ginger, can on its own further increase the average lifespan of *C. elegans* by up to more than 25 percent.[2664]

The lifespan enhancement may be due to DNA protection. If a tissue sample is taken from a random person, about 7 percent of their cells may show evidence of DNA damage, actual breaks in the strands of their DNA. If we then blast those cells with free radicals, we can cause even more damage, taking that number up to about 11 percent. But, if the person had been eating one and a half teaspoons of ginger powder a day for a week, oxidative stress–induced DNA damage drops about 25 percent, down to 8 percent of cells, which is similar to what's been found in those fed the same amount of rosemary. Researchers also tested cumin, paprika, sage, and turmeric. The first three don't seem to help in this regard, but turmeric worked best.[2665]

TURMERIC

Turmeric is another common component of traditional Okinawan cuisine that has been shown to prolong the longevity of model organisms, including yeast,[2666] invertebrates, and mammals. Turmeric compounds resulted in a 39

percent increase in the average lifespan of *C. elegans*,[2667] a 20 percent increase for fruit flies,[2668] and a 12 percent increase for mice,[2669,2670] along with anti-aging effects demonstrated in the brains of aged rats.[2671]

In the DNA damage experiment where people ate different culinary doses of spices for a week before having their cells blasted with free radicals, turmeric led the pack. When people were fed just a pinch of turmeric a day, DNA damage rates were cut by 55 percent. This was not some proprietary turmeric extract either; study participants consumed about an eighth of a teaspoon each day of the plain spice you can buy at any grocery store. And this was not mixing turmeric with cells in some petri dish. This was just comparing what happens to the cells of those randomized to eat a modest amount of the spice each week and merely counting the DNA fracture rates.[2672]

Without the free radical blast, counting the DNA breaks in people's cells before and after a week of eating spices revealed no significant intrinsic protection in the ginger or rosemary groups. However, the turmeric still appeared to reduce DNA damage by about 40 percent.[2673] This may be because turmeric can boost the activity of our body's own antioxidant enzymes. Catalase is one of the most active enzymes in our body. Each one of these enzymes can detoxify millions of free radicals every second. If we consume the equivalent of about three-quarters of a teaspoon of turmeric a day for a month, the activity of the catalase enzyme in our bloodstream may get boosted by more than 50 percent.[2674] Taking a daily half teaspoon of a 50:1 ratio of turmeric to powdered black pepper for five days before radiation therapy reduced a measure of oxidative damage by about 50 percent compared to control.[2675]

For a review of clinical effects and doubts surrounding turmeric, both founded and unfounded, see my video see.nf/turmericskeptic. My Daily Dozen recommends a quarter teaspoon of turmeric every day.

Okinawa-Inspired Smoothie

I've been experimenting with a recipe for a delectable bright-purple smoothie that tastes like you are drinking a pumpkin pie. The sweet potato gives it an especially silky-

smooth texture. There are a lot more recipes to come in my forthcoming *The How Not to Age Cookbook*, but to whet your appetite:

½ cooked then frozen purple sweet potato
¼-inch piece of turmeric root
¾ teaspoon matcha
1 cup unsweetened soymilk
1½ teaspoons ground flaxseed
1½ teaspoons wheat germ
¼ cup frozen cranberries
½ cup frozen strawberries
3 pitted dates
¼ teaspoon pumpkin pie spice
Dash of cardamom

Scrub one purple sweet potato under running water, then pierce it a few times with a fork. Microwave on high until it is fork-tender. When it is cool enough to be handled, cut it in half and freeze both halves. (You'll use half for this recipe and the other half next time you're craving this smoothie.) Place all the ingredients in a blender, and blend until smooth.

Tips: To preserve my turmeric root, I cut it into quarter-inch pieces, then freeze. Also, since learning about spermidine (see here), I've been cutting my ground flaxseed with wheat germ, half and half, so I just scoop in one full tablespoon of my flax–wheat germ mixture. Also, please note that the amount of matcha (2 g) used in this smoothie can carry more caffeine than a shot of espresso, so you may not want to drink this late in the day.

SPREAD THIN

Based on the best available studies with the longest follow-up, including an "unusually slim cohort" from the Oxford Vegetarian Study,[2676] the ideal body mass index (BMI) for the longest life appears to be 20 to 22 (kg/m^2).[2677] Okinawans traditionally fell smack dab in the middle at a stable BMI of 21. Although there was a cultural norm not to stuff oneself, the fact that they only averaged about 1,800 calories a day is probably more a function of the quality rather than quantity of the foods they were eating.[2678] The Okinawans were actually eating a greater amount of food, but whole plant foods are so calorically dilute that they were effectively practicing an 11 percent calorie restriction.[2679]

This mild, long-term restriction in calories consumed may have contributed to their exceptional survival, though the plant-based nature of the diet may trump caloric restriction. The one population who lives even longer than the Okinawa Japanese doesn't eat only a 98 percent meat-free diet, but rather 100 percent meat-free.[2680]

The Adventist vegetarians in California have "perhaps the highest life expectancy of any formally described population."[2681] Adventist vegetarian men and women live to be about eighty-three and eighty-six, respectively, which is comparable to Okinawan women, but longer-lived than Okinawan men.[2682] The best of the best were Adventist vegetarians who also practice such healthy lifestyle habits as exercising and not smoking. They live to the ages of eighty-seven and eighty-nine, on average. That's ten to fourteen years longer than the general population.[2683]

THE RED, WHITE, AND BLUE ZONE

Sadly, Okinawan longevity is a thing of the past. Okinawa is now home to more than a dozen KFC restaurants,[2684] and Okinawans' saturated fat intake levels have tripled in the years since World War II. They went from eating essentially no cholesterol on a daily basis to a few Big Macs' worth.[2685] They tripled their sodium intake and are now as potassium-deficient as Americans, getting less than half the recommended minimum daily intake of 4,700 mg. In just two generations, Okinawans have gone from the leanest

Japanese to the fattest.[2686] As a consequence, there has been a resurgence of interest from public health professionals in getting Okinawans to eat the Okinawan diet, too.

The same can be said of nearly all the other blue zones, like those in the Mediterranean: They are artifacts of history.[2687] Only one blue zone survives and thrives to this day in the modern era: the Seventh-day Adventists in Loma Linda, California. Another aspect that sets it apart is that it is nondistinctly situated, surrounded by the rest of society. All the other blue zones were geographically isolated from their respective mainlands, as mostly islands, which allowed for the maintenance of divergent diets and lifestyles.[2688]

The diets of other blue zones were also economically constrained; people were in effect "forced" to eat healthier. For example, the average Okinawan wasn't eating much meat, sugar, salt, cooking oil, and polished white rice because they simply couldn't afford it.[2689] Okinawa was Japan's poorest prefecture.[2690] After World War II, their reliance on sweet potatoes went from forming the bulk of their diet to constituting less than 5 percent as imported white rice and bread started to crowd out healthier foods.[2691] In contrast, the United States is one of the richest countries in the world, with an average per capita GDP exceeding $65,000 a year,[2692] yet ranks as low as forty-fifth in life expectancy.[2693] What can we learn from the Adventists in Loma Linda, the one remaining active blue zone community right here in the United States that seems to exceed all others in terms of life expectancy?[2694] How have they been able to retain their healthy eating habits surrounded by the excesses of the modern world?

Adventists have a health philosophy built around a biblical notion that the human body should be treated as a temple.[2695] As such, they've been promoting vegetarian eating for more than 140 years. Adventists are unique in that the majority have adopted a meat-free or low-meat diet.[2696] In the Adventist Health Study-2, for example, which has been following nearly 100,000 North American Adventists for more than a decade, approximately 50 percent are vegetarian or vegan and the other half only eat meat about three times a week on average.[2697]

LIVING RELIGIOUSLY

Seventh-day Adventists are a Protestant Christian denomination. Might religiosity play a role? A poll of one thousand U.S. adults reported that 79 percent of respondents believed that spiritual faith can help people recover from disease.[2698] Might there be some truth to that? A meta-analysis of more than seventy studies on the topic found that measures of religiosity or spirituality were associated with reduced mortality rates in healthy populations, but not sick ones, and also identified evidence of publication bias, implying that some studies non-flattering to spirituality may have been quietly shelved.[2699]

Even if the association were robust, there are important confounding factors. For example, mainline (non-evangelical) Protestants and Jews have the lowest mortality rates among major religious groups in the United States, but they are also likely to be disproportionally white, wealthy, and well educated, and each factor on its own is linked to longevity.[2700] There is also the specter of reverse causation. In these studies, a common measure of faith is attendance of religious services, and you can imagine how developing a disease may prevent you from attending.[2701]

Religious involvement has also been associated with longer telomeres,[2702] though, unexpectedly, the longest telomeres were found in the least religious—for example, people reporting never praying or studying holy books like the Bible. But, among those who were at least somewhat religious, more spiritual involvement was associated with longer telomere length.[2703]

Religiosity could certainly be related directly to health outcomes through lifestyle choices, such as electing not to smoke or drink in excess, which tend to be characteristic of religious people or, in the case of the Adventists, a healthier diet.[2704] Might a predilection to stricter adherence to codes of conduct enable religious people to better stick to healthy lifestyle advice?[2705] Many of the Adventist plant-based diet and lifestyle tips have been put into action in the Complete Health Improvement Program (CHIP, though recently rebranded as Pivio), the most extensively published community-based lifestyle intervention in the medical literature.[2706] (Read all about it in my Optimal Weight-Loss Diet section in *How Not to Diet*.)

The influence of religious affiliation on responsiveness to the program was tested in a group of 7,000 participants.

Even though Adventists make up less than 1 percent of the U.S. population, about one in five CHIP participants were in the church. How did they do compared to the nonbelievers? Substantial reductions in cardiovascular risk factors were achieved for both Adventists and non-Adventists, and some of the reductions were actually greater among the non-Adventists. The researchers concluded that this indicates that Seventh-day Adventists "do not have a monopoly on good health.…"[2707]

Fertility vs. Longevity?

Adventist vegetarians may be longest living, but might that come at a cost? A semen analysis in a Loma Linda fertility clinic raised questions about their sperm quality. Though still within the normal range,[2708] vegetarians had about a 25 percent lower sperm count.[2709] The few vegans tested also had a lower sperm concentration, though not significantly so, and this was made up for by their 30 percent greater ejaculate volume. The vegans did have significantly fewer activated sperm, however, which is a sign of decreased fertility. The researchers suggested soy consumption as a possible mechanism based on the potential for hormonal effects. Californian Adventist vegetarians average about a half serving a day of plant-based meats, many of which contain soy. But, when soy phytoestrogens were put to the test, months of consuming up to the equivalent of nearly twenty servings of soy a day resulted in no adverse effects on sperm parameters.[2710]

There were only five vegans in the study, so the sperm quality findings could just be a fluke, but, if verified, it could reflect an evolutionary trade-off between fertility and lifespan that was first proposed nearly a century ago.[2711] Using a finely tuned laser, it's possible to selectively destroy individual cells as *C. elegans* develops,[2712] and terminating

the cells that give rise to the sperm and eggs significantly extends lifespan.[2713] The same phenomenon can be demonstrated in fruit flies, potentially shifting the body's priorities from reproduction to survival.[2714]

The fertility versus longevity trade-off may be one reason why spaying and neutering our pets can extend their lives. Based on a study of millions of dogs and cats,[2715] sterilized male and female dogs live about 20 percent longer than "intact" dogs, spayed female cats live about 40 percent longer, and neutered male cats a remarkable 60 percent longer.[2716]

What about men who have been castrated? Eunuchs seem to live 25 percent longer than uncastrated men.[2717] In the United States, people who were deemed "feebleminded" were involuntarily sterilized by the government by the tens of thousands until the 1950s,[2718] a practice upheld by none other than famed Supreme Court justice Oliver Wendell Holmes. Writing for the eight-to-one majority in *Buck v. Bell*, the decision upholding the eugenics practice, he penned: "The principle that sustains compulsory vaccination is broad enough to cover cutting the Fallopian tubes."[2719] The heinous practice of compulsory sterilization did allow for a natural experiment, though, and one mental institution found that castrated men lived an average of fourteen years longer than intact men in the same hospital.[2720]

A genealogy database of nearly 200,000 men and women across three centuries in sixteen countries found that those who had fewer children seemed to live longer.[2721] Centenarians, for example, were found to have fewer children and had them at later ages.[2722] This is not to suggest that having fewer children will make you live longer but rather that constitutional factors that enhance human lifespan may come at the expense of reduced reproductive potential, another example of the antagonistic pleiotropy theory. (See here.) For instance, selection for lifespan extension in model organisms can lead to longer-lived

animals but with reduced fertility.[2723] It makes intuitive sense when you consider the context of food scarcity.

In lean times, it is reasonable to put off reproduction until more favorable conditions return to ensure long-term survival.[2724] Caloric restriction can extend the lives of animals but can also cause a reduction in the number of their progeny. A similar pattern may be seen in humans. In the Minnesota Starvation Study, the subjects rapidly lost their libidos after their calorie intake was cut in half.[2725] Remember the nutrient-sensing aging pathways—AMPK, IGF-1, and mTOR? There can be a seesaw between tissue acceleration and reproduction on one side and tissue preservation and rejuvenation on the other.[2726] Thankfully, we can shift the weight to a more optimal balance with diet.

The later girls start their periods, the longer they tend to live. Each year later is associated with significantly lower risk of dying from heart disease,[2727] cancer,[2728] and stroke, plateauing with the lowest overall mortality among those who don't start menstruating until age fifteen.[2729] Earlier breast development (before age ten versus twelve or thirteen) is associated with as much as 23 percent greater breast cancer risk later in life,[2730] and each year earlier a girl starts to menstruate is linked to significantly higher risk of cancers of the bladder, breast, colon, liver, lung, skin, and uterus.[2731]

A century ago, the age of first menstruation averaged as late as nearly seventeen,[2732] but now the average age is under twelve.[2733] Similarly, around the world, the age breast development begins has dropped an average of about three months per decade over the last half century, down to just nine or ten years old in the United States, necessitating a change in textbook definitions of "premature" puberty.[2734] But it's something over which we have a degree of control.

Higher levels of IGF-1 are associated with earlier sexual maturity,[2735] so it's no surprise that kids eating more animal protein experience puberty significantly earlier; this effect is

not seen with plant protein.[2736] A meta-analysis of sixteen studies on diet and development found that, for each additional 1 g of daily animal protein intake in childhood, one's first period appears to move up by two months.[2737] So, for example, seven-year-old girls consuming more than twelve servings of meat a week had 75 percent greater odds of beginning menstruation within the next five years or so compared to seven-year-olds who ate less than four servings a week,[2738] a relationship found for consumption of both red meat and poultry.[2739] IGF-1 and other aging pathways may not fully explain these findings, however, as persistent pollutants that build up in meat, like DDT,[2740] have also been linked to precocious puberty.[2741]

PLANT-BASED EATING

The principal component considered to be responsible for the extraordinary longevity of the Adventist blue zone in California is its plant-based diet.[2742] Vegetarian Adventists not only live longer than nonvegetarian Adventists who eat relatively little meat but they also have a lower incidence of all cancers combined and less high blood pressure and diabetes.[2743] Overall, a comprehensive meta-analysis and systematic review of the major observational studies examining plant-based eating and chronic diseases found that a vegetarian diet had a significant protective effect on getting or dying from heart disease and on the incidence of total cancer, with a vegan diet conferring about twice the reduced cancer risk.[2744]

What about those who decided to stop eating vegetarian and start eating meat? The Adventist Health Study found that, compared to those who stayed vegetarian, individuals who began eating meat suffered about a 230 percent increased risk of gaining weight, a 170 percent increased risk of developing diabetes, and a 150 percent increased risk of having a stroke or being diagnosed with heart disease.[2745] And, if they continued eating meat, they appeared to cut their lifespan by 3.6 years. A comparable flip-side survival advantage was found for long-term vegetarians. Those who

avoided meat for seventeen or more years had an estimated life expectancy of 86.5 years, while those who were vegetarian for fewer than seventeen years had an estimated life expectancy of 82.9.[2746] Compared to longtime vegetarians, those who ate any meat, including poultry and fish, were found to be three times as likely to develop dementia.[2747]

Without guaranteed mental and physical health, most people don't want to live extended lives.[2748] Beyond the longevity advantage, vegetarian Adventists also appear to be in better health as evidenced by taking fewer medications and logging fewer X-ray exams, surgical procedures, and overnight hospital stays. Vegetarians also enjoy the improved quality of life that just comes with suffering fewer chronic diseases.[2749] A study of 15,000 American vegetarians found that they have significantly less coronary artery disease, fewer strokes, less high blood pressure, less diabetes, less diverticulosis, fewer allergies, and significantly fewer diseases overall, after controlling for nondietary factors like smoking. The researchers also noted that the nonvegetarians were more likely to have had surgeries for conditions as varied as varicose veins and hemorrhoids to even more hysterectomies, as well as be on a slew of different drugs. Those eating meat had about twice the odds of being on aspirin, sleeping pills, tranquilizers, antacids, painkillers, blood pressure medications, laxatives, and insulin.

This all translates into significantly fewer medical costs. Compared to nonvegetarians who similarly didn't smoke or drink, vegetarians were found to have significantly lower inpatient, outpatient, and total medical care expenditures, including a nearly 50 percent drop in depression-related medical expenses.[2750] One reason there has been such good compliance with plant-based dietary intervention studies is that participants not only tend to get measurably better but also tend to feel much better. Those randomized to plant-based diets report a significantly better quality of life and significantly higher mood scores than their counterparts assigned to conventional diets, which presumably encourages them to sustain this eating pattern over the long run.[2751]

Success breeds success. After just a few days or weeks following the shift, patients may experience palpable benefits of plant-based eating, beyond just improvements in measurements like blood sugar levels and weight, reinforcing the positive impacts of their new eating habits and

providing further motivation to continue.[2752] In fact, sometimes, plant-based diets can work a little too well. In studies where people are switched on and off plant-based nutrition, they sometimes feel so much better eating healthier that they violate study protocol and refuse to go back to their original baseline diets.[2753]

Which do you think is more effective? Asking patients to make large dietary changes or smaller ones? Paradoxically, diet studies have shown that recommending greater changes leads to greater changes, leading researchers to conclude: "It may help to replace the common advice, 'all things in moderation' with 'big changes beget big results.'"[2754] But, it needn't be all or nothing.

SWAP MEAT

In the United States, the number one risk factor for dying is the American diet. Associated with the most deaths, primarily from cardiovascular disease, about half a million mothers, fathers, sisters, brothers, and friends die every year simply because of what they eat.[2755] In stark contrast, plant-based diets are associated with a lower risk of developing cardiovascular disease to begin with, a lower risk of dying from cardiovascular disease, and, in fact, a lower risk of dying from all causes put together. Progressively increasing our intake of plant foods by reducing how many animal foods we consume may enable us to live longer, healthier lives[2756]—and it doesn't take much.[2757]

As I mentioned, the largest cohort study of diet and health in history, the NIH-AARP study, found that replacing just 3 percent of daily calorie intake from animal protein with plant protein was associated with a 10 percent lower overall mortality in both men and women.[2758] Meat consumption alone was associated with greater risks of dying from heart disease, cancer, and prematurely in general.[2759] This led to an accompanying editorial titled "Reducing Meat Consumption Has Multiple Benefits for the World's Health," published in the *Archives of Internal Medicine*, the journal of the American Medical Association, calling for a "major reduction in total meat intake."[2760]

Of all the animal protein sources, eggs were found to be the worst. Swapping in 3 percent of daily calories with plant protein instead of egg

protein (found mostly in the egg whites) was associated with twice the benefit of swapping out meat protein, exceeding 20 percent lower mortality in men and women. So, eggs appeared to be worse than red meat. The researchers concluded that the finding that plant protein was preferable provides evidence for "dietary modifications in choice of protein sources that may promote health and longevity."[2761]

What about the effects of dietary intake of animal versus plant protein on aging? Healthy aging is defined as "the process of developing and maintaining the functional ability that enables wellbeing in older age." A higher intake of plant protein has been associated with less accumulation of deficits, based on functional impairments, self-reported health and vitality, mental health, diseases, and the use of health services.[2762]

Swapping in just 1 percent of calories from plant protein in place of animal protein led to significantly less deficit accumulation. Now, you may be thinking that animal protein and animal fat travel alongside each other in the same foods, so the benefits of this swap may have just been a saturated fat effect. But even after accounting for fat, there still seems to be something about the animal versus plant protein sources.[2763] It's still not clear, however, if the beneficial health effects are due to an avoidance of deleterious effects associated with animal foods or the addition of beneficial effects of plants, though it may be a little of both.[2764]

EATING PLANTISH

Since the benefits of the Mediterranean diet appear primarily due to the added plant foods,[2765] PREDIMED researchers created what they called a "provegetarian" scoring system to test the effects of one's dietary plant-to-animal ratio. They knew "pure" vegetarians lived longer but figured recommendations to just eat "more plant-based foods, less animal-based foods" might be easier to swallow. Would simply moving along the spectrum toward more plants actually enable people to live longer? Check out see.nf/flexitarian for details, but indeed, this appeared to translate into a 40 percent lower risk of premature death, evidence that "the simple advice to increase the consumption of plant-derived foods with compensatory reductions in the consumption of foods from animal sources confers a survival advantage."[2766]

Though there are vested interests that fight hard to maintain the status quo, such as the processed food and pharmaceutical industries, one corporate sector actually benefits from keeping people healthy: the insurance industry. In a nutritional update published about ten years ago in its official medical journal, Kaiser Permanente, the largest managed-care entity in the United States, urged its nearly 15,000 physicians that healthy eating may be "best achieved with a plant-based diet." The update read:

> Too often, physicians ignore the potential benefits of good nutrition and quickly prescribe medications instead of giving patients a chance to correct their disease through healthy eating and active living.… Physicians should consider recommending a plant-based diet to all of their patients, especially those with high blood pressure, diabetes, cardiovascular disease, or obesity.[2767]

In other words, doctors should give their patients the chance to first correct their diseases themselves. The major downside that Kaiser Permanente's nutritional update identified is that a plant-based diet may work a little too well. If individuals adopt the diet while still taking medications, their blood sugar or blood pressure could drop so low that they may need their physicians to adjust their meds or take them off them completely. Ironically, the "side effect" of the diet may be not having to take drugs anymore.

As with many articles, this one ends with a familiar refrain: "Further research is needed.…" In this case, though, the call was not for more studies on efficacy but rather: "Further research is needed to find ways to make plant-based diets the new normal.…"[2768]

In Kaiser Permanente's guide "The Plant-Based Diet: A Healthier Way to Eat," a plant-based diet is defined as completely excluding animal products, but it expressly points out: "If you find you cannot do plant-based eating 100% of the time, that's OK. Any movement toward more plants and fewer animal products, processed foods, and sweets can improve your health!"[2769]

Vegetarian vs. Mediterranean

The Mediterranean diet is primarily, but not exclusively, plant-based,[2770] so much so that vegetarians have three times the odds of having their diets rated as highly adherent in the classic Mediterranean diet scoring system and vegans have more than thirty times the odds.[2771] After all, the traditional Mediterranean diet itself can be considered to be a "near-vegetarian diet."[2772] What happened when the two diets were pitted head-to-head?

Researchers randomized overweight individuals to either a low-calorie Mediterranean diet plan or a low-calorie vegetarian one. With the same enforced caloric restriction, both groups lost the same amount of weight, but the vegetarian group edged out an advantage with a significant drop in LDL cholesterol.[2773] What if there were no specific calorie or portion restrictions? That's the tack a different study took, and obese subjects randomized to advice to eat a Mediterranean diet lost no weight at all over four months compared to thirteen pounds lost by those advised to eat a strictly plant-based diet with no added fats.[2774]

VEGAN JUNK FOOD IS STILL JUNK FOOD

Is a plant-based diet just another way of saying *vegan*? No. Although it's often confused with vegan or vegetarian diets, it can have very different health implications. Vegan diets are free of any animal-derived ingredients, and vegetarian ones are meat-free but can include dairy and eggs. Both may exclude animal products for religious or ideological reasons, but neither is necessarily focused on healthy choices. A plant-based diet, on the other hand, has been defined as a way of eating that minimizes consumption of meat, dairy, eggs, and processed junk, while maximizing intake of whole plant foods, such as vegetables, fruits, whole grains, legumes (beans, split peas, chickpeas, and lentils), mushrooms, nuts and seeds, herbs and spices —basically real food that grows out of the ground.[2775]

These days, "junk" is the predominant food group.[2776] Corporations willfully engineer products to maximize eating for profit, and the industry

will happily make all the vegan junk we're willing to buy.[2777] In fact, one study found that when the consumption of ultraprocessed junk, like ramen noodles, potato chips, and cookies, was compared across different eating patterns, vegetarians and vegans ate the most.[2778] Oreos are vegan, and there are vegan Doritos, Pop-Tarts, and Krispy Kreme pies. Vegan does not necessarily mean health-promoting.

From a health perspective, this may help explain why vegans in the United States tend to do better than vegans in the United Kingdom.[2779] The number one reason Americans choose to eat plant-based is for their health,[2780] so they tend to eat more plants (as evidenced by higher fiber and vitamin C intakes,[2781] which are only found concentrated in whole plant foods). On the other side of the Atlantic, however, the top reason for veganism is ethical concerns,[2782] so British vegans may be more likely to just switch to vegan crumpets.[2783] Similarly, U.S. vegetarians have been found to eat fewer refined grains and sweets than veg Brits.[2784]

In order to distinguish between healthful and unhealthful vegan diets, Cornell professor emeritus in nutritional biochemistry Dr. T. Colin Campbell introduced the term *whole food, plant-based diet*.[2785] If you look at India, for example, you see a decrease in the whole plant food content of their diet, along with increasing risk of obesity and noncommunicable chronic diseases. There's been a shift from brown rice to the more processed white rice and the substitution of other refined carbohydrates, packaged snacks, and fast food in place of India's traditional staples of vegetables, lentils, fruits, nuts, whole grains, and seeds. This may help explain why disease rates are on the rise even in a country with a large vegetarian contingent.[2786]

Professor Campbell's physician son and daughter-in-law tried putting a group of vegetarians and vegans on a whole food, plant-based diet for eight weeks. On average, the study participants lost ten pounds and dropped their LDL cholesterol by sixteen points.[2787] In other words, vegans may benefit from eating more plant-based, too.

SETTLING THE SCORE

In the medical literature, when "anti-aging diets" are discussed, the conversation isn't only about eating more whole plant foods and cutting

down on meat, but also cutting down on junk. Here are some examples: "A diet portfolio rich in fruits and vegetables, legumes and whole grains, but reduced in animal products and accompanying saturated fat, salt, sweets, and refined carbohydrates."[2788] "Such a diet would include wholegrain cereals, legumes, fruits and vegetables, with a low intake of saturated fat and trans fatty acids,"[2789] and "anti-aging" eating involves "minimizing meat, salt, added sugar, and heavily processed foods while emphasizing phytochemical-rich foods."[2790]

If people just concentrate on decreasing their intake of animal foods, they may end up increasing their consumption of highly processed junk, like Coke and Wonder Bread.[2791] It's worth repeating that you can't assume that simply avoiding animal foods will necessarily produce a healthy diet.[2792] In recognition of the fact that all plant foods are not created equal, "healthful" plant-based diet indexes were created that, like the "provegetarian" system, positively score healthy plant foods, but negatively score both animal foods *and* processed junk.[2793]

Using these more sophisticated plant-based scoring systems, we learned that simply giving points for any plant foods (junk or not) and docking points for any animal foods (meat, dairy, or eggs) results in scores that are associated with a significantly lower risk of premature death.[2794,2795,2796,2797] However, just replacing animal products with highly processed junk doesn't do your body any favors. Plant-based junk diets are associated with neutral[2798] or even increased mortality risk.[2799] Over time, as assessed in 75,000 health professionals over a dozen years in the Harvard cohorts, those who made the greatest improvements in minimizing all animal foods and increasing any plant foods, particularly healthy ones, had a lower risk of dying, but those who kept animal products to a minimum but piled on the most junk, like sodas and sweets, increased their risk of dying overall.[2800]

These studies suggest we shouldn't lump together all plant-origin foods. Kidney beans are different from jelly beans. All the animal foods were still being treated the same, though, so researchers tried making an animal food–based quality index as well. They put processed meats, red meat, and eggs in an "unhealthy animal foods" category but treated fish, other seafood, dairy, and poultry as "healthy animal foods." They found that the higher the quality of plant foods, the lower the all-cause mortality, but no independent association was found for the quality of animal foods, meaning they all

seemed to be roughly just as bad in terms of cancer mortality, heart disease mortality, and all-cause mortality.[2801]

The Simplest Dietary Quality Index

In general, the dividing line between foods that promote health and those that promote disease may be less plant versus animal and more whole plant foods versus everything else. This has been encapsulated by a dietary quality index that reflects the percentage of calories gotten from nutrient-rich, unprocessed plant foods on a scale of zero to one hundred. So, if half of your food calories are from unprocessed plants, you'd score a fifty. A strictly whole food, plant-based diet, meaning a vegan diet that excludes refined grains, white potatoes, alcohol, and added sugars and oils, could achieve a perfect score of a hundred.[2802] Sadly, most Americans hardly make it above a score of ten.[2803]

The standard American diet only rates an eleven out of one hundred. According to U.S. Department of Agriculture (USDA) estimates, 57 percent of our calories come from processed plant foods, 32 percent from animal products, and only 11 percent from whole grains, fruits, beans, nuts, and vegetables.[2804] In other words, on a scale of one to ten, the American diet only rates about a one.

Why do we care? Because those with higher scores appear to lose more body fat over time and have a lower risk of abdominal obesity,[2805] high blood pressure,[2806] high blood sugars,[2807] metabolic syndrome,[2808] high cholesterol, and high triglycerides,[2809] as well as depression, anxiety, and psychological distress.[2810] A higher score also correlates with 70 percent lower odds of benign breast diseases like fibrocystic lumps.[2811] What about malignant disease?

When researchers compared the diets of 100 women with breast cancer to 175 healthy women, they concluded

that scoring higher on the whole plant food diet index (eating just twice the proportion of plants compared to the standard American diet) may reduce the odds of breast cancer by more than 90 percent.[2812]

PRODUCE LONGEVITY

Probably the least controversial advice in all of nutrition is to eat more fruits and vegetables, which is to say: Eat more plants. After all, the term *vegetable* basically means all parts of the plant that aren't fruit. How much longer might we get to live if we eat more produce? Compared to those getting five servings of fruits and veggies a day, those only eating two daily servings may live seven fewer months. Having only one serving a day may equate to living about a year and a half less. With just a half serving a day, we may live two fewer years. And, if we don't eat any servings of fruits and vegetables a day, we could lose three years of our lives.[2813] So, for someone eating sufficiently unhealthfully, eating just a single serving of fruit each day, like one apple, could potentially mean a nineteen-month difference between life and death. One daily salad might mean years more time on this planet.

In contrast, the potential lifelong damage of any pesticides on those fruits and vegetables has been estimated to only cut a few *minutes* off the average person's life.[2814] So, while there are many reasons people choose organic produce over conventional, concerns over pesticide residues should not discourage us from stuffing our faces with as many fruits and vegetables as possible.

The fruit and vegetable dose-response longevity study mostly looked at people in their fifties and sixties.[2815] Is it too late to make a difference by the time we're in our seventies? Apparently not. Women in their seventies with the most carotenoid phytonutrients in their bloodstream were twice as likely to survive five years as those with the least, potentially doubling their likelihood of survival merely by eating more fruits and vegetables.[2816] In a study out of Taiwan, spending just fifty cents a day on fruits or vegetables appeared to buy participants about a 10 percent drop in mortality.[2817] That's quite a bargain. Imagine if there were a drug that could lower the risk of

death by 10 percent—with only good side effects. How much do you think drug companies would charge? Probably more than fifty cents.

Eating Low on the Food Chain

Eating from the lowest rung of the food chain gives plant-based eaters another advantage in the modern world: suffering less exposure to the industrial pollutants that bioaccumulate up the ladder.[2818] I explore the role of contaminants in aging and disease, such as PCBs, dioxins, and long-banned pesticides like DDT, in see.nf/eatlow. Studies of the pollutants in the breast milk of vegetarians dating back more than forty years found the average levels of some pollutants were fifty to one hundred times lower in the vegetarians compared to the national average. In fact, for six out of seven pollutants researchers investigated, there was no overlap in the range of scores: The highest vegetarian value was lower than the lowest value obtained in the general population.[2819] Lower pollutant levels may help explain why those on a plant-based diet appear to be less likely to develop all forms of cancer combined.[2820]

Based solely on levels of dioxin contamination, the USDA determined that American children who consume meat could be ingesting more than the daily safety limit.[2821] Surprisingly, as I explore in see.nf/organicmeat, the differences in pollutant contamination between organically and conventionally produced meats were minimal.[2822] Indeed, even just eating half of the average U.S. per capita meat intake[2823] could exceed the maximum tolerable limits, whether organic or not.[2824]

What, then, can we do to reduce our exposure? We can eat high-fiber foods, as fiber can bind to some of the contaminants and potentially flush them out of the body.[2825] We can exercise, as blood levels of persistent pollutants have been found to be lower among physically active

individuals,[2826] perhaps due to sweating,[2827] boosting detoxing enzymes,[2828] or increasing clearance through the bile.[2829] We also can trim fat when preparing meat and further trim and thoroughly drain fat after cooking,[2830] though given current contamination levels, a recent review concluded that "meat consumption in general … should be significantly modified downward, as much and as soon as possible."[2831]

THE VEGETARIANS' ACHILLES' HEEL

The largest association of nutrition professionals in the world, the Academy of Nutrition and Dietetics, is clear in its latest position paper on the subject: Plant-based diets are not only "appropriate for all stages of the life cycle" but may "provide health benefits in the prevention and treatment of certain diseases." (I'm honored to report that the academy directed readers to NutritionFacts.org as a trusted resource.)[2832] As the emeritus dean of the School of Public Health at Loma Linda University once said at a nutrition conference, "Attitudes toward vegetarian diets have progressed from ridicule and skepticism to condescending tolerance, to gradual and sometimes grudging acceptance, and finally to acclaim."[2833]

A comparison of the dietary quality of different popular diets scored Ornish's plant-based plan the highest and Atkins's low-carb plan the lowest.[2834] Using a number of nutritional quality indexes, researchers found that individuals' diet scores generally ranked healthier the more plant-based they ate.[2835] Despite plant-based eaters eschewing entire categories of foods, they ironically tend to get more nutrition. One study found that those eating more plant-based got more of nearly every nutrient—more fiber, more vitamins A, C, and E, more of the B vitamins thiamin, riboflavin, and folate, and more of the minerals calcium, magnesium, and iron.[2836] This shouldn't be surprising. Responded the *Journal of the American Dietetic Association* editor in chief, "What could be more nutrient dense than a vegetarian diet?"[2837]

Nowadays, the most widely published cases of classic nutrient-deficiency syndromes are people following extreme diets, like the American

service member who was hospitalized for a muscle tear due to scurvy. He reported eating only skinless chicken and candy bars.[2838] Ironically, one of the healthiest eating patterns, an exclusively plant-based diet, is perhaps the most life-threateningly incomplete, lacking vitamin B_{12}.

Vitamin B_{12} isn't made by plants. It isn't made by animals either, but rather by microbes that blanket the earth.[2839] However, B_{12} produced by bacteria in the guts of animals can suffuse through their tissues to provide a human source. Unfortunately, the B_{12} made in our colons is too far down to be absorbed.[2840] We all presumably used to get B_{12} by drinking out of a mountain stream or sipping well water,[2841] but today we chlorinate the water supply to kill off any bacteria. We don't get a lot of B_{12} in our water anymore, but we don't get a lot of cholera either!

Vegetarians living in developing world slums appear to have fewer B_{12}-deficiency problems,[2842] but the more hygienic our meals, the less B_{12} we may get.[2843] Our fellow great apes, like gorillas, get all the B_{12} they need by eating their own feces.[2844] I prefer supplements.

In our modern, sanitized world, vitamin B_{12} can be found reliably only in supplements, animal products, and B_{12}-fortified foods. Vegans and vegetarians should take supplements containing at least 50 mcg of cyanocobalamin (the most stable form[2845]) each day or at least 2,000 mcg once a week,[2846] as should all individuals between fifty and sixty-five, regardless of their diets (since we lose some of the ability to absorb B_{12} from food as we age).[2847] After that, however, the recommendations change.

After age sixty-five, a single dose of 50 mcg a day—even 100 daily mcg—may not be enough.[2848] Researchers set out to find an adequate dose for this age bracket, and it seems most need at least 650 mcg to 1,030 mcg a day, so I recommend 1,000 mcg of cyanocobalamin a day for *everyone* after age sixty-five, ideally as a chewable, sublingual, or liquid supplement.[2849] Absorption is boosted when B_{12} mixes with saliva, because we secrete a B_{12}-binding protein from our salivary glands that helps transport the vitamin safely through our digestive tract.[2850] Chewing a B_{12} tablet can cause our levels to go up ten times more than had we simply swallowed the exact same vitamin.[2851]

Vitamin B_{12} deficiency is serious business, with the potential to cause a wide range of disorders of the blood, gut, brain, and nervous system.[2852]

With the ever-increasing demand for cleanliness in our food chain, it is of special importance that we secure a regular, reliable source of B_{12}, and supplements are probably the easiest, safest, and cheapest.[2853]

What About Vitamin K_2?

For a deep dive, check out my video see.nf/vitamink, but in short, purported benefits for the bones, heart, and brain have failed to materialize (taking into account that some of the major trials were found plagued with admissions of data fabrication).[2854] Even if such evidence arose, we can get all the vitamin K we need from the vitamin K_1 in greens since there's no requirement for the vitamin K_2 found in certain animal products and fermented foods.[2855] And, even if some evidence arose that there was some unique benefit to K_2, our microbiome makes K_2 from the K_1 in greens, which we then absorb into our system. But what about the one type of K_2 made only by mammals? We're mammals! So even if we had some problem with our microbiome, our own cells can make K_2 from K_1 just like other animals.[2856]

Of all the dietary components correlating with all-cause mortality, the best evidence appears to support the intake of green leafy vegetables and salads to maximize our time on Earth.[2857] So it's no surprise that lower circulating levels of vitamin K_1 in the bloodstream—a marker of inadequate greens intake—are associated with dying prematurely.[2858] Eat. Your. Greens.

LIFESTYLE

In the thirteenth century, the renowned scholar Roger Bacon recommended a good diet, proper rest, exercise, moderation in lifestyle, and good hygiene

for lifestyle prolongation, as well as, all too conveniently, the "breath of a virgin."[2859] But he was right about the first few!

"Diet" derives from the ancient Greek word *diaita*, which means "way of living," not just dietary needs.[2860] In 1903, Thomas Edison predicted that "[t]he doctor of the future will give no medicine, but will instruct his patient in the care of human frame in diet and in the cause and prevention of disease."[2861] A hundred and one years later, the American College of Lifestyle Medicine (ACLM), of which I am a proud founding member, was born.[2862]

As physicians, we still prescribe medicines when necessary, but we understand that lifestyle behaviors are most often the root causes of what ails us and, as such, place an emphasis on what we put into our mouths. Food and cigarettes are our leading causes of disability and death.[2863] More broadly, a recent research summit described lifestyle medicine as "the use of a whole food, plant-predominant diet, regular physical activity, restorative sleep, stress management, avoidance of risky substances and positive emotions/social connection as a primary therapeutic modality for treatment and reversal of chronic disease."[2864]

Based on seventy-four studies that enrolled millions of participants, those with the healthiest lifestyles had less than half the risk of dying compared to those checking all the unhealthy boxes during the average study's more-than-decade-long duration.[2865] We have all heard stories of cigar-chomping, gin-guzzling hundred-year-olds that capture the public's imagination, but the truth about lifestyle and longevity is more prosaic.[2866] Adhering to just four simple healthy lifestyle factors can have a strong impact on the prevention of some of our deadliest diseases: not smoking, not being obese, getting thirty minutes of exercise a day, and eating more healthfully, which is defined as consuming less meat and more fruits, vegetables, and whole grains.

Those four factors alone appear to account for 78 percent of our chronic disease risk. If you start from scratch and manage to tick off all four, you may eliminate more than 90 percent of your risk of developing diabetes and more than 80 percent of your risk of suffering a heart attack, halve your risk of having a stroke, and reduce by more than a third your overall cancer risk.[2867] For some cancers, like our number two cancer killer, colon cancer, up to 71 percent of cases appear to be preventable through simple diet and

lifestyle changes.[2868] Think of what that means in terms of the numbers. As it stands now, each year, a million Americans will suffer their first heart attack or stroke, a million will get diabetes, and a million will be diagnosed with cancer.[2869] It's time we stop blaming genetics and focus on the 80 percent or so of risk that appears to be directly under our control.[2870]

What does that mean for mortality? A similar batch of healthy behaviors predicted a fourfold difference in total mortality, with an estimated impact equivalent to fourteen years in chronological age. Put another way, those taking better care of themselves were dying at such a slow rate that it was as if they were fourteen years younger.[2871] Imagine turning back the clock fourteen years—not with a drug or a DeLorean but just by eating and living more healthfully.

What if you already decided to go the drug route and are treating your risk factors like high blood pressure and cholesterol with medications? Adherence to basic healthy lifestyle behaviors appeared to effect the same mortality advantage for users and nonusers of preventive medications alike.[2872] What's more, it's never too late to turn back the clock. A midlife switch to even the basics—eating at least five daily servings of fruits and vegetables, walking just about twenty minutes a day, maintaining a healthy weight, and not smoking, for instance—results in a substantial reduction in mortality even in the immediate short-term future. We're talking about a 40 percent lower risk of dying in the subsequent four years. The researchers concluded that "making the necessary changes to adhere to a healthy lifestyle is extremely worthwhile, and that middle-age"—in this case, ages forty-five through sixty-four—"is not too late to act."[2873]

Healthier lifestyles can also delay the emergence of chronic disease by about a decade.[2874] Most seventy-two-year-olds who don't smoke or have diabetes, obesity, hypertension, or a sedentary lifestyle make it to age ninety, but among those plagued with those risk factors, the probability dropped to less than 5 percent.[2875] Even over the age of seventy-five, basic behaviors—not smoking, walking at least a half hour a day, and eating at least three daily servings of fruits and vegetables—may delay death and disability by about eighteen months.[2876]

No, Sitting Is Not the New Smoking

A media analysis found hundreds of news articles claiming that prolonged sitting each day is comparable to smoking cigarettes. This is decidedly not the case. Smoking is expected to cause a billion deaths in this century.[2877] Tobacco use is responsible for up to ten times or more greater mortality risk:[2878] twenty excess deaths per thousand people each year for the heaviest smokers, compared to less than two such deaths for the heaviest sitters. Even light smoking of a few cigarettes a day is associated with a higher risk.[2879] The good news is that quitting cigarettes even as late as age sixty-five may add years onto our lifespan.[2880]

Plummeting tobacco use is one of our great public health victories. The share of adults who smoke declined from 42 percent in 1965[2881] to just 14 percent today.[2882] Cigarettes now kill only about a half million Americans a year, whereas our diets kill many thousands more.[2883] To be victorious in the dietary realm, plant-based diets have been proposed to be "the nutritional equivalent of quitting smoking."[2884]

EXERCISE

When people retire, they don't appear to improve their diets, but they do tend to become more active.[2885] For many, leaving the workforce allows for more time for activities like playing sports, gardening, or entertaining friends and family. What role may physical activity play in longevity? In terms of combating the hallmarks of aging (see here), aerobic exercise can induce autophagy, lower inflammation, decrease DNA damage, and facilitate DNA repair,[2886] though, after controlling for weight reduction, it may not actually affect the rate of aging.[2887] There is, however, a strong body of evidence supporting its role in preserving higher functioning as we

age.[2888] A meta-analysis of cohort studies of middle-aged and older individuals with follow-ups lasting as long as twenty years found that adults who exercised were more likely to age successfully than those who were sedentary,[2889] though less than 3 percent of those sixty and older may meet the recommended physical activity guidelines.[2890]

EXERCISE IS MEDICINE

Population studies have found a correlation between regular aerobic exercise and decreased risk of at least thirty-five different diseases,[2891] but what have interventional trials proven in terms of cause and effect? Randomized controlled experiments of older adults have demonstrated that physical activity can improve muscle mass, strength, balance,[2892] and mobility,[2893] as well as decrease the risk of falls[2894] and, potentially, fractures, while helping to minimize bone loss.[2895,2896] Exercise has also been shown to improve cognition,[2897] enhance mood,[2898] successfully treat depression as well as the prescription antidepressant drug Zoloft,[2899] improve erectile function in men,[2900] and generally improve quality of life.[2901] The evidence supporting the overall health benefits of physical activity is overwhelming.[2902] More on aging benefits in see.nf/perks.

Who Should Check with Their Doctor First?

If you are a man over the age of forty-five or a woman over fifty-five, have diabetes, or experience symptoms such as chest pain, dizziness, or shortness of breath, I would recommend checking with your health professional before starting a new exercise regimen.[2903]

SURVIVAL OF THE FITTEST?

Researchers who accept grants from the Coca-Cola Company[2904] call physical inactivity "the biggest public health problem of the 21st century."[2905] Not true. Exercise is fantastic, but in terms of risk factors for

death and disability in the United States, physical inactivity ranks down at number ten and eleven, respectively.[2906] Globally, inactivity doesn't even scratch the top twenty when it comes to years of healthy life lost.[2907] A poor diet, as I've discussed, is by far our greatest killer, followed by smoking cigarettes.[2908]

Exercise has been described as the "only intervention that has shown a remarkable efficacy for … increasing mean and maximum lifespan in humans."[2909] View see.nf/lifelongexercise for an extensive review. But whether physical inactivity is said to be related to 6 percent of premature mortality,[2910] 9 percent,[2911] or even 15 percent,[2912] these estimates are all derived from observational studies and predicated on the presumption of cause and effect. I was surprised by how much controversy appears in the medical literature over whether the apparent longevity benefits of exercise are even real. You can imagine the confounding factors and potential for reverse causality. I review some of the critical studies in see.nf/fitnesslongevity.

For example, researchers have compared the effects of leisure-time physical activity to occupational physical activity. If the link between exercise and longevity were truly causal, then the context in which you exert yourself shouldn't matter.[2913] As you can probably guess, manual labor is associated with a shorter, not longer, life, again suggesting the primacy of confounders like socioeconomic factors.[2914]

CAN WE EXERCISE POWER OVER OUR LIFESPAN?

Is it possible a genetic predisposition to physical fitness is what accounts for the exercise-longevity link, rather than the physical activity itself? This question was raised by experiments comparing two strains of rats, one bred to have a high intrinsic running capacity and another bred to have a low one. Even without exercising, the rats with high fitness ability lived longer than those with the low fitness ability. But unexpectedly, when the rats were provided with running wheels, longevity dropped for both the high and low fitness strains. Voluntary exercise cut their lives short.[2915]

Using twin studies, we can show there are also genetic predispositions to exercise in humans. When identical twins leave home to start their separate lives, their exercise habits are much more likely to be "concordant"

than those of fraternal twins, meaning if one twin vigorously exercises, the other twin is more likely to do the same if the two share 100 percent of their DNA instead of just 50 percent, like typical brothers and sisters. By looking at the rare cases of identical twins whose exercise habits diverge, we can tell if it's this genetic predisposition to exercise or actual exercise that accounts for athletic longevity. With the same DNA, would intense physical activity make a difference? Apparently not. The same mortality rates were found in identical twins whether they exercised vigorously or not.[2916]

So, does working out make you live longer or not? A critical analysis concluded that "the undisputed health-related benefits of exercise have yet to translate into any proven causal relationship with longevity." More details in see.nf/exerciselongevity.

HOW MUCH IS TOO MUCH?

Centuries ago, Hippocrates said, "Everything in excess is opposed to nature." Is it possible to exercise too much?[2917] Details in see.nf/toomuch, but basically, like any powerful medicine, there may be a safe range of dosing.[2918] It may be prudent to limit chronic, vigorous exercise to no more than an hour a day and no more than five hours a week, with at least a day or two off.[2919] For runners, the recommended upper limit for potential longevity benefits is thirty miles a week.[2920] Only about half of U.S. adults even reach the recommended minimum exercise level, though,[2921] so public health advocates tend to focus on the "even a little is great" message[2922] rather than worry about the 2 to 3 percent of Americans who may be overdoing it.[2923]

RUNNING THE RISK

What's the best diet to support our physical fitness? I was shocked to learn that endurance athletes, compared with sedentary individuals, have been found to have *worse* atherosclerosis.[2924] See see.nf/athletes for a review of that research. It's not that they seem to be overstressing their heart with movement but rather with meals.[2925] Endurance athletes can eat five, six, or even seven thousand calories a day. So, if they're eating twice the saturated fat and cholesterol, no wonder their hearts are getting hammered.

What do you think happened when researchers put people on a paleo diet, along with a CrossFit-based, high-intensity circuit training exercise program? Normally, if you lose enough weight by any means—whether by working out, getting your stomach stapled, or developing tuberculosis for that matter—you can temporarily lower your cholesterol levels no matter what you eat. However, after ten weeks of intensive workouts and weight loss on the paleo diet, the participants' LDL cholesterol levels actually went *up*. Counterbalancing changes in LDL cholesterol size or HDL cholesterol are not considered sufficient to offset this risk.[2926] And, those who started out the healthiest experienced the worst increase. The subjects who began the study with optimal LDL levels (under 70) experienced a 20 percent increase in this leading risk factor for our number one killer, heart disease.[2927] Exercise is supposed to make things better, not worse.

On the other hand, people placed on a plant-based diet and a modest, mostly walking-based exercise regimen, can drop their bad cholesterol by 20 percent within three weeks,[2928] whereas the paleo diet appeared to have "negated the positive effects of exercise."[2929] That is why all athletes should eat more plant-based. It doesn't matter how shred if you're dead.

PLANT POWERED

There has been a surging interest in plant-based eating among athletes,[2930] thanks in part to documentaries like *The Game Changers*. (I was honored to play a small role in that film as a scientific adviser.) There is a desire not only to score long-term health benefits but to improve performance and accelerate recovery.[2931] The artery-dilating, antioxidant, and anti-inflammatory properties of plant-based nutrition can certainly lead to improved blood flow and reduced oxidative stress and inflammation, and indeed, plant-based athletes have been found to have superior cardiorespiratory fitness[2932] and an endurance advantage,[2933] perhaps due to superior heart function.[2934] (Check out see.nf/fitness for a run-through of all the studies.) The more important question from a public health standpoint, though, is what about dietary effects on fitness for exercise training programs in *non*athletes?

Type 2 diabetics were randomized to a vegetarian versus conventional calorie-controlled diet and exercise program. All meals were provided to

enhance compliance, and the exercise was closely monitored. Despite the same allotment of exercise in each group, VO_2 max (a measure of aerobic fitness) increased by 12 percent and maximal performance increased by 21 percent in the vegetarian group, both significantly better than the nonvegetarian group, who didn't significantly improve at all in either dimension. In other words, the results indicated that a more plant-based diet more effectively leads to improvements in physical fitness—in terms of better aerobic capacity and power output—than a less plant-based diet after the same aerobic exercise program.[2935]

The meat-free group also experienced reduced feelings of depression[2936] and a greater improvement in quality of life and mood.[2937] This is consistent with randomized crossover trials that show that covertly increasing saturated fat intake can reversibly induce negative changes in brain function, inflammation, mood, and resting metabolic rate, and perhaps even undercut exercise motivation.[2938,2939] Study participants became 12 to 15 percent less physically active when they were on diets high in saturated fat compared to low.[2940]

Compared to the conventional calorie-controlled diet group, the vegetarian group also experienced superior effects on body weight, blood sugar control, cholesterol, insulin sensitivity, and oxidative stress. Both diets contained the same number of calories, yet simply eating meat-free led to about six pounds more weight loss, as well as more *waist* loss (a significantly slimmer waist); less superficial fat, meaning the external jiggly fat; and, most important, significantly greater loss of visceral fat, the most metabolically dangerous deep belly fat.[2941] This is all in addition to leading more effectively to improvements in physical fitness.

WEIGHT CONTROL

Over the last forty years, obesity rates have tripled among older adults.[2942] Forty-three percent of Americans over the age of sixty are not just overweight but obese.[2943] This can't just be ascribed to a slower metabolism. Resting metabolic rate (the calories we burn just to keep us alive) remains stable from the time we're twenty through sixty, after which it only declines

by about ten calories a day per year.[2944] So, don't blame your metabolism. As I documented in detail in my book *How Not to Diet*, blame the food.

Obesity is associated with accelerated cellular aging, as measured by telomere shortening or advanced epigenetic age,[2945] presumably due to the oxidative stress[2946] and systemic inflammation that accompany excess body fat.[2947] Obesity is associated with declining physical function in terms of mobility limitations, as well as declining cognitive function.[2948] MRI scans of hundreds of individuals across the age spectrum found that the brain shrinkage of white matter in overweight and obese individuals corresponded to having a brain that was up to ten years older.[2949] A meta-analysis of nineteen studies following more than a half million people for up to forty-two years found that midlife obesity was associated with a 33 percent increased risk of developing dementia,[2950] and each one-point increase above a body mass index (BMI) of 20 at age fifty appears to move up the onset of Alzheimer's disease by about seven months.[2951] What about obesity and mortality?

VISCERAL REACTION

Thanks in part to the obesity epidemic, we may now be raising the first American generation to live shorter lives than their parents.[2952] This downward trend in lifespan is expected to accelerate as the current younger generation, who started out even heavier, earlier, ages into adulthood.[2953] Some predict that, in the coming decades, we may lose two to five years of life expectancy in the United States, or even more. To put that into perspective, a miracle cure for *all* forms of cancer would only add three and a half years to the average American lifespan.[2954] In other words, reversing the obesity epidemic might save more lives than curing cancer.

Even a moderate midlife weight gain of approximately ten to twenty pounds may significantly reduce the odds of healthy survival later in life.[2955] In a study of more than six hundred centenarians, less than 2 percent of the women and not one of the men were obese.[2956] After the age of forty, obesity may reduce life expectancy by as much as six or seven years.[2957]

As we age, the fat on our body also tends to redistribute from the superficial jiggly flab under our skin (subcutaneous fat) to deep stores that wrap around our internal organs and bulge out our abdomens (visceral fat),

especially in women.[2958] Between twenty-five and sixty-five, women lose approximately thirteen pounds of bone and muscle, while quadrupling stores of visceral fat. (Men's visceral fat stores typically only double.[2959]) So, even if the bathroom scale doesn't indicate any weight gain, a woman may be gaining the worst kind of fat. Even at the same overall body fat or BMI, the greater one's waistline, the shorter one's lifeline.[2960]

Visceral fat is the killer fat. In contrast, superficial fat is relatively benign. *The New England Journal of Medicine* published a study of fifteen obese women, assessed before and after having about twenty pounds of superficial fat sucked from their bodies, which resulted in an almost 20 percent decrease in their total body fat.[2961] Significant improvements in blood sugars, inflammation, blood pressure, cholesterol, and triglycerides are typically seen with just a 5 to 10 percent loss of body weight in fat,[2962] but, after the massive liposuction, none of those benefits materialized.[2963] This suggests that the subcutaneous fat under our skin is not the problem, but, rather, the visceral fat is what's responsible for the metabolic insults of obesity. The good news is the riskiest fat is the easiest to lose. Our body appears to preferentially shed the villainous visceral fat first.[2964] And lifestyle interventions appear to have a similar weight-loss efficacy in older compared with younger people.[2965]

The life-shortening effects of visceral fat have been proven in rats. Surgical removal resulted in a significant extension in average and maximum lifespans.[2966] What about in people? Those who get bariatric weight-loss surgery do go on to live significantly longer than weight-matched controls who don't[2967] (details in see.nf/bariatric), but there haven't been any randomized trials to confirm it. There are, however, randomized weight-loss trials using diet and lifestyle interventions.

ALL FAT CALORIES AREN'T THE SAME

A meta-analysis of fifteen studies that randomized men and women to weight-loss regimens for up to twelve years found that losing weight doesn't only decrease inflammation, blood pressure, blood sugars, and disability, but it extends life, decreasing the risk of premature death by about 15 percent.[2968] So, what's the best weight-loss diet?

A whole food, plant-based diet was found to result in the greatest weight loss ever reported in the medical literature at six and twelve months compared to any other diet in randomized control studies that similarly didn't limit calories or mandate exercise.[2969] One of the reasons may be its lower fat intake. When people were randomized to eat a low-fat plant-based diet, they naturally ate about 600 fewer calories a day compared to those randomized to a high-fat ketogenic diet. This led to a significant loss of body fat and a preservation of lean body mass, the opposite of what was found with the ketogenic dieters, who saw no significant loss in body fat but did experience a reduction of lean body mass as their bodies appeared to cannibalize their own body protein (even though they were eating more protein).[2970]

All fat is not equal, though.

In *How Not to Diet*, I bust the myth that "a calorie is a calorie." A calorie from one source isn't always as fattening as a calorie from any other. If you eat about the same number of calories and the same amount of fat, for instance, but replace meat and butterfat with nuts, avocados, and olive oil, you could lose nearly six more pounds of fat in just one month.[2971] Saturated fat can also cause twice the accumulation of visceral fat compared to the same amount of other fats.[2972] Why? One reason saturated fats may be more fattening is that they appear more likely to be stored immediately rather than burned. For instance, oleic acid, the primary monounsaturated fat in nuts, avocados, and olives, is promptly burned about 20 percent more readily than palmitic acid,[2973] which is sourced mainly from meat and dairy and is the predominant saturated fat in the American diet.[2974] In fact, you can drip palmitic acid on muscle cells in a petri dish and openly demonstrate the suppression of fat utilization.[2975]

For other reasons why healthier eating can be so effective at weight loss, check out *How Not to Diet* from your local library.

Going to BAT Against Fat

At birth, we emerge, all wet and slimy, from the balmy 98.6°F (37°C) of our mothers' wombs directly into room temperature. To maintain warmth, we developed an adaptive

mechanism around 150 million years ago—the appearance of a unique organ called *brown adipose tissue*, or *BAT* for short, which enables us warm-blooded mammals to maintain our high body temperatures.[2976] BAT generates heat by consuming fat calories in response to exposure to the cold. The white fat in our belly stores fat, but the *brown* fat that is found high in our chest *burns* fat. BAT activation is not only a potential means to blunt the age-related decline in metabolic rate but it may also play a role in longevity.[2977]

BAT activity appears to be higher in long-lived animals and diminished in short-lived ones,[2978] and a gene that increases longevity in mice was found to boost BAT activity.[2979] Experiments surgically removing and transplanting brown fat between animals confirmed the role of BAT in healthy aging, at least in mice.[2980] If the same is true for humans, that could possibly help explain why women live longer than men, as females have greater BAT deposits throughout life.[2981] BAT activation enhances secretion of the fasting and longevity hormone FGF21 (see the Protein Restriction chapter), but, unfortunately, BAT activity decreases with age.[2982] Cold-stimulated BAT activity can be as high as 100 percent in those younger than forty, but that may drop down to less than 10 percent in older individuals.[2983]

You don't have to be left out in the cold, though. As I describe in *How Not to Diet*, there are dietary components that can boost BAT activation. Chili pepper compounds, for example, can do it and have been tested up through age sixty-four.[2984] The dosing works out to a whole raw jalapeño pepper or a half teaspoon of red pepper powder a day.[2985] To help beat the heat, finely chop or very thinly slice the jalapeño to reduce its kick, or mix the red pepper into soup or the whole-food vegetable "V8" smoothie I feature in one of my cooking videos on NutritionFacts.org. Alternately, there's ground ginger. It increases weight loss (potentially

through BAT activation[2986]) at a teaspoon a day,[2987] which you can just stir into hot water to make ginger tea.

WHAT'S THE IDEAL WEIGHT FOR LONGEVITY?

We seem to have become inured to the mortal threat of obesity. If you go back a half century or so in the medical literature, when obesity wasn't run of the mill, the descriptions are much more grim: "Obesity is always tragic, and its hazards are terrifying."[2988] But it's not just obesity. Of the four million deaths attributed to excess body fat each year, nearly 40 percent of the victims are merely overweight, not obese.[2989]

But what about the so-called obesity paradox, evidence suggesting overweight individuals live longer? The Global BMI Mortality Collaboration busted this myth using data from more than ten million people from hundreds of studies conducted in dozens of countries around the world.[2990] (Go to see.nf/paradox for details.) So, what's the optimal BMI?

The largest studies in the United States[2991] and around the world found that having a normal body mass index between 20 and 25 is associated with the longest lifespan.[2992] When you put together all the best available studies with the longest follow-up, that ideal range can be narrowed down even further to a BMI of 20 to 22,[2993] which is about 124 to 136 pounds for someone who stands five feet six inches tall.[2994] You can use this unisex chart to see what your optimal weight might be based on your height:

Optimal Weight Based on Height

Height	Ideal Weight	Height	Ideal Weight	Height	Ideal Weight	Height	Ideal Weight
4'9"	92–102	5'2"	109–120	5'7"	128–140	6'	147–162
4'10"	96–105	5'3"	113–124	5'8"	132–145	6'1"	152–167
4'11"	99–109	5'4"	117–128	5'9"	135–149	6'2"	156–171
5'	102–113	5'5"	120–132	5'10"	139–153	6'3"	160–176
5'1"	106–116	5'6"	124–136	5'11"	143–158	6'4"	164–181

SLEEP

I'm wondering if calling this section "Do as I Say, Not as I Do" would have been more accurate. (I find I'm just not as productive when I'm unconscious!) In fact, in the wee hours this morning, I thought, *I've got to get up and write the sleep chapter!* It's something I'm working on.

There is a perception that time spent sleeping is time wasted,[2995] but inadequate sleep is associated with multiple acute and chronic conditions and may result in increased risk of death and disease.[2996] Force people to go one week with six hours of sleep a night, and you change the expression of more than seven hundred genes.[2997] The most dire effect may be endothelial dysfunction.[2998] The endothelium is the thin layer of cells that covers the internal surface of blood vessels and is responsible for allowing our arteries to properly relax and dilate open.[2999] Randomize people for about a week to get five rather than seven hours of sleep, though, and just that difference of two hours a night results in a significant impairment in artery function.[3000] But how significant?

Sleep deprivation is no joke. The magnitude of impairment from a week of five-hour nights is similar to that reported in people who smoke, have diabetes, or have coronary artery disease. Yet, more than a quarter of the population may routinely get six or fewer hours a night.[3001] Sufficiently long, restful sleep sessions each night are considered an "indisputable cornerstone of good health."[3002] However, whether or not the link between sleep and mortality is cause and effect remains controversial.

In Living Color

In my research for this chapter on the potential for light therapy to help with insomnia, I ran across some supremely weird research findings—for example, a paper titled "Green Light Extends *Drosophila* Longevity" from the journal *Experimental Gerontology.* Researchers found they could "dramatically" increase by 24 percent the lifespan of fruit flies by raising them under green light.[3003] Conversely, they could dramatically reduce their lifespans by exposing them

to blue light, and this was true even in mutants that had no eyes! Even when the flies couldn't detect the color of the light at all, their lifespans were significantly altered. How?

A clue was unearthed when the researchers found that the longevity-boosting effect of green light was greatly reduced when the flies were fed an antibiotic, suggesting that their gut flora may somehow be involved.[3004]

In humans, skin exposure to ultraviolet light can alter the intestinal microbiome, but this is assumed to be an effect of vitamin D.[3005] It makes some sense that flies might somehow be nourished by green, a predominant color in their natural environment.[3006] I have videos on NutritionFacts.org about the beneficial effects of "forest bathing" for humans, though they appear to be due to the aromatic compounds, like pinene, which are given off by the trees,[3007] rather than the colors of the woods.

Lest you be tempted to order some green bulbs, note that in rats, green light (but not red or blue) induces glucose intolerance, which means higher blood sugars.[3008]

THE BIG SLEEP

There have been dozens of prospective studies on sleep duration and mortality. The most consistent finding is that there is no association at all. The second most common finding is a link between premature death and sleeping *longer*, typically more than nine hours a night. A quarter of the findings support a U-shaped effect, where those who don't get much sleep (typically less than six or seven hours) or get too much (more than nine) died at higher rates than those in the sweet spot, getting around seven to eight hours. Less than 5 percent of findings found a higher mortality risk only for those not getting enough sleep.[3009] Given these results, it's not surprising that a 2020 meta-analysis concluded that the only sleep category associated with higher risk for both older men and women was those sleeping the most at eight or more hours a night.[3010]

Seven hours of sleep a night may not sound like enough, but it may actually be what's natural for our species. Scientists studied three preindustrial societies, isolated from one another across two continents, and found surprising uniformity. Despite the absence of electric lighting or electronic gizmos, they usually stayed up until three or so hours after sunset and then arose before dawn, getting a solid six and a half hours of sleep out of about seven and a half hours in "bed."[3011] Even the studies showing risk at both ends of the sleep-duration spectrum tended to find a greater risk on the longer side.[3012]

A mechanism by which excess sleep might be harmful remains elusive, so a cause-and-effect relationship between sleeping eight or more hours a night and increased risk of death and disease has been dismissed by some as implausible.[3013] Could it be reverse causation, like sickness leading to more time in bed instead of vice versa? Maybe it's due to confounding factors, such as employment status?[3014] After all, who may be more apt to sleep in? Those without a job. Long sleepers (those sleeping at least nine hours a night) are more likely to be sedentary, obese, depressed, unmarried, and diabetic, and have a host of diseases that could confound the link between mortality and sleeping late.[3015] Studies have taken socioeconomic status and health conditions into account, but it's hard to control for everything.[3016] The bottom line? For adults sixty-five and older, the National Sleep Foundation recommends seven to eight hours of sleep a night,[3017] which correlates with about the sleep duration associated with the lowest risk of frailty[3018] and age-related muscle loss.[3019]

How to Get a Good Night's Sleep

Those who have sleep apnea, a common consequence of obesity that interferes with sleep, can benefit from the use of CPAP machines while they're losing the weight to treat the underlying cause.[3020] But what if that's not your problem and you still have difficulty falling or staying asleep? Check out my four rules of sleep conditioning and hygiene in see.nf/sleeprules, which involves cognitive behavioral therapy techniques,[3021] along with regulating the dose and

timing of exercise, caffeine, nicotine, and alcohol, as well as establishing the best bedtime routines and sleep environment.

RISK WITHOUT REWARD

There is a common misconception that older individuals need less sleep.[3022] The reality is sleep may just be harder to get as we age. Insomnia symptoms increase with advancing age, with prevalence rates approaching 50 percent in adults sixty-five and older, and remission rates as high as 50 percent over three years.[3023] Thankfully, insomnia symptoms do not appear to correlate with mortality risk, though this may be partly because most people diagnosed with insomnia may actually end up getting more than six hours a night when their sleep is measured by objective means.[3024] Based on twin studies, insomnia has a heritability of 40 percent, meaning our genes account for less than half of insomnia risk.[3025] What can we do to flex the bulk we may have control over?

Sleeping pills are a nonstarter. Hypnotics are the class of sleeping pills that includes Ambien, the one most commonly prescribed.[3026] People who are prescribed even just half a dose or more a year appear to have more than three times the risk of dying prematurely compared to those receiving none.[3027] Up to 10 percent of the adult population are prescribed these drugs,[3028] so if these pills are truly killing people, that means they could be responsible for a six-figure death toll each year.[3029] Not surprisingly, the manufacturer of Ambien questioned the study,[3030] but it wasn't a one-off. It was one of two dozen studies that found a significant association between sleeping pills and premature death.[3031] In response to criticism for "reporting alarmingly high death risks from commonly used medications,"[3032] the principal investigator at the Scripps Clinic Sleep Center replied: "We cannot hide risks, even if they might frighten patients out of taking hypnotics. Patients have a right to know."[3033]

We also have a right to know that they may not even work. The most authoritative meta-analysis concluded that Ambien and Ambien-type drugs do not significantly increase total sleep time.[3034] How can that be? My patients used to tell me how much better it made them sleep. As it turns out,

people only *think* they sleep better. Despite reporting that hypnotics gave them an extra half hour of sleep, objective measurements tell us they weren't getting significantly more sleep at all.[3035] The subjective sense that you sleep better after popping a pill appears to be a result of the drug's amnesic properties, meaning the hypnotics can erase your memories of just how badly you slept.[3036] The American Academy of Sleep Medicine recommends against the use of these drugs as a primary treatment for chronic insomnia.[3037]

Dip Your Toes In

Eating late at night not only exacerbates weight gain, as I cover in *How Not to Diet*, but may hinder our ability to fall asleep. Normally, around bedtime, there is a drop in our core body temperature,[3038] which seems to be one of our cues that it's time to sleep, but late-night munchies may interfere with that. In that case, wouldn't taking a hot shower be counterproductive? No. The moment you step out of the bath, the rapid decline in your skin temperature can enhance that natural nighttime drop and actually improve your sleep.[3039] Just soaking your feet in a warm bath may help you fall asleep about fifteen minutes faster.[3040]

Footbaths have been called a "safe, simple, and non-pharmacological method to improve sleep quality."[3041] A meta-analysis of trials found that enjoying a warm shower, footbath, or full-body bath for just ten minutes one to two hours before bedtime can help people fall asleep more quickly and sleep better.[3042]

Special blood vessels that connect the arteries and veins in the palms of our hands and the soles of our feet are dilated by the warm water, enhancing the transfer of heat from our core to our hands and feet, where it can be dissipated more efficiently to achieve that sleep-inducing drop in core temperature.[3043] Older adults have a blunted temperature response—perhaps helping to explain some of

the age-related sleep difficulties—and that potentially makes measures to increase circulation in our hands and feet even more important.[3044]

Is there any way to accomplish this without getting wet? A hot water bottle by our feet might do it.[3045] Can we just wear warm socks? A study in which young men wore socks starting an hour before bedtime didn't subjectively improve sleep quality. Objectively, however, they slept about a half hour more than when sockless, thanks to falling asleep more quickly and waking up fewer times throughout the night.[3046]

MELATONIN AND LONGEVITY

Some experts recommend melatonin, a hormone secreted by the "third-eye" pineal gland in the middle of our head, as a first-line agent to treat insomnia in older adults.[3047] The World Sleep Society disagrees, due to its low efficacy.[3048] Subjectively, people report better sleep on melatonin,[3049] though, objectively, a meta-analysis of studies found that melatonin only helped people get to sleep four minutes faster and extended overall sleep duration by thirteen or so minutes.[3050] Concerning contaminants have also been found[3051] (see.nf/melatoninsupplements), though there are also natural sources in the diet (see.nf/melatoninfoods). I was more intrigued by its purported anti-aging benefits, but, as I document in see.nf/melatoninaging, the data are all over the place.[3052] In rats, for example, melatonin significantly improved survival, but so did a drug that *blocks* melatonin![3053]

Herbal Sleep Aids?

Valerian root is one of the most frequently studied herbs for sleep.[3054] However, most studies, including all the latest, most methodologically sound ones, found no significant benefit over placebo.[3055] Randomized controlled trials found that lemon verbena could help insomnia patients, at least subjectively,[3056] but chamomile could not.[3057] Chamomile

may improve subjective sleep quality in noninsomniacs, though, based on a meta-analysis of five trials.[3058]

DON'T SLEEP WITH THE FISHES

In terms of food, low fiber intake, as well as high saturated fat and sugar intake, is associated with lighter, less restorative sleep.[3059] Meat consumption is associated with napping, which has been suggested as a proxy for sleepiness.[3060] This may be one of the reasons insomnia has been reported as a side effect of low-carb, ketogenic diets.[3061] Even after controlling for obesity, higher meat consumption appears to double the odds of snoring, with each daily serving of meat associated with 60 percent higher odds of diminished sleep quality and quantity in older adults. Both red meat and poultry were implicated,[3062] and no significant difference in objective sleep measures has been found for fish compared to chicken, pork, and beef.[3063]

Researchers have suggested that the amino acids like methionine in meat compete with tryptophan, which is the precursor to both melatonin and the "happiness hormone" serotonin, for transport to the brain.[3064,3065] This may help explain why randomizing people to restrict fish, poultry, and red meat has been shown to improve mood within two weeks.[3066] Plant proteins, on the other hand, tend to be relatively lower in methionine, which may help explain why a study of thousands of people put through the plant-based Adventist CHIP program reported a greater than 50 percent drop in reported insomnia and restless sleeping, not to mention declines in easy emotional upset and feelings of fearfulness or depression within four weeks.[3067,3068]

Salad Nights

Any vegetables that might help? *Lactuca sativa* is a plant that has traditionally been used in the treatment of insomnia.[3069] What is this exotic-sounding vegetable? Lettuce![3070] Lettuce extracts have evidently been used from

the time of the Roman Empire for sedation and sleep induction. Lettuce has a hypnotic substance in it called *lactucin*, which is what makes lettuce taste a little bitter. Sleep in both mice and rats is enhanced by romaine lettuce,[3071] which tends to have a higher lactucin content compared to other lettuces,[3072] but what about in people? I go through all the studies in see.nf/lettuce. The bottom line: A quarter teaspoon of ground lettuce seeds beat out placebo in a double-blind trial for improving sleep quality.[3073]

STRESS MANAGEMENT

According to the director of the largest and most comprehensive study of centenarians in the world,[3074] the average life expectancy with optimal health behaviors—meaning no tobacco or alcohol use, regular exercise, vegetarianism, and the effective management of stress—should reach into the late eighties. "[T]he vast majority of why one lives to their sixties or seventies versus these later octogenarian years," he and a colleague wrote, "would be explained by health habit choices."[3075] I've discussed diet and exercise. How important is stress management?

The American Psychological Association conducted national surveys and found that the majority of Americans report moderate to high levels of stress.[3076] Even though the prevalence of anxiety disorders has not experienced much change over the last few decades, the level of general psychological stress seems to be worsening.[3077] What implications does this have for life expectancy?

When stressed, the majority of people not only eat more[3078] but they tend to gravitate toward foods high in calories, fat, and sugar.[3079] When study participants were randomized to solvable and unsolvable word puzzles, for example, those in the more stressful situation chose less healthy snacks, M&M's rather than grapes.[3080] It's called *comfort food* for a reason. Overeating may be a sign that something is eating us.

Similar experimental studies have shown that acute stress tests can also induce cigarette cravings,[3081] increase alcohol intake,[3082] and contribute to

relapses in illicit drug use.[3083] So, when studies show stressful life events, like the death of a child or a spouse, are associated with a shortened lifespan,[3084] what's really to blame? Might it just be these concomitant unhealthy behaviors?

Once you control for these secondary mediators, the significant link between stress and mortality does appear to disappear.[3085]

Keeping Occupied

Among the most poignant illustrations of the subordinate role of stress to lifestyle behaviors are the natural experiments set up by wartime deprivations. After all, what could be more stressful than living under Nazi occupation? Heart attack rates must have skyrocketed, right? No, studies in Nazi-occupied Norway,[3086] Finland, and blockaded Sweden showed the rates plummeting, dropping down to as little as only about one-fourth the preceding rate.[3087] Check out see.nf/worldwars to see what happens when meat, eggs, and butter are rationed,[3088] and food shortages result in diets dominated by garden produce.[3089] In reference to the Nazi occupation of Norway, an editorial in the *Journal of the American Medical Association* noted, "[S]tress has little or no effect if the diet is poor in animal fat."[3090]

SOCIAL TIES

Social connectivity is a blue zone attribute scrutinized for its potential role in supporting longevity.[3091] People who are married, for example, appear to have lower mortality rates than those who are single.[3092] The loss of a spouse or partner appears to increase mortality risk for both widowers and widows. However, "death from a broken heart"[3093] may be due in part to bereavement's association with increased use of cigarettes and alcohol.[3094] Higher mortality rates haunt those who lose a spouse not only through death

but also through divorce. The never-married also seem to be at higher risk. Most of the studies documented no difference by gender, but, of the minority that did, most found that the risk of premature dying was greater for single men than single women.[3095]

The marriage advantage may be a consequence of selection bias or confounding factors. For example, healthier individuals are more likely to marry or stay married, and higher socioeconomic status and better health behaviors are found among married individuals. Nevertheless, studies that have tried to control for such factors continue to find a betrothal benefit.[3096]

Single or not, social isolation—an objective measure of social disconnectedness[3097]—and the subjective feeling of loneliness[3098] are both associated with an increased risk of premature death. But the effect is diminished when controlling for confounding factors,[3099] such as tobacco use or problems with alcohol associated with feelings of loneliness.[3100] There is also the nagging chicken-or-the-egg possibility of reverse causation, where, instead of social isolation leading to impaired health, the correlation may be due to ill health leading to the isolation.[3101]

Who Is Rescuing Whom?

Does slobbery social contact count? More than two-thirds of U.S. households, including mine, include a pet.[3102] In an "awww"-inspiring paper published in the prestigious journal *Science* titled "Oxytocin-Gaze Positive Loop and the Coevolution of Human-Dog Bonds," researchers found that petting or looking into the eyes of a canine companion leads to oxytocin release in the brains of both the humans and the dogs—the same "love hormone" that bonds breastfeeding mothers to their infants.[3103]

I was reading about the potential mechanisms by which our animal companions might improve our survival after a heart attack when I ran across a passage about a "profound" cardiovascular response when petting dogs or horses. "This response usually takes the form of a significant reduction in the heart rate and blood pressure." I could totally see that.

But then the next sentence made me do a double take: "Unfortunately, we have no information about the physiological responses of the person doing the petting."[3104] The researchers were talking about the heart rate and blood pressure of the animals!

To my surprise, studies of the effects of companion animals on human health have, as one review put it, produced a "mishmash of conflicting results."[3105] For all the details, check out my video see.nf/pets. As you can imagine, the observational studies are rife with the potential for confounders[3106] and reverse causation,[3107] and the one interventional study that actually put animal companionship to the test involved "pet insects."[3108] Still, it can't hurt to heed this advice from a medical journal article published in 1925: "The best prescription to be written for a walk is to take a dog, a cane and a friend."[3109]

III. Preserving Function

PRESERVING YOUR BONES

Literally meaning *porous bone*, osteoporosis is characterized by reduced bone formation, excessive bone loss, or a combination of both, which leads to bone fragility[3110] and contributes to millions of fractures a year.[3111] Overall, the disease is estimated to affect two hundred million people worldwide.[3112]

Bone mineral density is used as a robust and consistent predictor of osteoporotic fracture.[3113] Although the bone density cutoff for an osteoporosis diagnosis is arbitrary,[3114] using the current definition, the disease may affect about one in ten women at age sixty, two in ten by age seventy, four in ten by age eighty, and six or seven out of ten by age ninety. Osteoporosis is typically thought of as affecting mostly women, but one-third of hip fractures occur in men.[3115] For fifty-year-old white women and men, for example, the lifetime risks for osteoporotic fractures are 40 percent and 13 percent, respectively.[3116]

The good news is that osteoporosis need not occur. Based on a study of the largest twin registry in the world, less than 30 percent of osteoporotic fracture risk is heritable. Researchers concluded that "fracture-prevention efforts at older ages should be focused on lifestyle habits."[3117] This is consistent with the enormous variation in hip fracture rates around the world, with the incidence of hip fracture varying tenfold, or even a hundredfold, between countries, suggesting that excessive bone loss is not an inevitable consequence of aging.[3118]

The U.S. Preventive Services Task Force (USPSTF), an independent scientific panel that sets evidence-based clinical prevention guidelines,

recommends osteoporosis screening (such as the DXA scan of bone mineral density, also called DEXA) for all women from age sixty-five and potentially even earlier for postmenopausal women at increased risk, such as having a history of parental hip fracture, smoking, excessive alcohol consumption, or low body weight.[3119] What should you do if you're diagnosed? More important, what should you do to never *get* diagnosed? Before we explore the drugs on offering to treat osteoporosis, let's look at the drugs that may cause the disease.

ACID BLOCKERS MAY BE BAD TO THE BONE

Stomach acid–blocking "proton pump inhibitor" (PPI) drugs with brand names like Prilosec, Prevacid, Nexium, Protonix, and AcipHex are among the most popular medications in the world, raking in billions of dollars a year,[3120] but they come with a cost. As I document in see.nf/ppi, dozens of studies totaling more than two million people show higher hip fracture rates among both long- and short-term users at all dose levels.[3121] This class of drugs has been linked to increased risk of other possible adverse effects, such as pneumonia,[3122,3123] intestinal infections, kidney failure,[3124,3125] stomach cancer,[3126] cardiovascular disease,[3127] and premature death.[3128] What's more, once you start them, it can be hard to stop due to withdrawal symptoms.[3129] And, as I document in the video, the irony is that most people taking these drugs shouldn't even be on them in the first place.[3130]

To deal with acid reflux without drugs, recommendations include weight loss,[3131] smoking cessation,[3132] avoiding fatty meals,[3133] not eating within two to three hours of reclining,[3134] increased fiber consumption,[3135] and an overall more plant-based diet.[3136]

Bones and Joints

For decades, we've recognized that cigarette smoking can have a major effect on bone health, increasing the lifetime risk of hip fracture by about half.[3137] It also appears to impair bone healing,[3138] so much so that surgeons ask if they should discriminate against smokers because wound and

bone healing complication rates are so high.[3139] Instead of cigarettes, what about smoking cannabis?[3140] I cover that in see.nf/joints. The bottom line: Heavy cannabis use does appear to be an independent predictor of weaker bones.[3141]

HOW EFFECTIVE ARE OSTEOPOROSIS DRUGS?

Drug therapy for osteoporosis is recommended for postmenopausal women or men aged fifty and older with a history of past hip or vertebral (spine) fractures, those with hip or spine "T-scores" ≤ -2.5, or those who don't make that cutoff but have an estimated 20 percent or greater risk of a major osteoporotic fracture over the subsequent decade or, specifically, an estimated 3 percent or higher risk of hip fracture.[3142]

T-score? That's a measure of how dense your bones are compared to the average thirty-year-old white woman. (Seriously.) Since we tend to lose bone as we get older, we can be labeled as having osteoporosis even if we have completely normal bone density for our age. However, just because our bone density may be normal doesn't mean it's necessarily optimal. That's one reason why the National Osteoporosis Foundation set out guidelines for drug treatment. Another reason, perhaps, is that it gets substantial funding from the pharmaceutical companies that rake in literally billions of dollars in profits from osteoporosis drugs.[3143] What does the science say? I run the numbers in see.nf/drugefficacy. Basically, surveys show that most people wouldn't take these osteoporosis drugs if they knew the truth,[3144] but it's for you to decide.

HOW SAFE ARE OSTEOPOROSIS DRUGS?

Most people prescribed these drugs stop taking them within a year, and it's not just because of the lack of perceived efficacy.[3145] Osteonecrosis of the jaw and atypical femur fractures are two rare but serious side effects. When they came to light, they contributed to more than a 50 percent drop in the use of these drugs.[3146] A *New York Times* article noting the decline began: "Reports of the drugs' causing jawbones to rot and thighbones to snap in two have shaken many osteoporosis patients so much that they say they

would rather take their chances with the disease."[3147] In see.nf/drugsafety, I review just how likely these are and what can be done to reduce the risk.

HOW SAFE AND EFFECTIVE ARE CALCIUM SUPPLEMENTS?

Are there any supplements that might help reduce the risk of osteoporosis? In the Preserving Your Muscles chapter, I discuss how creatine can benefit muscle health in older adults, which could potentially translate into lower risk of falls, but it failed to do so when put to the test.[3148] The vast majority of studies show no benefit from creatine for bone health.[3149] What about supplementing calcium and vitamin D?

In just a dozen years, expert panels shifted from suggesting widespread calcium supplementation to prevent osteoporosis[3150] to telling patients "do not supplement,"[3151] the suggestion still in effect for most people today.[3152] I detail what happened in my video see.nf/calciumsafety. In short, calcium supplements appear to raise the risk of heart attacks and strokes[3153] by leading to unnaturally large, rapid, and sustained calcium levels in the blood[3154] that increase the risks of abnormal clotting.[3155]

Having a heart attack or stroke can be devastating, but so can fracturing your hip. How effective are calcium supplements in preventing hip fractures? Calcium intake in general does not seem to be related to hip fracture risk at all.[3156] If anything, randomized controlled trials suggest a 64 percent *greater* risk of hip fractures with calcium supplementation compared to placebo. In my video see.nf/calciumeffectiveness, I explore how we even got the idea that taking calcium supplements might help our bones. Basically, evidence suggests that dietary calcium intake is not something most people need to worry about,[3157] given our body's ability to absorb more and excrete less at lower intakes.[3158] Don't push it too far, though. Once you get down to just a few hundred milligrams per day, you can suffer significantly more bone loss.[3159]

THE BEST VITAMIN D DOSING TO PREVENT FALLS

Too much vitamin D can be harmful, too. In my video see.nf/vitamindfalls, I run through the studies showing that periodic megadoses, like a single dose of 500,000 units once a year, can increase fall risk compared to

placebo.[3160] Increased falls were also seen after giving 100,000[3161] or 60,000 units once a month.[3162] On a daily basis, a yearlong randomized, double-blind, placebo-controlled trial of seven different doses of vitamin D found that elderly women randomized to the medium doses (1,600, 2,400, or 3,200 units a day) were significantly less likely to fall than those given either the lower doses (400 or 800 units a day) or the higher doses (4,000 or 4,800 units a day).[3163] Additionally, taking 4,000 or 10,000 units a day for three years *decreased* bone mineral density,[3164] especially in women,[3165] so you don't want to overdo it.

DOES MILK REALLY DO A BODY GOOD?

Which foods might help our bones? Milk comes to mind, but it appears that's just an empty marketing ploy. There haven't been any randomized controlled trials,[3166] but most meta-analyses of dairy milk consumption and hip fracture population studies have shown no overall protection.[3167] In fact, Dr. Walter Willett, past chair of Harvard's nutrition department, went so far as to suggest that it might even contribute to the high incidence of hip fractures in countries with the greatest milk consumption.[3168] It was that enigma that inspired a Swedish research team to perform a set of studies involving 100,000 men and women followed for up to twenty years.[3169] They found that milk intake appeared to *increase* bone and hip fracture rates, as well as shorten people's lives.[3170]

As I explore in my video see.nf/milkbones, the culprit appears to be the galactose, a breakdown product of the milk sugar lactose. Galactose is actually used by scientists to induce premature aging in lab animals. In one such study, after being given galactose, the "life-shortened animals showed neurodegeneration, mental retardation and cognitive dysfunction … diminished immune responses and reduction of reproductive ability."[3171] It doesn't take much, either—just the human equivalent of one to two glasses' worth of milk a day.[3172] But humans aren't lab animals. We've known for nearly a century, for instance, that you can cause cataracts in rats by feeding them a lot of lactose or galactose.[3173] The epidemiological data, however, are mixed as to whether dairy does the same in people.[3174]

With the then largest-ever study on milk intake and mortality showing such adverse effects, Harvard researchers stepped in with three of their

cohorts to form a study twice as big to see whether the Swedish findings were just a fluke. After following more than 200,000 men and women for up to three decades, they confirmed the bad news in 2019. Those who consumed more dairy lived significantly shorter lives.[3175] Every additional half serving of regular milk a day was associated with a 9 percent increased risk of dying from cardiovascular disease, an 11 percent increased risk of dying from cancer, and an 11 percent increased risk of dying from all causes put together. More details in see.nf/milkupdate.

Highly influential advocacy organizations, such as the U.S. National Osteoporosis Foundation and the European-based International Osteoporosis Foundation, continue to push dairy, drugs, and calcium supplements. Perhaps their objectivity is compromised by the influence of their commercial sponsors, which include companies that market (you guessed it) dairy, drugs, and supplements.[3176] Conflict of interest is a legitimate concern. Most recent reviews on dairy and osteoporosis in the English-language medical literature were found to be written by those with ties to the dairy industry.[3177] A primary justification for inclusion of dairy in federal nutrition recommendations is based on purported bone benefits that are not supported by the available scientific evidence.[3178]

What if dietary guidelines were drafted without commercial influence? As I've mentioned, Canada recently decided to exclude industry reports and stick to the science in the formation of its new dietary guidelines. Major changes included a new emphasis on plant-based food intake, along with the removal of the dairy food group.[3179]

ACID/BASE BALANCE AND BONE

For most of the last century, a prevailing theory within the field of nutrition was that eating acid-forming foods such as meat was, in essence, putting us at risk of peeing our bones down the toilet.[3180] But as I describe in my video see.nf/acidbone, we've come to learn that most of the extra calcium people lose in their urine after a protein-rich meal comes from increased calcium absorption, not their bones.[3181] So, if our body isn't using our bones to primarily buffer the acid formed from our diet, how is it neutralizing the acid? As I explore here in Caught Off Base, the answer may lie with our

muscles. (Our kidneys can buffer acid with a base they make from the muscle breakdown product *glutamine*.[3182])

At high enough acid loads, though, bone may be affected, too. Sadly, bone fractures are a side effect that disproportionately plagues kids with intractable epilepsy who are placed on ketogenic diets.[3183] Even a few weeks on a keto diet may have negative effects on bone remodeling markers.[3184] Such diets appear to cause a steady rate of bone loss as measured in the spine,[3185] thought due to the fact that ketones themselves are acidic[3186] and can result in a mild metabolic acidosis.[3187] It could also be all the saturated fat. The predominant saturated fat, palmitic acid, is toxic to bone-building cells in a petri dish.[3188] In general, the intake of saturated fat is significantly associated with increased hip fracture risk.[3189]

As we grow older, the pH of our blood falls to the lower (more acidic) end of the spectrum, perhaps due in part to the declining ability of our kidneys to excrete acid with age.[3190] In vitro studies suggest that this drop in pH may lead to activation of the cells that break down bone, as well as an inhibition of bone-building cells.[3191] This may explain why, when researchers removed alkaline-forming foods (fruits and vegetables) from people's diets, a marker of bone formation (bone-specific alkaline phosphatase) significantly dropped and a bone resorption marker (carboxyterminal cross-linking telopeptide) shot up, and vice versa when they then added six cups of fruits and vegetables to the participants' daily diets.[3192]

In individuals sixty-five or older, the greater the estimated ratio between acid-forming foods and alkaline-forming foods, the greater the risk of hip fracture.[3193] (To see which foods are which, see the figure here.) To prove cause and effect, two-year randomized, double-blind, placebo-controlled trials were performed in which three added servings of fruits and vegetables[3194] or the equivalent of six failed to have an effect, but nine daily servings of fruits' and vegetables' worth[3195] of an alkaline-forming compound (potassium citrate) was able to successfully increase bone volume and density.[3196] This shows that buffering the dietary acid load of a typical Western diet with enough fruits and vegetables may help prevent bone loss.

PRUNING YOUR SKELETON

Inflammation and oxidative stress may also play a role in osteoporosis. The intake of pro-inflammatory foods[3197] and an elevation of inflammatory markers in the blood, such as C-reactive protein, are both associated with osteoporotic fractures,[3198] and postmenopausal women with osteoporosis tend to harbor greater signs of oxidative damage and fewer antioxidants in their blood.[3199] These are two more reasons why a higher intake of fruits and vegetables is associated with lower fracture risk.[3200] Vitamin C is a third. The consumption of vitamin C–rich foods is associated with lower risk of bone loss, osteoporosis, and hip fracture[3201]—a 5 percent lower hip fracture risk for every 50 mg of vitamin C a day, which is about the amount in one orange.[3202] Are there any fruits and vegetables that are particularly good?

After feeding rats more than fifty different foods, the fruit found to preserve their bones the best was the prune and the leading vegetable was the onion.[3203] What about in people? I review the available evidence in see.nf/prunes. The bottom line is that five or six prunes a day may help preserve bone density.[3204]

CRY YOUR WAY TO THE BANK

What was that about onions? I review both the preclinical and clinical data in see.nf/onionstomatoes. Basically, onions can lead to an improvement in a marker of bone loss in people,[3205] but the study didn't last long enough to see if this translated into tangible bone benefits. However, a clinical trial on the other vegetable put to the test did.

HITTING THE SAUCE

In the same video (see.nf/onionstomatoes), I review all the tomato juice[3206] and sauce[3207] studies, as well as the Scarborough Fair Diet (which includes prunes, onions, tomatoes, and presumptive bone-protecting herbs parsley, sage, rosemary, and thyme, from the song popularized by Simon and Garfunkel).[3208] The bottom line is that we can probably just focus on stuffing our faces with fruits and vegetables of any stripe.

TEA AND TEETOTALING

What about beverages? A meta-analysis on the effect of alcohol on osteoporosis found that, compared to abstainers, people who sipped one to two drinks a day had a 34 percent increased risk of developing osteoporosis.[3209] Having more than two a day bumped up that elevated risk to 63 percent, which appears to translate into an increase in hip fracture risk.[3210] This may be partially from alcohol's negative effect on bone health and also because of fall risk due to impaired coordination.[3211]

One way sugary soda appears to cause negative effects on bone is the same way[3212] sodium does: by increasing calcium loss through the urine.[3213] It doesn't appear to be the caffeine, though: Drinking three or more cups of coffee daily is associated with a doubling of hip fracture risk, but habitual tea consumption is associated with significantly *lower* risk.[3214] Hope was raised that the tea link was cause and effect when a randomized trial found an improvement in bone turnover markers in women[3215] and higher actual bone mass in tea-fed rats.[3216] But, in the Minnesota Green Tea Trial, the largest and longest clinical trial on the effects of green tea extracts on postmenopausal women, no significant benefit on bone mineral density was found.[3217]

NUTS AND BONES

Researchers in the world-famous lab of Dr. David Jenkins exposed human osteoclasts, the bone-eating cells, to blood obtained before, as well as four hours after, eating a handful of almonds. Details in see.nf/bonenuts, but basically, almonds may be able to help prevent bone loss but not build bones,[3218] whereas the opposite was found for prunes—so a combo prune-and-almond trail mix may be in order.

ESTROGENS VS. PHYTOESTROGENS

When the Women's Health Initiative study found that menopausal women taking hormone replacement therapy suffered "higher rates of breast cancer, cardiovascular disease, and overall harm," a call was made for safer alternatives.[3219] Yes, the Women's Health Initiative found that supplemental estrogen does have positive effects, such as reducing menopausal

symptoms, improving bone health, and reducing hip fracture risk, but negative effects include increased risk of blood clots to the heart, brain, and lungs, as well as breast cancer.[3220]

Ideally, to get the best of both worlds, we'd need what's called a selective estrogen receptor modulator—something with pro-estrogenic effects in tissues like bone but, at the same time, *anti*-estrogenic effects in other tissues like the breast.[3221] Drug companies are trying to make these, but the phytoestrogens in soybeans like genistein, which is structurally similar to estrogen, appear to function as natural selective estrogen receptor modulators. How could something that looks like estrogen act as an *anti*-estrogen?

In my video see.nf/phytoestrogens, I explain how soy can have it both ways, thanks to the discovery of two different types of estrogen receptors in the body—bone-strengthening effects without this risk of clots[3222] and cancer.[3223] A 2020 meta-analysis of more than five dozen randomized controlled trials of soy phytoestrogens with postmenopausal women found significantly improved bone mineral density compared to control in the hip, spine, and wrist.[3224] When tested head-to-head, it was even comparable to hormone replacement therapy.[3225] In a two-year study, for example, soymilk was compared to a transdermal progesterone cream and a placebo control group. The control group lost significant bone mineral density in their spine over the two years, whereas the progesterone group lost significantly less. However, the group drinking two glasses of soymilk a day ended up with *more* bone than when they started.[3226]

Soymilk also appears to have the additional benefits of reducing risk of breast[3227] and prostate[3228] cancers, improving gut health,[3229] and decreasing inflammation[3230] and free radical DNA damage compared to rice milk or dairy milk.[3231] It can also improve insulin resistance[3232] and help with stroke rehabilitation, improving walking speed, exercise endurance, grip strength, and muscle functionality,[3233] as well as lower blood pressure better than dairy milk.[3234] Soymilk can even lower your LDL cholesterol as much as 25 percent after just twenty-one days.[3235] Nutritionally, soymilk is considered the best choice for replacing dairy milk in the human diet.[3236]

The reason we care about bone mass is that we want to prevent fractures. Dairy products can also increase bone density,[3237] but this fails to translate into decreased hip fracture risk.[3238] Soy foods, however, have

consistently been significantly associated with 20 to 50 percent lower risk of fracture in women,[3239] starting with as little as a single serving of soy a day—the equivalent of just 5 to 7 g of soy protein or 20 to 30 mg of phytoestrogens,[3240] which is about a cup of soymilk or, even better, a single serving of a whole soy food like tempeh, edamame, or the mature beans themselves.[3241] We have no fracture data on soy supplements, but it's better to stick to whole foods anyway rather than taking pills or powders, especially since "huge differences" have been found in isoflavone content when identically labeled commercial soy isoflavone supplements have been tested.[3242]

WHAT ABOUT THE "ANTI-NUTRIENTS" IN BEANS?

So-called anti-nutrients are plant compounds that purportedly reduce the absorption of nutrients. But recently, the whole concept of "anti-nutrients" has been called into question, and some of them may in fact be beneficial.[3243] Details in see.nf/milks.

Plant-Based Bones

With studies showing that an increased consumption of plant foods is associated with increased bone mineral density,[3244] while a more animal-sourced nutrient pattern is associated with a higher risk of fractures, one would expect less osteoporosis in those eating plant-based diets. The data, however, are mixed.[3245] In see.nf/vegbone, I review the last half century of available evidence.

Vegetarians and vegans tend to have lower bone mineral density compared to meat eaters,[3246] but most of the difference effectively disappeared once body size was taken into account. Thus, it's not so much the composition of the diets of vegetarians and vegans as much as it's the fact that they are typically so much slimmer.[3247]

Hip fracture risk goes down as weight goes up. Nearly half of underweight women have osteoporosis, for example,

but less than 1 percent of obese women, which makes total sense.[3248] Being obese forces your body to make your bones stronger to carry around extra pounds. That's why weight-bearing exercise is important; it constantly puts stress on your skeleton. And vegetarians—especially vegans—have such low rates of obesity that it's no wonder they would have lower bone density on average. Does this translate into elevated fracture risk?

I review all the fracture data in my video see.nf/vegfractures, but, in short, the answer is yes[3249]—and not only because vegans are generally more slender[3250] but because of the potential for inadequate vitamin D status and calcium intake.[3251] I recommend 2,000 IU of supplemental vitamin D a day for those getting inadequate sun exposure[3252] and at least 600 mg of calcium daily[3253] via calcium-rich plant foods—preferably low-oxalate dark green leafy vegetables, which include all greens except spinach, chard, and beet greens. (All very healthy foods, but just stingy with their calcium.)

EXERCISE EARLY AND OFTEN

When it comes to bone health, it's use it or lose it. That's why astronauts can lose 1 percent of their bone mass *every month* they're not on planet Earth.[3254] Their bodies aren't stupid. Why waste all that energy making a strong skeleton if you're just floating around and not putting any weight on it? Physical activity is considered a "widely accessible, low cost, and highly modifiable contributor to bone health."[3255] However, some exercises are more effective than others, as I detail in see.nf/weightbearing.

Not by Any Stretch

Lower-impact activities like yoga are generally not considered to be bone-building,[3256] despite misleading

studies[3257] purporting otherwise. (Details in see.nf/yogabones.) In fact, yoga may even result in vertebral compression fractures. Safer poses include those with mild spine extension and leg stretching, like the warrior pose; poses to be avoided include extreme spinal flexion or extension (like the forward fold or the camel), neck strain (like the plow), or low back/hip strain (like the one-legged pigeon), which may cause fractures even in people with normal or near-normal bone mass density.[3258]

Based on a systematic review involving more than 9,000 yoga practitioners, the risk of yoga-associated injuries is lower than from higher-impact activities[3259] such as running,[3260] with the exception of meniscus damage in the knee, presumed to be due to yoga postures like the lotus position.[3261] Hot (Bikram) yoga carries its own risk.[3262] Watch see.nf/yogarisk for a list of recommendations to stay safe.

THE SINGLE MOST IMPORTANT THING TO DO TO PREVENT OSTEOPOROTIC FRACTURES

Bone mineral density screening is a billion-dollar industry,[3263] so it shouldn't be that surprising that's the focus of osteoporosis and treatment. But among women sixty-five and older, only 15 percent of low-trauma fractures (meaning from a fall from no more than standing height) are due to osteoporosis.[3264] Between the ages of sixty and eighty, hip fracture risk increases thirteenfold in men and women, whereas the age-related decline in bone mineral density accounted only for a twofold increased risk.[3265] So, 85 percent of the age-related rise in hip fracture risk has nothing to do with the measured density of your bones.

Without a fall, even fragile hips don't fracture. The primary cause of fractures—including vertebral fractures—are falls.[3266] The disparity between men and women in hip fracture rates seems primarily not because men have stronger bones but because women fall more often.[3267] Doctors simply asking the question *"Do you have impaired balance?"* can predict

about 40 percent of all hip fractures,[3268] which is more than a bone scan diagnosis of osteoporosis can.[3269] Even a weak osteoporotic bone is strong enough to survive normal life activities without the excessive loading that comes from the impact of a fall or, in the case of the spine, bending with your back rather than your knees to lift something.[3270]

The primacy of falls in fracture risk explains a number of apparent osteoporosis paradoxes. For example, despite the fact that about 70 percent of bone mass is determined by your genes,[3271] the heritability of hip fractures appears negligible[3272] because the propensity to fall is much less inherited.[3273] It also explains the poor predictive value of DXA scanning for fractures. Adding bone mineral density measures to a hip risk score based just on age, sex, height, weight, the use of a walking aid, and cigarette smoking status did little to improve its predictive power.[3274] A provocative editorial published in the *Journal of Internal Medicine* titled "Osteoporosis: The Emperor Has No Clothes" suggested it would therefore be safer and more effective to focus on fall prevention rather than pharmaceutical intervention.[3275]

Though only about 5 percent of falls result in a fracture, falls are very common among the aged.[3276] Due in part to age-related muscle weakness and loss of balance,[3277] more than a third of those sixty-five and older fall each year.[3278] After a hip fracture, less than 50 percent may regain their pre-fracture function in terms of walking ability and independence.[3279] What can we do to prevent injurious falls? Exercise.[3280] Based on dozens of randomized controlled trials, exercise is the single intervention most strongly associated with a reduction in falls rate.[3281]

HOW TO PREVENT FALLS

Based on eighty-one trials, compared to control groups, those randomized to exercise reduced the rate of falls by 23 percent and lowered the number of people who end up falling by 15 percent. So, if you followed 1,000 people around age seventy-five for a year and 480 of them fell a total of 850 times without exercise, adding exercise would be expected to result in 72 fewer people falling and 195 fewer falls. Tai Chi appears to reduce falls by 19 percent, balance and functional exercises (like sit to stand) may reduce falls by 24 percent, and multiple exercises—typically balance and

functional exercise plus strength training—may reduce falls by 34 percent.[3282]

The reduced-falls rate translates into fewer fractures. A recent meta-analysis found that exercise interventions—ones mostly using a combination of resistance exercise to improve lower limb muscle strength training and balance training—cut fracture rates nearly in half.[3283] One yearlong trial combining strength training with step and jumping aerobics that focused on balance and agility[3284] resulted in 74 percent fewer fractures over the five-year period after the study ended.[3285] More than 70 percent of the women in the exercise group did not have a single injurious fall during those five years, compared to more than half in the control group who did.

Trials on hip protectors, which use plastic shields or foam pads sewn into special underwear to cushion a sideways fall on the hip, are often plagued with poor compliance due primarily to discomfort, particularly in bed.[3286] Studies have not found them to be useful for reducing hip fracture rates among those living at home, but trials in nursing homes and residential care facilities do show a small reduction in risk, translating into about eleven fewer people out of a thousand suffering hip fractures due to wearing hip protection.[3287]

There are also commonsense measures we can employ. Quality improvement trials involving interventions like patient education have shown a 10 percent reduction in falls rates.[3288] We can, for example, keep things within reach so we don't need to use step stools, use nonslip mats in the bath and shower,[3289] add grab bars in the bathroom, keep floors clutter-free, remove small throw rugs or use double-sided tape to keep them from slipping, and make sure all staircases have handrails and adequate lighting.[3290] We could also avoid walks during inclement weather and, for those of us who walk leashed dogs, consider adopting smaller breeds or ensuring proper training to prevent them from lunging.[3291]

Otherwise, the main ways to prevent fractures may not have changed much over the last thirty years since the classic paper titled "Strategies for Prevention of Osteoporosis and Hip Fracture"[3292] exhorted us to "stop smoking, be active and eat well."[3293]

PRESERVING YOUR BOWEL AND BLADDER FUNCTION

Lasting for more than 3,000 years, ancient Egypt was one of the greatest early civilizations. They had a vastly underestimated knowledge of medicine, which even included medical subspecialties. The pharaohs, for example, had access to dedicated physicians to serve as "guardian[s] of the royal bowel movement,"[3294] a title alternatively translated from the hieroglyphs to mean *Shepherd of the Anus*.[3295] How's that for a résumé builder?

Today, the primacy of the bowel movement's importance continues. Some have called for bowel habits, along with heart rate, blood pressure, and breathing rate, to be considered a vital sign of how the body is functioning.[3296] Optimal frequency, as derived in see.nf/bms, is probably two or three bowel movements a day. However, the most important criterion for establishing a constipation diagnosis is not frequency[3297] but, rather, consideration of the most prevalent symptom: straining.[3298] Ideally, bowel movements should be effortless.

CONSTIPATION

Constipation is considered the most common gastrointestinal complaint in the United States,[3299] leading to millions of doctors' appointments each year[3300] and 800,000 emergency room visits.[3301] Older adults are at increased risk, perhaps due to decreased dietary fiber, fluids, and physical activity.[3302] Constipation affects up to 30 percent of those sixty-five and older, up to 50 percent of individuals older than eighty-five,[3303] and as many as two-thirds of those living in geriatric-care facilities.[3304] Other than straining at hard stool and infrequent bowel movements, symptoms of constipation can include abdominal discomfort and pain, bloating, nausea, and rectal bleeding during defecation.[3305] Though it can often be benign, any sign of blood from bathrooming should always be something you get checked out by a medical professional. Other red-flag symptoms include unintentional weight loss of more than 10 percent over three months, a family history of inflammatory bowel disease or colorectal cancer, jaundice, new-onset

symptoms starting after age fifty, and rectal tenesmus, which is the sensation of being unable to empty your bowels even though there's nothing in there.

DON'T STRAIN YOURSELF

A systematic review of the impact of constipation on people's lives found that the decrease in quality of life was comparable to that experienced by persons suffering from conditions such as osteoarthritis, rheumatoid arthritis, chronic allergies, and diabetes.[3306] Despite the shadow cast over everyday life, surveys show that many U.S. adults suffering from chronic constipation have never discussed their symptoms with a healthcare provider. The taboo appears to go both ways, as health professionals seldom pay sufficient attention to bowel function,[3307] which has been recognized as a "serious oversight" of the medical profession by a consensus panel of experts.[3308]

Even people who don't think they are may very well be clinically constipated.[3309] In one study in Ohio, for example, a quarter of the so-called healthy subjects reported experiencing incomplete emptying and almost half indicated increased straining when defecating[3310]—so much so, in fact, that more than half had found blood on their toilet paper within the past year.

Straining when trying to pass small, firm stools can certainly cause discomfort, but, beyond the pain, firm stools may contribute to a variety of health problems. For example, more than one in five Americans suffer from hiatal hernias,[3311] a condition where part of the stomach is pushed up and through the diaphragm into the chest. Hiatal hernias are uncommon among populations eating plant-based diets, who have rates closer to one in a thousand.[3312] Why such a great discrepancy? Plant-based eaters tend to smoothly pass large, soft stools. If you routinely strain during bowel movements, over time, the increased pressure to push out stool can actually push part of the stomach up and out of the abdomen, which allows acid to reflux up toward the throat and cause symptoms like heartburn.[3313] This same pressure exerted on the toilet week after week can also cause other issues, including hemorrhoids and varicose veins,[3314] as well as anal fissure and other painful conditions.[3315]

Have you ever squeezed a stress ball? If you have, then you know how tightening your hand around it causes balloon-like bubbles to bulge out. Similarly, the pressure from straining on the toilet may cause pockets to pop out from the wall of the colon, a condition known as diverticulosis. The increased abdominal pressure may also back up blood flow in the veins around the anus, causing hemorrhoids, and even push blood flow back into the legs, resulting in varicose veins.[3316] But, a fiber-rich diet can relieve the pressure—in both directions. Those who eat diets that revolve around whole plant foods tend to pass unforced bowel movements,[3317] which results in more than twenty-five times lower rates of "pressure diseases," such as diverticulitis, hemorrhoids, varicose veins, and hiatal hernias.[3318]

(As a TMI side note—don't say I didn't warn you!—once when I was showering, to my chagrin, I detected a … well … "posterior" lump. How could I, of all people, have a hemorrhoid? I even named one of my guinea pigs after "fiber man" Denis Burkitt! After a few more seconds of inspection, I realized that I *wished* I just had a hemorrhoid. The lump had legs. Thus concludes the story of how I discovered a huge, bloated anal tick.)

Protracted straining can also cause heart rhythm disturbances and a reduction in blood flow to the heart and brain, which may result in defecation-related fainting and even, under certain circumstances, death.[3319] Just fifteen seconds of straining can temporarily cut blood flow to the brain by 21 percent[3320] and to the heart by nearly 50 percent, thereby providing a mechanism for "bedpan death" syndrome.[3321] If you think you have to strain a lot while sitting, try having a bowel movement while you're flat on your back. Bearing down for just a few seconds while supine can send up our blood pressure to nearly 170 over 110, which may help account for the notorious frequency of sudden and unexpected deaths of patients while using bedpans in hospitals.[3322]

When treated inadequately, constipation can also lead to fecal impaction, which could require emergency hospitalization.[3323] Older individuals facing a "half in, half out" crisis[3324] may try manual self-disimpaction—removing stool by hand—a procedure that can be painful, distressing, and potentially harmful.[3325] The optimal remedy is to prevent constipation in the first place.

Best Pooping Position for Constipation

What about the influence of body position on defecation? While squatting remains the traditional position in some parts of Asia and Africa, Westerners have become accustomed to sitting on toilet seats. When you sit upright, however, your "anorectal angle" doesn't straighten enough. That kink at the end of the rectum helps keep us from pooping our pants. In a sitting toilet posture, your poop must make a nearly ninety-degree turn, defeating the purpose of this brilliant design.[3326] Trying to poop while seated is like trying to drive a car without releasing the parking brake.[3327] Check out see.nf/positioning for all the research, but basically, we can manipulate the anorectal angle through squatting or leaning to more easily pass unnaturally firm stools, but why not just treat the cause and eat enough fiber-containing whole plant foods to create stools so large and soft that you could pass them effortlessly at any angle?[3328]

LAX LAXATIVE EFFICACY

The desperation to treat constipation is embodied by medical gadgets that range from automated abdominal massage devices that strap around your midsection[3329] to vibrating capsules you swallow to buzz you from the inside out.[3330] More ominously, colectomies for chronic constipation are on the rise.[3331] Complications of colon resection occur in approximately 1 in 4 operations, and 1 in 250 procedures result in death.[3332] The most common treatments, though, are over-the-counter remedies, such as laxatives, that cash out in excess of a billion dollars in sales every year.[3333]

Despite more than a hundred randomized clinical trials on various constipation treatments,[3334] we still lack high-quality evidence on the safety and effectiveness of laxatives in older adults.[3335] The stool softener docusate, for example, which is sold as Colace, doesn't appear to effectively relieve constipation despite its frequent use as one of the most

common over-the-counter agents.[3336] Stimulant laxatives, such as senna or bisacodyl (Dulcolax), are only approved for short-term usage of fewer than four weeks, but, unfortunately, long-term use for months or even years is widespread.[3337] Biopsies taken from long-term stimulant laxative users show that the nerves innervating their colon can be "severely damaged."[3338]

The over-the-counter laxative with the best safety[3339] and efficacy[3340] record is probably polyethylene glycol, which is sold as MiraLAX or Glycolax—not to be confused with *ethylene* glycol, or antifreeze, which can be fatal if ingested.[3341]

The majority of drugs currently available for the treatment of constipation are generally safe when used as directed, but their effectiveness leaves much to be desired.[3342] In a survey of more than one thousand men and women suffering from chronic constipation, the majority taking over-the-counter medications reported little or no satisfaction at all with the drugs' effect on their constipation (62 percent) or constipation-related abdominal symptoms (78 percent).[3343] There has got to be a better way.

SMOOTH MOVES

There are many lifestyle approaches to treating constipation, such as eating breakfast with a hot beverage to help kick off the gastrocolic reflex,[3344] but the holy trinity that doctors preach about most often is dietary fiber, fluids, and exercise.[3345] In terms of exercise, population studies don't seem to show a clear association between constipation and physical activity after other factors, like fiber consumption, are taken into account, but you can't know for sure until you put it to the test.[3346]

Inactivity does seem to slow things down. When active older individuals became sedentary, dropping their daily step counts from about 13,000 down to 4,000, they nearly doubled their colonic transit time within two weeks.[3347] (The time it takes food to get from mouth to anus can be measured by using the "blue poo" test with food coloring or just eating some beets.[3348]) Conversely, even mild physical activity has been shown to reduce symptoms of abdominal distention and bloating, but what about constipation?

To date, there have been nine randomized controlled trials in adults of exercise for constipation. Even moderate aerobic exercise, such as walking twenty minutes a day, was shown to be able to improve mild constipation symptoms,[3349] though this has not been tested for severe constipation.[3350] What about fluids?

I review all the interventional studies on increasing fluid intake and constipation in see.nf/mineralwater, including the risks and benefits of using Epsom salts (magnesium sulfate) and minerals introduced in the opposite direction via sodium phosphate enemas (sold as Fleet). I conclude that the best remedy for constipation may be to *treat the cause* by ensuring an adequate intake of fiber, considered the first-line treatment for the management of constipation.[3351]

A FIBER DEFICIENCY DISEASE

Constipation can be considered a disease of nutrient deficiency—and that nutrient is fiber.[3352] Not even 3 percent of Americans meet the recommended minimum daily intake of fiber, meaning Americans are not eating enough whole plant foods, the only place fiber is found in abundance.[3353] No wonder those eating strictly plant-based diets are three times more likely to have daily bowel movements.[3354] If just half of the adult U.S. population ate an additional 3 g of fiber a day—a quarter cup of beans or a bowl of oatmeal—we could potentially save billions in medical costs for constipation alone, based on an estimate that, on a population scale, a daily increase of just 1 g of dietary fiber would lead to about a 2 percent reduction in constipation prevalence.[3355] It's hard to create a shredded wheat placebo, but you can prove cause and effect with randomized, double-blind, placebo-controlled trials using fiber supplements.

FIBER SUPPLEMENTS

By far the most commonly used treatment for constipation,[3356] fiber supplements are recommended as first-line management by American, European, and global guidelines.[3357] Soluble nonfermentable fibers, such as psyllium (also known as ispaghula and sold as Metamucil), are touted as the most appropriate first choice.[3358] Psyllium traps water in the intestine,

increasing stool water content and bulk to ease defecation, but it's for this very reason that it's important to take it as directed—with sufficient fluid intake.[3359] Otherwise, psyllium itself can cause its own intestinal obstruction.[3360] Check out see.nf/fibersupplements for details on efficacy and potential ancillary benefits.

FIBER FROM FOODS, NOT FILLERS

The best way to get fiber is not from the supplement aisle but from the produce aisle and, even more so, from the bulk bean and whole grain section. In addition to bowel regularity, high dietary fiber intake is associated with a reduced risk of heart disease,[3361,3362] cancer,[3363] obesity,[3364] diabetes,[3365] depression,[3366] and premature death in general.[3367] Every 7 g of daily fiber intake correlates to a 9 percent reduced risk in heart disease, our number one killer.[3368] So, would 77 g a day drop our risk by 99 percent? That's about how much fiber they used to eat in Uganda,[3369] a country in which coronary heart disease was almost nonexistent.[3370]

Heart disease was so rare among those eating traditional plant-based diets in Uganda that papers were published with such titles as "A Case of Coronary Heart Disease in an African."[3371] After twenty-six years of medical practice in East Africa, doctors finally recorded their first case of coronary heart disease. (The patient was a judge who consumed a "partially Westernized diet," in which fiber-free foods, such as meat, dairy, and eggs, displaced some of the plant foods in his traditional diet.) Of course, since eating habits have been westernized across the continent, cardiovascular disease is now the noncommunicable disease killing the most people there as well—going from virtually nonexistent to an epidemic.[3372]

The early rarity of typical Western diseases in rural regions of sub-Saharan Africa led to the *dietary fiber hypothesis*, which suggested that diets centered around whole plant foods are so protective against chronic disease because of their fiber content.[3373] Predictably, a multibillion-dollar fiber supplement market arose.[3374] There's a problem, though. They don't work.[3375]

Fiber supplements can be helpful with constipation, but they don't seem to provide any of the other chronic disease benefits. Indeed, studies associating lower risk of disease and death with high fiber intake relate

exclusively to fiber from *food—not* from fiber isolates or supplements.[3376] This may be because fiber is a marker of healthy, whole plant food intake, or because of its role as a smuggler.[3377]

The primary role of dietary fiber may be to encapsulate nutrients to deliver them to our gut microbiome. Fiber is the brick that builds the cell walls of plants, and those cell walls act as indigestible physical barriers. So, when you eat structurally intact plant foods, some of the nutrition remains trapped. You can chew all you want, but you'll still end up with nutrients like starch completely surrounded by fiber, delivering sustenance to your friendly flora. Your good gut flora then get to eat not only the fiber but all the food it's wrapped around, too. Fiber supplements like psyllium, however, fail to carry any bounty to our bacteria and aren't even fermentable themselves, so we may miss out on all the auxiliary benefits high-fiber diets give your microbiome.[3378]

Flax and Rye

Ground flaxseeds are an excellent whole-food source of fiber.[3379] For twelve weeks, constipated diabetics were randomized to cookies containing about a tablespoon a day of milled flaxseeds or flax-free placebo cookies. Not only did the flax improve constipation symptoms, such as defecation pain, straining, and hard stools, but, compared to placebo, its consumption resulted in an eight-pound weight loss, twenty-five-point lower fasting blood sugars, an astounding 1.8 percent lower HbA1c, and a seventeen-point lower LDL cholesterol.[3380] For a head-to-head test between flaxseed and psyllium, a second cookie group was added containing 10 g of psyllium. The flaxseed still won, beating out the psyllium for constipation relief, weight loss, blood sugars, and cholesterol.[3381] (Flax can also be about four times cheaper than even generic psyllium.) Flaxseeds have also been compared directly to—and beat—the laxative lactulose, increasing bowel movement frequency from two per week to seven per week, as opposed to six per week for lactulose.[3382]

High-fiber rye bread with 5 g of fiber per slice has also been tested, with study participants randomized to eight slices a day. Compared to white bread with only 1 g per slice, the fiber-rich rye "clearly relieved constipation," increasing bowel movement frequency, comfort, stool softness, and intestinal transit time. The rye group experienced increased

flatulence and bloating, however, especially in the first week, but, as the gut flora adapted and a balance of gas-producing and gas-utilizing bacteria was established, those symptoms diminished.[3383] (As an aside, the term "old farts" may not only be derogatory but a misnomer. Based on a survey of 16,000 Americans, older individuals tend to wind less often than younger age groups.[3384])

Prunes and Mangos

Decades ago, a paper was published in the journal *Geriatric Nursing* titled "A Special Recipe to Banish Constipation," anecdotally documenting the efficacy of an ounce a day of a specific concoction. The basic recipe was two cups applesauce, two cups unprocessed wheat bran, and one cup of 100 percent prune juice, doled out in little medicine cups for nursing home residents.[3385] Such a regimen might only cost about half that of psyllium (calculated at $77 a year versus $147 for the psyllium).[3386] But how good is the science on prunes?

I review the evidence in see.nf/prune. Basically, ten prunes a day beat out psyllium in a head-to-head test in terms of stool frequency and consistency, increasing regularity from two bowel movements a week to four in the prune group versus three in the Metamucil group.[3387] (For context, those eating plant-based diets average about eleven bowel movements a week.[3388]) With the acknowledged caveat that their study was funded by the California Dried Plum Board, the researchers proposed that prunes should be "considered as a first line therapy for chronic constipation."[3389]

Figs failed,[3390] but a Mango Board–funded study found that fresh mangos were also able to beat out psyllium. Men and women with chronic constipation were randomized to eat either a mango a day or the equivalent amount of added fiber in the form of psyllium, which was one daily teaspoon. At the end of one month, not only did the mangos work better in terms of constipation relief but the fruit had a significant anti-inflammatory effect, dropping blood IL-6 levels by more than 20 percent.[3391] This was assumed to be due to the prebiotic effect of mango pulp based on mice microbiome studies,[3392] which was confirmed in humans in 2020 when a mango a day for eight weeks was found to significantly increase the abundance of *Lactobacillus*, the good bacteria in our gut.[3393]

COLORECTAL CANCER

Colorectal (colon and rectal) cancer takes 50,000 lives annually in the United States and is one of the most commonly diagnosed of all cancers. Over the course of their lifetime, the average person has about a one-in-twenty chance of developing it.[3394] Fortunately, it is one of the most treatable cancers if caught early enough, and routine screening has enabled physicians to detect and remove it before it metastasizes. In the United States alone, there are more than one million colorectal cancer survivors, and, for those who are diagnosed before the cancer has spread beyond the colon, the five-year survival rate is about 90 percent.[3395] In its early stages, however, colorectal cancer rarely causes symptoms. If left uncaught until a later stage, treatment is less effective and more difficult. In *How Not to Die*, I recommend getting screened for colorectal cancer starting at age fifty,[3396] but forty-five may be the new fifty.

In 2018, the American Cancer Society became the first major organization to suggest that individuals at average risk for colorectal cancer begin screening from age forty-five instead of fifty.[3397] The American College of Physicians, however, reaffirmed starting at fifty, while the U.S. Preventive Services Task Force, the most prestigious U.S. guidelines organization I mentioned earlier, debated the pros and cons. Given the recent increase in late-stage tumors among those in their forties,[3398] the USPSTF agreed in 2021 that the starting age for colorectal cancer screening should probably be moved up to forty-five.[3399]

"Early-onset" colorectal cancer, defined as diagnosis before age fifty, still accounts for only about 10 percent of cases, but that number has increased by 50 percent since the mid-1990s.[3400] The current incidence rate among forty-five-year-olds is comparable to the rate among fifty-year-olds back in the nineties that led to the original recommendations to begin screening at fifty.[3401] This rise has been blamed partly on the growing prevalence of obesity,[3402] though the increased overuse of antibiotics in children may have also played a role.[3403] African American men are at particular risk,[3404] as illustrated by the tragic death of actor Chadwick Boseman from colorectal cancer at age forty-three. Compared to white Americans, Black Americans have a 40 percent greater risk of dying from colorectal cancer,[3405] yet, when surveyed, most mistakenly thought they

were at lower risk for the disease.[3406] The American College of Physicians has recommended that African Americans begin screening at age forty.[3407]

SCOPING OUT COLONOSCOPIES

According to the USPSTF, there are six acceptable colon-cancer screening strategies. From age forty-five, everyone should do one of the following screening procedures: get a colonoscopy once a decade; have their stool tested for hidden blood every year; have their stool tested for DNA markers every one to three years (by Cologuard, for example); get a "virtual" colonoscopy using CT scan X-rays; or have a flexible sigmoidoscopy either every five years or every ten years with annual DNA marker testing.[3408]

Why do nearly all U.S. doctors recommend colonoscopies[3409] when noninvasive stool testing appears to be the preferred screening method in most of the rest of the world?[3410] Perhaps it's because most doctors practicing in the rest of the world do not get paid by procedure.[3411] As one U.S. gastroenterologist framed it, "Colonoscopy … is the goose that has laid the golden egg."[3412] See my extensive coverage of colonoscopy risks versus benefits in *How Not to Die* to help you make your decision. In the end, the best method of screening is the one that you will actually do.[3413]

COLORECTAL CANCER PREVENTION

Ironically, one downside of screening is what's been called the "health certificate effect," in which those who pass their screenings perceive themselves to be certified as healthy and have a reduced incentive to adopt healthy lifestyles.[3414] Indeed, those randomized to colorectal cancer screening ended up lowering their intake of fruits and vegetables,[3415] which could potentially end up outweighing the beneficial effect of screening.[3416] The answer may be to introduce lifestyle counseling as part of the screening visit.[3417]

While regular screenings to detect colorectal cancer are certainly sensible, preventing the cancer in the first place is even better. The fraction of colorectal cancer cases that might be prevented by colonoscopies and sigmoidoscopies has been estimated at about 30 percent,[3418] but up to 71 percent of cases appear to be preventable through a simple portfolio of diet and lifestyle changes, such as decreasing meat intake.[3419] To home in on the

most consequential lifestyle elements, researchers looked to where colon cancer rates are lowest.

While colon cancer remains the second leading cancer killer in the United States, rural Africa has ten times lower incidence. Migrant studies show that the differences in global rates aren't genetic, since it may only take a single generation for immigrants to assume the colon cancer incidence of their new home country. Changes in diet are considered most likely to be responsible, but there are all sorts of changes when you move from one culture to another—from smoking rates to different exposures to chemicals, infections, and antibiotics.[3420] You don't know if it's the diet until you put it to the test.

Watch my video see.nf/switchdiets to find out what happens inside the colons of African Americans switched to a traditional, high-fiber African-style diet and the colons of native Africans given the SAD standard American diet.[3421] In short, as the lead investigator put it, "change your diet, change your cancer risk!"[3422]

Based on studies of more than three million individuals, plant-based diets are associated with significantly lower rates of tumors of the digestive tract, including cancers of the colon and rectum.[3423] Given the "stunningly positive impact" a diet centered around whole plant foods can have on cancer risk, one commentator concluded: "While it would be unrealistic to expect rapid and profound lifestyle changes in the general population, it is gratifying to have sound, effective advice to offer to those who are willing to take the steps needed to optimize their healthful longevity."[3424]

URINARY INCONTINENCE

We've covered the ins and outs of preserving our bowel function. What about our bladder? Urinary incontinence is defined as any involuntary leakage of urine.[3425] There are two types: urgency incontinence, defined as an involuntary loss of urine associated with a sudden strong desire to urinate, and stress incontinence, where an activity such as sneezing triggers an involuntary accident.[3426] Women are affected at two to three times the rate of men, especially as they age.[3427] The number of voluntary muscle fibers in the female urethral sphincter decreases as they mature.[3428] This is combined with a decline in the ability of aging kidneys to concentrate urine

and a bladder with reduced capacity, which can also become more irritable and less likely to empty completely. All this may be complicated by delays in sensations of bladder fullness.[3429]

About a third of people surveyed in the United States believe the myth that incontinence is an inevitable part of aging, but it certainly does become more common as we get older.[3430] Over the age of seventy, 40 percent of women may be affected,[3431] and over eighty, that number may rise to 55 percent.[3432] At whatever age, urinary incontinence is associated with a poorer quality of life.[3433] What can we do to prevent and treat it?

PISS OFF WITH DIET

One of the reasons women tend to be more affected than men is a history of childbirth. Compared to cesarean section, vaginal birth can triple the future prevalence of urinary incontinence,[3434] thought due to the stretching of muscles and nerves during the birthing process.[3435] This especially appears to be the case when having children later in life.[3436]

Obese women are at three times the odds of severe incontinence compared to healthy-weight women.[3437] This may be due to increased intra-abdominal pressure bearing down on the bladder.[3438] Beyond observational data, interventional studies show that even modest weight loss may help.[3439] For example, the Program to Reduce Incontinence by Diet and Exercise (PRIDE) trial randomized hundreds of overweight and obese women to a weight-loss program or a control group that just got general educational health sessions. The weight-loss program participants lost an average of about fourteen pounds more than the control group and experienced significantly fewer episodes of incontinence. At the end of six months, the frequency of incontinence was cut by more than half in 61 percent of women in the weight-loss group compared to only 34 percent in the control group.[3440]

With or without incontinence, overactive bladder is defined as urinary urgency, often accompanied by increased urinary frequency. More than one in three women experience an overactive bladder in their lifetime, with an increasing prevalence with advancing age.[3441] However, a randomized, double-blind, placebo-controlled trial showed that relief may just be ½ g of dried cranberry powder away. Bladder-relaxing drugs to control symptoms,

like tolterodine (Detrol), are a multibillion-dollar industry,[3442] yet may only reduce average monthly urinations by sixteen, about one less pee every other day.[3443] But, less than a quarter teaspoon of cranberry powder worked nearly four times better, resulting in almost two fewer trips to the bathroom a day. And, that's without suffering from the drug's side effects, which may include dry mouth, constipation, sedation, impaired cognitive function, rapid heartbeat, urinary retention, and visual disturbances that lead almost two-thirds of users to discontinue taking it.[3444]

In the popular press, sufferers are counseled to reduce their consumption of "bladder irritants," such as spicy, salty, and acidic foods. There doesn't appear to be any published evidence to support this recommendation, but the beauty of safe, simple dietary tweaks is that there isn't any harm in giving them a try and seeing if you feel better.[3445] The only two dietary components found to be significantly associated with stress incontinence in a longitudinal study of more than 5,000 women were saturated fat and cholesterol,[3446] though they may just be proxies for unhealthier diets and/or lifestyles. There doesn't appear to be any association between phytoestrogen intake (such as soy or flaxseeds) and urinary symptoms.[3447] What about cutting down on coffee?

U.S.[3448] and European[3449] guidelines both suggest reducing caffeine intake. This makes sense. Caffeine is a mild diuretic, especially at doses found in more than two or three cups of coffee, though daily consumers may habituate to the effect.[3450] Surprisingly, though, a meta-analysis of observational studies did not uncover any link between urinary incontinence and coffee intake, or caffeine more generally.[3451] Two of four interventional studies of caffeine reduction found a reduction in urinary frequency (and the other two found no notable effects), but only two of seven such studies measuring episodes of incontinence found a significant benefit. Again, though, what's the harm of giving it a try?

Fluid restriction in general may be counterproductive, as more concentrated urine may irritate the bladder lining and, paradoxically, worsen symptoms of frequency and urgency.[3452] I would, however, suggest trying to cut out diet drinks. A head-to-head comparison found that Diet Coke increased urinary frequency and urgency more than regular Coke. The researchers blamed the artificial sweeteners based on in vitro studies on rat bladders showing increased muscle contraction.[3453]

Drugs that inhibit the bladder muscle from contracting can be prescribed for urge incontinence.[3454] The average cure rate is nearly 50 percent, but they have the list of common side effects I describe above.[3455] This may help explain why only 14 to 35 percent of people prescribed these drugs are still on them one year later.[3456] There are no FDA-approved drugs for stress incontinence,[3457] but surgical interventions have a cure rate exceeding 80 percent.[3458]

Surprisingly, there is considerable evidence that systemic (oral) estrogen therapy may actually worsen incontinence.[3459] For example, in the Women's Health Initiative, continent women receiving estrogen were approximately twice as likely to develop stress incontinence within the first year, compared to placebo.[3460] Topical (vaginal) estrogens do seem to help, though, reducing one or two accidents a day.[3461] However, first-line management for urinary incontinence is nonpharmacological and nonsurgical.[3462] Working five times better than local estrogens in a head-to-head test: pelvic floor (Kegel) exercises.

In 1948, Dr. Arnold H. Kegel published a paper describing a successful therapy for urinary incontinence that involved exercising the hammock of muscles extending from the pubic bone in the front, down and around to the tailbone in the back.[3463] To find the right muscles, stop urination midstream. The Mayo Clinic suggests you imagine sitting on a marble and trying to lift it up with your vaginal muscles.[3464] Contractions held for ten seconds and followed by at least ten seconds of relaxation are recommended thirty to a hundred times day for at least a month to start seeing results.[3465] For added motivation to stick with it, improved orgasms and sexual satisfaction are a happy side effect of a toned pelvic musculature.[3466]

Once your pelvic muscles are in shape, you can use the "freeze and squeeze" technique to suppress the need to pee when urgency strikes or before you sneeze.[3467] For urge incontinence, this can be combined with bladder training, which consists of an hourly pee schedule while you're awake, extending that a half hour a week until you are able to wait two and a half to three hours between each bathroom break.[3468] A meta-analysis of thirty-one studies involving more than 1,800 women with urinary incontinence in fourteen countries found that those who were randomized to

pelvic floor muscle (Kegel) training were, on average, five times more likely to be cured (and eight times more likely for women suffering stress incontinence).[3469]

A Bit of a Stretch

Physical activity has been associated with lower urinary incontinence risk, but the only interventional studies for exercises not exclusive to the pelvic floor are yoga trials.[3470] Check out see.nf/yogatrials for details, but basically, compared to a strict time- and attention-control group involving nonspecific muscle stretching and strengthening exercises, those randomized to actual yoga saw a significant benefit for stress incontinence but not for urgency incontinence.[3471]

PROSTATE ENLARGEMENT

Urinary symptoms in older men are most commonly caused by an enlarged prostate gland, a condition known as benign prostatic hyperplasia, or BPH. BPH affects millions of men in the United States[3472]—as many as half by the time they're in their fifties and 80 percent of men by their eighties,[3473] making it one of the most common diseases to affect men in Western populations.[3474] The male prostate surrounds the outlet from the bladder, so it can obstruct normal urine flow if it grows too big. This obstruction can cause a weak or hesitant urine stream and inadequate emptying of the bladder, necessitating frequent trips to the restroom. What's more, stagnant urine retained in the bladder can become a breeding ground for infection.

PHARMACEUTICAL AND SURGICAL APPROACHES

Unfortunately, the problem appears to worsen as the gland continues to grow larger. Millions of American men have undergone surgery for BPH, and billions have been spent on drugs and supplements.[3475] Current medical treatments, like finasteride (Proscar), are clinically effective, but their

efficacy is compromised by adverse effects and low compliance rates.[3476] Side effects include sexual dysfunction, high-grade prostate cancer, and depression. No wonder men don't like to take it![3477] A study of more than a million American men reported the one-year adherence rate at only 29 percent.[3478]

Sexual dysfunctions linked to finasteride include impotence, decreased libido, ejaculatory disorders, and gynecomastia (male breast enlargement).[3479] In 2021, internal documents from Merck, the drug company that makes Proscar, were made public, thanks to legal action from the Reuters news agency. It turns out that Merck knew as far back as 2009 that its drug appeared to cause persistent erectile dysfunction (even after the drug was stopped), but Merck's "Risk Management Safety Team" decided to basically sit on the information.[3480]

That brings us to the "gold standard" treatment for BPH: surgery.[3481] Procedures involve a slew of different Roto-Rooter-esque techniques with innocent-sounding acronyms, like TUMT, TUNA, and TURP. The *T*s stand for *transurethral*, or going inside and up the penis with an instrument called a resectoscope. TUMT is *transurethral microwave thermotherapy*, in which doctors use an antenna-like tool to essentially tunnel up the penis and, with microwaves, burn out a shaft.[3482] TUNA stands for *transurethral needle ablation*, which involves burning out a column with a pair of heated needles. And these are so-called *minimally* invasive techniques.[3483] In the gold standard procedure, called TURP for *transurethral resection of the prostate*, surgeons use a loop of wire to core out the gland. Side effects include "postoperative discomfort."[3484]

There has got to be a better way.

BPH IS NOT INEVITABLE

Most doctors may assume BPH is just an inevitable consequence of aging since it is such a common condition, but that wasn't always the case. In the 1920s and '30s in China, for instance, a medical college in Beijing reported that BPH affected not 80 percent of male patients but only about 80 *individual cases* over fifteen *years*. The historic rarity of both BPH and prostate cancer in China and Japan has been attributed to the countries' traditional plant-based diets.[3485] Recent studies on Tsimane men, Bolivian

subsistence farmers who center their diets around starchy staples like plantains,[3486] found that advanced cases of BPH were almost nonexistent, confirming its noninevitability.[3487]

Population studies suggest that low intake of animal protein and high intake of fruits and vegetables may be protective.[3488] Compared to men eating meat less than once a week, those eating meat on a daily basis had more than twice the odds of suffering from BPH-type symptoms.[3489] In a more granular study, researchers found that poultry and eggs seem to be the worst, along with refined grains, but no association was found for red meat or dairy.[3490] Of all plant foods, eating onions and garlic has been associated with significantly lower BPH risk.[3491] In general, cooked vegetables may work better than raw, and legumes—beans, split peas, lentils, and chickpeas—have also been associated with lower risk.[3492] Men consuming the isoflavones found in just a cup a day of soymilk[3493] also harbored lower risk.[3494] Textured vegetable protein, known as TVP, is a soybean product often used in veggie chilis and pasta sauces. Although I prefer less processed soy foods, I would recommend this type of TVP over the TVP used in urology, which stands for *transurethral vaporization of the prostate*.[3495]

PLANT YOUR PROSTATE

In *How Not to Die*, I detailed a series of experiments by Ornish and colleagues, who pitted the blood of individuals before and after a plant-based diet against cancer cells growing in a petri dish. The blood of men on the standard American diet slowed the growth rate of prostate cancer cells by 9 percent. But, when men followed a plant-based diet for a year, the blood circulating within their bodies could suppress cancer cell growth by 70 percent. Nearly eight times the cancer-fighting power with a plant-centered, rather than meat-centered, menu.[3496] (Similar studies have found that women on plant-based diets appear to dramatically strengthen their defenses against breast cancer in just two weeks.[3497]) What if the same experiment was performed on the type of normal prostate cells that grow to obstruct urine flow?

Within just two weeks, the blood of men eating plant-based diets acquired the ability to suppress the abnormal growth of noncancerous

prostate cells. What's more, the effect didn't seem to dissipate over time. The blood of long-term plant-based eaters had the same beneficial effect for up to twenty-eight consecutive years. So, it appears that as long as we continue to eat healthfully, the rates of prostate cell growth will go down—and stay down.[3498] However, some plants may be particularly prostate positive.

Saw Palmetto and a Supplement That Actually Works

Saw palmetto berry is "undisputedly" the most common herbal supplement used for BPH,[3499] but it doesn't work.[3500] One supplement that may help prevent[3501] and treat[3502] BPH is vitamin D. Details on both in see.nf/saw.

GO TO SEED

Flaxseeds can be used to treat BPH. Men given the equivalent of around three tablespoons of flaxseeds daily experienced relief comparable to that achieved with commonly prescribed drugs such as Flomax or Proscar[3503]—but without their side effects. Pumpkin seeds also work,[3504] as detailed in see.nf/seeds, leading the European equivalent of the FDA to conclude that they can be used for the "relief of lower urinary tract symptoms related to an enlarged prostate after more serious conditions have been excluded by a medical doctor."[3505]

Wee Hours of the Night

One of the most burdensome symptoms of BPH is nocturia, frequently having to get up in the middle of the night to pee.[3506] Common sense might tell us to just try to drink less before bed, but, remarkably, there is not a clear association between fluid intake and nocturia.[3507] One study of about 150 men did find a correlation between the frequency of

nocturia and nighttime water intake, as well as how much water you drink in the four hours before bedtime,[3508] but another study, with more than one thousand older adults, found no relationship between the amount of bedtime fluids and having to repeatedly get up to urinate.[3509] I was surprised to learn that fluid restriction has never been properly put to the test. There was a study in which a group of older men averaging four pees a night were told to reduce their daily fluid intake from about seven cups to around five cups and were able to shave nightly bathroom trips down to three,[3510] but it and other similar studies[3511,3512] failed to include a control group to really nail down cause and effect.

It's even harder to get people to restrict sodium. Nocturia reviews with titles asking the question "Which Matters Most, the Water or the Salt?"[3513] note that salt intake has been associated with nocturia frequency,[3514] presumably due to increased thirst-driven fluid intake. This has led to recommendations to cut down on salt to control nocturia severity, but sodium restriction is hard to study because compliance is notoriously poor.[3515] You can, however, compare the change in nocturia episodes of those who successfully cut down on salt intake versus those who didn't. Based on that, it appears that even cutting back on as little as a half teaspoon of salt a day may reduce nightly episodes by 40 to 60 percent.[3516,3517]

Evening protein intake may also contribute to nocturia. The main determinant of urine concentration is not sodium but urea, which is a breakdown product of protein excretion. Protein-rich suppers were found to correlate with excess overnight urine production, leading to the as-of-yet-untested conclusion that a "reduction of evening protein consumption may be an effective lifestyle intervention in the management of nocturia.…"[3518]

HIT A SOUR NOTE

What other foods have been shown to help? Cranberries were evidently used by Native Americans to treat urinary ailments.[3519] Cranberries can successfully shrink rodent prostates by as much as 33 percent,[3520] but the first human trial, "The Effectiveness of Dried Cranberries (*Vaccinium macrocarpon*) in Men with Lower Urinary Tract Symptoms," wasn't published until 2010. The dried cranberries weren't those sugary, oily Craisins but rather just straight, whole cranberry powder. Significant improvements in BPH symptoms, quality of life, and all urination parameters studied were noted for about three-quarters of a teaspoon a day of powdered cranberries.[3521]

What about less than a quarter of a teaspoon or even an eighth of a teaspoon? Both of those doses beat out placebos for decreasing BPH symptoms.[3522] The researchers used a branded supplement, but since it was just straight cranberry fruit powder, you might as well buy it in bulk, which is much cheaper, and just throw it into a smoothie or sprinkle it on some oatmeal. An eighth of a teaspoon would cost less than a penny a day.

A pilot study also concluded that cranberries might prevent recurrent urinary tract infections in elderly men with BPH, but the controlled study lacked a placebo or even randomized allocation, making the findings suggestive at best.[3523]

GARLIC AND TOMATOES

What about a berry that's a little tastier? Welch's-funded researchers put purple (Concord) grape juice to the test for BPH, but it failed to show any benefit.[3524] If cranberries are the most effective fruit, what might be the most effective vegetable? I review trials done on tomato paste[3525] and garlic extracts[3526] for BPH in see.nf/garlictomatoes. Unfortunately, they were both before-and-after studies without control groups so the purported benefits offer only suggestive evidence.

PRESERVING YOUR CIRCULATION

A noted seventeenth-century physician was quoted as saying, "A man is as old as his arteries."[3527] Women are, too, though few seem to recognize it. A nationally representative survey of U.S. women found that most considered their greatest personal health risk to be cancer. Only 13 percent correctly identified cardiovascular disease, which is the actual leading killer of women (and men,[3528] and centenarians[3529]). Sadly, between 2009 and 2019, American Heart Association surveys have noted a "concerning decline" in the proportion of women who understood heart disease to be their leading cause of death.[3530]

A recent editorial in the journal *Aging Medicine* rhapsodized that "the blood vessel is the candle of life," boldly asserting that "[a]ll disease stems from vessels."[3531] There's even a microcirculatory theory of aging that suggests the loss of blood vessel density as we age—by as much as 50 percent in some tissues, such as areas of the brain—may be contributing to organ deterioration as the removal of waste and the delivery of oxygen and nutrients are impaired.[3532] You could say that what brings us blood brings us life.

HOW TO BOOST YOUR EPCs

How can we remain young at heart? The capacity of our blood vessels to repair themselves is dependent on endothelial progenitor cells that emerge from stem cells in our bone marrow to patch up any holes in our endothelium, the innermost lining of our blood vessels that keeps our blood flowing smoothly.[3533] Watch see.nf/epc for a demonstration of the power of endothelial progenitor cells[3534] and what we can do to increase their number and function, such as avoiding even secondhand cigarette smoke[3535] and getting regular aerobic exercise,[3536] considered a "first-line" strategy for helping to prevent and treat arterial aging.[3537] What about diet?

A randomized controlled trial showed that reducing intake of saturated fat (mostly butter) significantly elevated endothelial progenitor cell numbers,[3538] consistent with a study on baboons showing that even a few weeks of a high-cholesterol, high-fat diet could cause dramatic, premature endothelial cell senescence.[3539] Individual foods that have been shown to

increase circulating endothelial progenitor cells include berries,[3540] onions,[3541] and green tea,[3542] and a diet centered completely around whole plant foods not only showed a boost in endothelial progenitors but an improvement in endothelial function, along with a drop in LDL cholesterol.[3543]

A NORMAL CHOLESTEROL LEVEL IS A DEADLY CHOLESTEROL LEVEL

Scientific consensus panels going back decades established—"beyond a reasonable doubt"—that lowering LDL cholesterol reduces the risk of heart attacks.[3544] Consistent evidence "unequivocally" establishes that LDL causes our number one killer, heart disease. This evidence base includes hundreds of studies involving literally millions of people.[3545] In other words, "[i]t's the cholesterol, stupid," quipped *American Journal of Cardiology* editor in chief[3546] William Clifford Roberts. His CV is more than a hundred pages long, and he's published about 1,700 articles in the peer-reviewed medical literature.[3547] Yes, there are at least ten traditional risk factors for atherosclerosis, but, as Dr. Roberts notes, only one is required for the progression of the disease: elevated cholesterol.[3548] All the other factors, such as smoking, high blood pressure, diabetes, inactivity, and obesity, merely exacerbate the damage caused by high cholesterol.[3549]

Phew! you say, because your bloodwork just came back and your doctor said your cholesterol is "normal." But, hold on. Having a *normal* cholesterol level in a society where it's *normal* to drop dead of a heart attack isn't necessarily something to celebrate. With heart disease the top killer of men and women, we definitely don't want to have *normal* cholesterol levels. We want to have *optimal* levels—and not "optimal" by arbitrary laboratory standards but optimal for human health.

Normal LDL cholesterol levels are associated with the buildup of atherosclerotic plaques in our arteries[3550] even in those with so-called optimal risk factors by current standards: blood pressure under 120 over 80, normal blood sugars, and total cholesterol under 200.[3551] If you went to your doctor with those kinds of numbers, you'd get a gold star. But, when ultrasound and CT scans were used to actually peek inside the bodies of

patients boasting those numbers, overt atherosclerotic plaques were detected in 38 percent. Maybe those digits ain't so optimal after all.

Perhaps we should define an LDL cholesterol level as optimal only when it no longer causes disease.[3552] (What a concept!) How would we go about figuring that out?

When more than a thousand men and women in their forties were scanned, most of those with "normal" LDL levels under 130 had frank atherosclerosis. No atherosclerotic plaques were found only when LDL was down around 50 or 60,[3553] which just so happens to be the level most people had before our diets changed to what they are today.[3554] The majority of the global adult population had LDLs around 50 mg/dL. So, average values today are regarded as normal based on a sick society.[3555] What we want is a cholesterol level that is normal for the human species, which is considered to be around 30 to 70 mg/dL (or 0.8 to 1.8 mmol/L).[3556]

Although an LDL level in this range might seem excessively low by modern American standards, it is precisely the normal range for individuals living the lifestyle and eating the diet[3557] for which our ancient ancestors were genetically adapted over millions of years: a diet centered around whole plant foods.[3558] Given that the LDL level our body was designed for is less than half of what is presently considered "normal,"[3559] it's no wonder that we are awash in a pandemic of atherosclerotic heart disease.

Why is there a tendency in medicine to accept small changes in risk factors[3560] when the goal shouldn't be just decreasing risk but *preventing* plaques from forming in the first place?[3561] In that case, how low should we go?[3562]

One noted professor of vascular biochemistry noted: "In light of the latest evidence from trials exploring the benefits and risks of profound LDL cholesterol-lowering, the answer to the question *How low should we go?* is, arguably, a straightforward *As low as you can!*"[3563] How we get there, though, matters. Low may indeed be better, but if we're lowering our LDL with drugs, then we need to balance the benefit with the risk of pharmaceutical side effects.[3564]

There's a reason we don't try to drug everyone with statins by putting them in the water. Yes, it would be great if everyone's cholesterol was lower, but the drugs themselves have countervailing risks.[3565] So, doctors aim to use statins at the highest dose possible to achieve the largest LDL

cholesterol reduction possible without increasing the risk of muscle damage the drugs may cause.[3566] Statins also increase the risk of developing type 2 diabetes.[3567] However, when you use healthy lifestyle changes to bring down cholesterol, all you get are the benefits[3568]—including a significant *drop* in diabetes risk.[3569] But, can you get your LDL low enough with only your diet?

Ask some of the country's top cholesterol experts what levels they shoot for, and odds are you'd hear something like an LDL under 70 or so.[3570] Just cutting down on the saturated and trans fats found in meat, dairy, and junk, as well as reducing intake of the dietary cholesterol found mostly in eggs, is unlikely to get most people to the target.[3571] However, those eating completely plant-based diets can *average* an LDL that low.[3572] It's no wonder plant-based diets are the only dietary patterns ever proven to reverse the progression of coronary heart disease.[3573]

Pressure Points

A similar "normal"-as-deadly paradigm exists for blood pressure. We know the leading risk factor for death in the United States is the American diet, with tobacco number two, but killer number three is high blood pressure, also known as hypertension.[3574] It's so deadly because it increases your risk of dying from so many different diseases, from heart disease and stroke to heart and kidney failure.[3575]

Check out my video see.nf/bloodpressure for an evolution of the guidelines, but basically, there is an exponential increase in risk of dying from a stroke or heart disease as our blood pressures go up, starting from around 110 over 70.[3576] Forcing pressures that low with drugs would have unacceptable consequences, though. For example, if high-risk individuals are given enough drugs at high enough doses to lower their blood pressure even down to a top number of 120 or so, more than 100,000 deaths and 46,000 cases of heart failure might be prevented every year. At the

same time, this would be expected to cause, for example, 43,000 cases of electrolyte abnormalities and 88,000 cases of acute kidney injury.[3577] You can see the conundrum that guidelines committees face.

On the one hand, lowering blood pressure is good for your heart, kidneys, and brain, but, at a certain point, the side effects from the drugs could outweigh the benefits.[3578] Ideally, we want to get patients' blood pressures as low as possible,[3579] but we may only want to use drugs to do it "when the effects of treatment are likely to be less destructive than the elevated BP [blood pressure]." The problem is that most people who die from heart disease, heart failure, and stroke may be in the borderline range—at risk, but not sufficiently elevated to warrant drug treatment.[3580]

If only there were some way to lower blood pressures without drugs to get the best of both worlds. Thankfully, there are: regular aerobic exercise, weight loss, smoking cessation, increased dietary fiber intake, decreased alcohol intake, consumption of a more plant-based diet, and cutting down on salt. The advantage is not limited to the lack of bad side effects. Lifestyle interventions like plant-based diets can actually work *better* than drugs because you're treating the underlying cause and can actually have beneficial side effects.[3581]

LOWER FOR LONGER

On the standard American diet, atherosclerosis, the hardening of our arteries, can start when we're just teenagers.[3582] Investigators collected about 3,000 sets of coronary arteries and aortas—the main artery in the body—from accident, homicide, and suicide victims aged fifteen to thirty-four and found fatty streaks in teens, which can turn into atherosclerotic plaques when we're in our twenties and get worse in our thirties before they start killing us off.[3583] How many of the teens, though? All of them. One

hundred percent of the teenaged victims had fatty streaks building up inside their arteries. All of them had the first stage of the disease, and those streaks were already blossoming into atherosclerotic plaques bulging into the arteries of 55 to 65 percent of those in their early thirties. It's chilling, I know, to realize that most people in their early thirties already have plaques in their arteries. In other words, most of you probably have heart disease—whether you know it or not. The researchers conclude with the line: "Atherosclerosis begins in youth."[3584]

If you had diabetes, would you wait until you started going blind to start treating it?[3585] With heart disease, you can't just wait until you become symptomatic, because your first symptom may be your last. For the majority of Americans who die from heart disease, the first symptom is called "sudden cardiac death."[3586]

An ounce of prevention is worth much more than a pound of cure, because there is no cure for dead.

How do you prevent atherosclerotic heart disease? By lowering your LDL cholesterol through a diet that is sufficiently low in saturated fat and cholesterol—that is, one that restricts meat, junk, dairy, and eggs.[3587] "Is such a radical proposal totally impractical?" asked a review in the *Journal of the American Heart Association*.[3588] It would take an "all-out commitment," but the reviewers evoked the successful public health triumph of slashing smoking rates and lung cancer deaths to argue that anything is possible.

What evidence do we have that a lifelong suppression of LDL will prevent heart disease? There is a genetic mutation of a gene called PCSK9 that about one in fifty African Americans are lucky to be born with because it gives them about 40 percent lower cholesterol levels throughout their whole lives.[3589] This gives them dramatically lower rates of coronary artery disease, a whopping 88 percent drop in risk—despite otherwise ominous risk factors.[3590] Most with the mutation had preexisting conditions such as high blood pressure, being overweight or a smoker, or having diabetes, but that all just goes to show that a lifelong history of reduced LDL cholesterol levels significantly lowers the risk of coronary heart disease even in the presence of multiple other risk factors.

This near 90 percent drop in cardiac events, like heart attacks or sudden death, occurred only at an average LDL of 100 mg/dL, compared to 138

mg/dL in those without the mutation. With drugs or diet, you could easily achieve an LDL even lower than that.[3591] But, wait. Why does the lowering of LDL cholesterol by about 40 mg/dL in those with the lucky mutation reduce the incidence of coronary heart disease by nearly 90 percent, whereas that same forty-point drop with a statin drug would reduce coronary heart disease prevalence by only about 20 percent? The most likely answer is duration.[3592] The longer the arteries are exposed to higher LDL levels in the blood, the more cholesterol can accumulate within the artery wall and inflame it.[3593]

Just as tobacco exposure is measured in pack-years, the amount smoked multiplied over time, an editorial in the *Journal of the American College of Cardiology* introduced the concept of cholesterol-years to take into account the full extent to which our arteries have been bathing in it.[3594] This explains why the indigenous Tsimane, the farmers in Bolivia I mentioned here, are practically free of coronary artery disease at an average LDL of only down around 90. An eighty-year-old Tsimane appears to possess the "vascular age" of an American in their midfifties.[3595] When it comes to lowering LDL, it's not only how low, but how long, and the lower, the longer, the better.[3596]

If you're being treated with drugs later in life, you may have to get your LDL under 70 mg/dL to halt the progression of atherosclerosis.[3597] But if we start early enough in life, it may be sufficient to lower LDL to only about 100 mg/dL, which is consistent with country-by-country data that suggested heart disease would bottom out at a population average of about one hundred.[3598] That's why healthy lifestyle choices may wipe out 90 percent or so of our risk for having a heart attack, whereas drugs may only reduce it by 20 to 30 percent.[3599] But that 90 percent is only if you can keep it down your whole life.

If you're using drugs late in life to try to stop the *progression* of your disease, you have to get your LDL under 70 mg/dL, but in order to *reverse* a lifetime of bad food choices with drugs, you probably have to get it down to around 55. And, if your heart disease is so bad you've already had a heart attack and you're trying not to die from another one, ideally, you might need your LDL to be pushed down to about 30.[3600] Once you get that low, not only would you prevent any new atherosclerotic plaques[3601] but you'd help stabilize the plaques you already have so they'd be less likely to burst open and kill you.[3602]

HOW EFFECTIVE ARE STATINS?

Why cut down on any foods when you can just take a pill? I discuss the efficacy of statin drugs in depth in see.nf/statins. The absolute risk reduction is only 1 percent, so for every hundred people who take a drug like Lipitor for a few years, only one person averts a heart attack.[3603] However, in order to take a cholesterol-lowering drug every day, most say they want an absolute risk reduction at least about twenty-five times higher than that. So, the dirty little secret is if patients knew the truth, if they knew how little these drugs actually worked, nearly no one would agree to take them. A study on patient expectations titled "Are Preventive Drugs Preventive Enough?" concluded that this suggests "at best a lack of discussion and patient education and at worst a degree of misinformation on the benefits of these drugs."[3604]

This sounds terribly paternalistic, but hundreds of thousands of lives are at stake. Quite simply, if patients were told the truth, a lot of people would die. More than thirty million Americans are on statins.[3605] Even if the drugs saved one in a hundred, that could mean hundreds of thousands of lives lost if everyone stopped taking them. As a paper titled "The Preventive-Pill Paradox" concluded: "It is ironic that informing patients about statins would increase the very outcomes they were designed to prevent."[3606]

Are Statins Right for You?

If you have a history of heart disease or stroke, taking a statin drug is recommended. Period. Full stop. If you do not have any *known* cardiovascular disease, then the decision should be based on calculating your own personal risk, which you can easily do online if you know your cholesterol and blood pressure numbers.[3607] See, for example, the American College of Cardiology risk estimator[3608] (see.nf/acc), the Framingham risk profiler[3609] (see.nf/framingham), or the Reynolds Risk Score[3610] (see.nf/reynolds).

I prefer the American College of Cardiology's estimator because it not only gives you your current ten-year risk but also your lifetime risk. Under the current guidelines, if your ten-year risk is below 5 percent, then you should just stick to diet, exercise, and smoking cessation to further bring down your numbers unless there are extenuating circumstances. If your ten-year risk hits 20 percent or higher, the recommendation is to add a statin drug on top of lifestyle modification. Between 5 and 7.5 percent, the tendency is to adhere to lifestyle interventions unless you have risk-enhancing factors, and between 7.5 and 20 percent, most lean toward adding drugs. Risk-enhancing factors your doctor should take into account when helping you make the decision include a family history of heart disease or stroke, really high LDL (≥ 160 mg/dL), metabolic syndrome, chronic kidney or inflammatory conditions, and persistently high triglycerides (≥ 175 mg/dL), C-reactive protein (≥ 2.0 mg/L), or Lp(a) (≥ 50 mg/dL—see here).[3611]

If you're still not sure if you should take statins, the American Heart Association guidelines suggest considering getting a coronary artery calcium score,[3612] though the U.S. Preventive Services Task Force has said explicitly that the current evidence is insufficient to conclude that the harms of the test outweigh the benefits (even though the radiation exposure is relatively low these days).[3613]

HOW SAFE ARE STATINS?

Studies show that as many as 75 percent of people stop taking statins prescribed to them.[3614] When asked why, most former statin users cited muscle pain as the primary reason for discontinuing the pills.[3615] Up to 72 percent of all side effects of statins are muscle symptoms associated with the drug.[3616] Taking coenzyme Q_{10} supplements as a treatment for statin-associated muscle symptoms seemed like a good idea in theory[3617] but failed to actually help when put to the test.[3618] Normally, the symptoms go away

after you stop the drug, but they can sometimes linger for a year or more.[3619] Muscle-related side effects could also be coincidental or psychosomatic and have nothing to do with the drug. Many clinical trials show that such side effects are rare, though it's also possible that those same trials, funded by the drug companies themselves, under-recorded the side effects.[3620]

However, even in Big Pharma–funded trials that attributed only a small minority of symptoms to statins, researchers found that those taking the drugs were significantly more likely to develop type 2 diabetes than those randomized to placebo pills.[3621] Why? We're still not exactly sure, but statins may have the double-whammy effect of impairing insulin secretion from the pancreas and also diminishing insulin's effectiveness by increasing insulin resistance.[3622] Tragically, this elevated risk persists for years even after statins are stopped.[3623]

What About Red Yeast Rice Supplements?

Red yeast rice supplements, which contain a statin-producing mold, are not recommended,[3624] as "dramatic" variations in the active components have been found (for example, hundredfold differences in lovastatin levels). Also, a third of retail red yeast rice supplements tested were contaminated by a potential kidney-damaging fungal toxin called *citrinin*.[3625] An updated 2021 analysis found citrinin exceeding safety levels in 97 percent of sampled supplements, including supplements labeled "citrinin-free," posing a "serious health concern."[3626]

In view of the benefit of statins in the reduction of cardiovascular events, our top killer, any increase in the risk of diabetes, which is typically our seventh leading cause of death (eighth with COVID),[3627] would be outweighed by the cardiovascular benefits.[3628] Statin users would be expected to develop an extra two cases of diabetes mellitus per thousand patient-years, during which time six and a half cardiovascular events, such as heart attacks or strokes, would be prevented.[3629] Of course, that's a false

dichotomy.[3630] We don't have to choose between heart disease and diabetes. We can treat the cause of both with the same diet and lifestyle changes. The diet that doesn't only stop the progression of heart disease but reverses it[3631] is the very same way of eating that can reverse type 2 diabetes into remission.[3632] A healthy enough plant-based diet may prevent further major cardiac episodes in as many as 99.4 percent of patients with significant heart disease.[3633]

What About PCSK9 Inhibitors?

Extrapolating data from graphs from large cholesterol-lowering trials suggests that the incidence of cardiovascular events like heart attacks would approach zero if LDL cholesterol can be brought below 60 mg/dL in individuals who had never had a heart attack and down around 30 mg/dL for those trying to prevent another one.[3634] Is it even safe to have cholesterol levels that low? We didn't really know until PCSK9 inhibitors were invented.[3635]

If you remember, PCSK9 is the gene that gave some people lifelong low LDL.[3636] Drug companies were inspired by the natural mutation to target the gene pharmacologically.[3637] See see.nf/pcsk9 for a full discussion, but basically, on PCSK9 inhibitors, people can achieve an LDL below 40 mg/dL and some even under 15 mg/dL.[3638] The risk of heart attacks falls in a straight line as LDL gets lower and lower, even down below 10 mg/dL without apparent safety concerns, such as impairments of the synthesis of adrenal, ovarian, or testicular hormones that the body makes from cholesterol.[3639]

We can take comfort in the fact that those with extreme PCSK9 mutations, which lead to a reduction in levels of LDL-C to below 20 mg/dL their whole lives, remain healthy and have healthy kids.[3640] There's another type of genetic mutation that leaves people with LDLs of about 30 mg/dL throughout their lives, and they are known to have an

exceptionally long life expectancy.[3641] Mutations that affect cholesterol are in fact what cause the so-called longevity syndromes, but that doesn't necessarily mean the drugs are safe.[3642] The bottom line is that we should try to get our LDL cholesterol down as low as we can, but much longer follow-up data are necessary any time a new class of drugs is introduced.[3643] So far, so good, but we're only a few years out. We didn't know, for instance, that statins increased diabetes risk until a decade *after* they had been approved and millions had already been exposed.[3644] It's also worth mentioning that PCSK9 inhibitors cost about $14,000 a year.[3645]

THE GREAT STENT SCAM

Besides personal habits and biases, another reason lifestyle efforts are often neglected may be the preoccupation many cardiologists have with all the fancy gadgets and new procedures out there.[3646] Some might feel as if they had been trained to be highly skilled fighter pilots, ready to go into combat with high-tech weaponry, but then are asked to go on a boring, preventive diplomatic mission instead. Beyond missing an opportunity to treat the underlying cause, certain common cardiology practices have been shown to do more harm than good. This is not to pick on cardiologists. Many current medical practices have been found to offer potential harms with no benefit.[3647] Physicians themselves estimate that about a fifth of medical care is unnecessary.[3648]

My seven-part video series on stents and angioplasty starts with see.nf/stents. The bottom line: During a heart attack, placing stents can be lifesaving, but hundreds of thousands of these procedures are done for stable angina, meaning on a nonemergency basis.[3649] It was thought they would relieve symptoms,[3650] but they don't actually prolong life or reduce the risk of having a heart attack in the future, compared to "medical therapy," which includes lifestyle interventions and taking statins.[3651] As the *Harvard Heart Letter* put it, "Stents are for pain, not protection."[3652] But

then it was discovered in a famous double-blind, randomized, controlled trial[3653] that stents may not even help with pain.

Hold on. A double-blind, randomized, controlled trial involving *surgery*? In a drug trial, you can give study participants a placebo sugar pill so they won't know if they're in the active treatment group or the control group, but wouldn't you notice if someone cut into your groin? Not if you got *sham* surgery.[3654] Yes, placebo surgery is a thing. In the study, the researchers cut into every subject, threaded up the catheter, then did or did not place the actual stent. And, those who got the sham surgery experienced the same pain relief as those who got the real surgery.[3655]

If heart attacks are caused by blocked arteries, then why doesn't physically opening them up help? Because most heart attacks are caused by narrowings blocking less than 70 percent of your arteries, so the killer plaques don't tend to show up on angiograms.[3656] Before rupture, these plaques often don't limit blood flow, so they may be invisible to angiography and stress tests.[3657] The most dangerous lesions may therefore not be amenable to angioplasty and stents, which do nothing to modify the underlying disease process itself.

TREATING THE CAUSE

To drastically lower LDL cholesterol, we need to drastically reduce our consumption of the three components that raise it: trans fat, saturated fat, and dietary cholesterol.[3658] Once a common ingredient in processed foods in the United States, trans fat–laden partially hydrogenated oils have since been effectively banned in the country and restricted in dozens of others around the world.[3659] These days, in three-quarters of the countries surveyed, most exposure to trans fats now comes from meat and dairy.[3660] Cholesterol-raising saturated fat is found mainly in animal products and junk foods. Dairy (including pizza) is our top source of intake in the United States, followed by chicken, then pastries, pork, and burgers.[3661] Dietary cholesterol is found exclusively in animal-derived foods,[3662] and, overwhelmingly, eggs are our number one source. Chicken is our second leading source, followed by beef, dairy, and pork.[3663] It is therefore no surprise that the core dietary recommendation from the leading scientific societies of cardiology for cardiovascular disease prevention is to

"emphasize the consumption of plant-based rather than animal-based foods."[3664]

Randomized controlled trials involving more than 50,000 people have shown that cutting down on our saturated fat intake leads to a reduction in cardiovascular disease, and the more we decrease saturated fat content, the more our cholesterol drops. The gold-standard Cochrane review concluded: "[T]o lower risk population groups should continue to include permanent reduction of dietary saturated fat."[3665] (Archie Cochrane was an evidence-based medicine pioneer whose legacy is memorialized in an eponymous nonprofit respected for its high-quality systematic reviews.) The American Heart Association got so fed up with "butter-is-back" industry attempts to convince people that butter is not harmful that it released a Presidential Advisory[3666] "to set the record straight on why well-conducted scientific research overwhelmingly supports limiting saturated fat in the diet."[3667]

The proscription against saturated fat extends to tropical oils, which are often used in junk foods, including coconut oil, palm oil, and palm kernel oil,[3668] though animal-derived sources appear to be worse. The Animal and Plant PROtein And Cardiovascular Health (APPROACH) trial randomized people to diets high or low in saturated fats, composed of protein sources from red meat, white meat, or nonmeat (bean, grain, and nut). Researchers adjusted the different diets to achieve the same saturated fat intake across all three, tweaking with butterfat for the two meat groups and tropical oils for the nonmeat group. Their findings? At the same saturated fat intake, red meat and white meat both elevated LDL cholesterol higher than plant-based protein sources.[3669] Red meat and white meat appeared to be equivalently bad, which is the case even in randomized controlled trials that didn't normalize saturated fat levels. Swapping out beef for chicken and/or fish doesn't significantly lower LDL cholesterol levels.[3670]

Dietary cholesterol has also long been known to be a significant contributor to atherosclerosis.[3671] A 2020 meta-analysis of more than fifty randomized controlled trials found that egg consumption significantly increases LDL cholesterol.[3672] Even studies funded by the egg industry show that eggs increase our blood cholesterol.[3673] This appears to translate into significantly higher coronary artery calcium scores among those who eat more eggs, which is a sign of atherosclerotic plaque buildup in the arteries[3674] and, most important, to a significantly greater risk of heart

attacks and death. Based on a half dozen populations studied in the United States, following tens of thousands of people for up to thirty years, each additional half an egg consumed per day was significantly associated with higher risk of developing cardiovascular disease and dying from all causes put together.[3675] And this higher risk of death persisted even after taking other lifestyle behaviors into account, including overall dietary quality. In other words, it does not appear to be just because those eating more eggs were eating more bacon.[3676]

Despite pressure from the egg industry,[3677] the 2015 to 2020 Dietary Guidelines for Americans explicitly told people to "eat as little dietary cholesterol as possible," as recommended by the Institute of Medicine,[3678] advice that was reiterated in the 2020 to 2025 guidelines: "The National Academies recommends that *trans* fat and dietary cholesterol consumption to be as low as possible,"[3679] using the rationale that any intake above zero increases LDL cholesterol concentration in the blood and therefore increases the risk of our number one killer.[3680]

As noted by J. David Spence, director of the Stroke Prevention and Atherosclerosis Research Centre, "After conviction for false advertising," for suggesting that eggs were safe, "the egg industry has spent hundreds of millions of dollars trying to convince the public, physicians, and policy makers that dietary cholesterol is harmless." In reality, regular consumption of eggs should be avoided by people at risk of cardiovascular disease, Dr. Spence wrote, which "essentially means all North Americans who expect to live past middle age."[3681]

What About Lp(a)?

Lipoprotein(a), also known as Lp(a), is an underrecognized independent risk factor for cardiovascular disease. It contributes to coronary artery disease, heart attacks, strokes, peripheral arterial disease, calcified aortic valve disease, and heart failure. These can occur even in people without high cholesterol[3682] because Lp(a) *is* cholesterol. It's basically an LDL cholesterol molecule linked to another protein,[3683] which, like LDL alone, transfers cholesterol into the lining

of our arteries, contributing to the inflammation in our atherosclerotic plaques.[3684] For more on Lp(a) and what we can do about it, check out see.nf/lpa and see.nf/lpadiet. In short, Lp(a) blood concentrations are mostly genetically determined,[3685] but there are some dietary tweaks that can help.

We've known for years that the trans fats found in meat and dairy are just as bad as the industrially produced trans fats found in partially hydrogenated oil in junk food when it came to raising LDL cholesterol levels.[3686] When it comes to Lp(a), though, the trans fats in meat and dairy appear to be even worse.[3687] However, merely cutting out meat and following a lacto-ovo vegetarian diet does not appear to be sufficient.[3688] There are some specific plants that may help a bit, including ground flaxseeds[3689] and amla (dried Indian gooseberry powder).[3690] When study participants were put on a whole food, plant-based diet packed to the hilt with fruits and vegetables, their Lp(a) levels dropped by 16 percent within four weeks. In those twenty-eight days, they also lost fifteen pounds, on average,[3691] but weight loss does not appear to improve Lp(a) levels, so the researchers figured it must have been the food.[3692] In addition to causing weight loss, a month of plant-based eating can dramatically improve blood pressure even as people cut down on their blood pressure medications.[3693] You can also get a twenty-five-point drop in LDL cholesterol and a 30 percent drop in C-reactive protein, as well as significant reductions in other inflammatory markers for a "systemic, cardio-protective effect."[3694]

VEGETARIAN STROKE RISK

Healthy plant-based diets have been associated with lower all-cause mortality,[3695] with up to a 34 percent lower risk of death from any cause over an average of an eight-year period.[3696] If sustained through adulthood,

that would translate into more than four extra years of life.[3697] A meta-analysis of a dozen studies prospectively following more than half a million people for up to twenty-five years similarly found significantly lower heart disease and overall death rates among those eating more plant-based.[3698] That's no surprise, a systematic review concluded, given the evidence that plant-based lifestyle programs have "potentially stabilized or even reversed coronary artery disease."[3699]

Those eating plant-based tend to be slimmer and have significantly lower LDL cholesterol, triglycerides, blood sugars, and blood pressures,[3700] as well as less carotid artery wall thickening[3701] and plaque buildup[3702] measured via ultrasound in the neck. Changes in risk factors can happen fast, as evidenced by results from one-[3703] to three-week[3704] ad libitum (eat-all-you-want) plant-based "kick-start" programs. For example, the nonprofit Rochester Lifestyle Medicine Institute created an at-home fifteen-day program, called Jumpstart. Of its first few hundred participants on a whole food, plant-based diet, obese patients lost an average of seven pounds without controlling portions or counting calories; diabetics saw their fasting blood sugars drop by twenty-eight points; those with LDL cholesterol levels over 100 mg/dL experienced a thirty-three-point drop,[3705] which is comparable to some statin drugs;[3706] and hypertensive individuals experienced a seventeen-point drop in systolic blood pressure,[3707] which is better than drugs. All this was achieved within just two weeks on the diet.[3708]

If you compare the artery function of those who don't eat meat to those who do, the healthy ability of arteries to dilate normally and let more blood flow is four times better among those eating vegetarian, and, apparently, the longer, the better. The degree of superior artery function correlated with the number of years eating meat-free. Instead of their artery function worsening over time as they aged, it was getting better the longer they ate more healthfully.[3709]

Studies dating back thirty-five years show that those eating plant-based also have improved blood "rheology," meaning fluidity or flowability,[3710] which may play a role in their cardiovascular protection.[3711] Subsequent interventional studies putting these cross-sectional findings to the test show that switching people to a plant-based diet can improve rheology measurements within just three[3712] to six weeks.[3713] Might the blood of

vegetarians flow a bit too well, though? A study of thousands of British vegetarians found that they were at higher risk of hemorrhagic (bleeding) stroke,[3714] but the twelve-part video series I produced on vegetarians and stroke risk triggered by the study (starting with see.nf/vegstroke) was in vain, since, as I note in see.nf/strokeupdate, six subsequent studies[3715,3716,3717] found that, if anything, there is a lower stroke risk among those eating more plant-based.[3718]

LOW-CARB DIETS ARE LOW-LIFESPAN DIETS

While those eating plant-based diets appear to enjoy lower risk of cardiovascular disease and longer lives,[3719] those eating low-carb diets suffer significantly higher rates of cardiovascular disease and shorter lives—a 22 percent increase in overall mortality risk.[3720] So, the side effects of low-carb ketogenic diets may not only include, as a recent review recited, "chronic fatigue, nausea, headaches, hair loss, reduced tolerance to alcohol, reduced physical performance, heart palpitations, leg cramps, dry mouth, bad taste, bad breath, gout, or constipation,"[3721] but premature death as well.[3722]

Low-carb diets have been found to worsen heart disease[3723] and impair arterial function.[3724] Within just three hours of eating a meal rich in saturated fat—even from a plant source like coconut oil—there is significant impairment of artery function.[3725] Artery function worsens on a ketogenic diet,[3726] even after about a dozen pounds of weight loss, and this appears to be the case with low-carb diets in general.[3727]

Lower-carb diners also suffered significantly higher risk of dying from cancer.[3728] This could be due to higher IGF-1 induced by higher animal protein intakes[3729] (see the IGF-1 chapter) or perhaps even greater industrial toxin exposure. Ninety percent of persistent pollutant exposure comes from foods derived from animals,[3730] so it's no surprise that those eating diets that are lower in carbohydrates and higher in protein have higher levels of pollutants circulating throughout their bodies, including mercury, lead, PCBs 118 and 153, DDE (from DDT), trans-nonachlor (a component of the banned pesticide chlordane), and hexachlorobenzene (a banned fungicide). Mediterranean diet scores have also been correlated with elevated levels of

PCBs (118, 126, 153, and 209), trans-nonachlor, and mercury, presumably due to the focus on fish consumption.[3731]

A FISH TALE

Thanks in part to the American Heart Association's recommendation that people who are at high risk for heart disease should ask their doctors about omega-3 fish oil supplementation,[3732] fish oil pills have exploded into a multibillion-dollar industry,[3733] yet the most extensive systematic assessment of the evidence found that increasing the intake of fish fats (EPA and DHA) has "little or no effect on deaths and cardiovascular events."[3734] Longevity experiments on mice found no benefits for aging or lifespan either.[3735] Where did we even get this idea that the omega-3 fats in fish and fish oil supplements were good for you? I review the whole saga in see.nf/fishoil and discuss contaminants, rancidity, and the five massive new trials that have been published, randomizing tens of thousands of participants to various formulations of fish oil versus placebo.[3736,3737,3738,3739,3740] It's possible some fish oil formulation will eventually prove to be helpful,[3741] but, for now, meta-analyses "unequivocally demonstrate that there is no cardiovascular benefit" to over-the-counter fish oil supplements.[3742]

SWAP MEAT

What about simply eating fish? In population studies, it's hard to separate the effects of fish consumption with the attributes of fish consumers. People who eat fish tend to smoke less, exercise more,[3743] be in a higher socioeconomic class, and eat fewer prepared meals, more organic foods, less high-fat dairy and meat, more vegetables, and fewer sweets.[3744] When researchers try to tease out some of these other factors, most studies on fish consumption show no association with cardiovascular mortality.[3745]

However, one of the key questions that always needs to be addressed in nutrition studies is, *instead of what?*[3746] For example, are eggs healthy? Compared to sausage links? Yes. Compared to oatmeal? No.[3747] In this way, the inclusion of seafood in the diet may displace foods that are even less healthy.[3748] Surprisingly, randomized controlled trials show that fish is even

worse than red meat when it comes to LDL cholesterol.[3749] So, fish may be worse than beef, but it's still better than bacon.

Harvard researchers found that when it comes to sources of protein and the risk of premature death, processed meat was the worst, followed by eggs, whereas plant protein sources were the best.[3750] In essence, they found that eating tuna salad was better than egg salad or a BLT, but a bean burrito beat out the bunch. When it came to all-cause mortality, plant protein beat out every type of animal protein—red meat, chicken, fish, dairy, or egg. Swapping red meat for white meat, such as poultry and fish, would not be expected to significantly reduce mortality rates,[3751] but something like swapping chickpeas for chicken would. Swapping in just 3 percent of calories of plant protein in place of any source of animal protein was associated with a significantly lower risk of all-cause premature death.[3752]

Disappearing Act

Since heart disease is our number one killer, it is the primary determinant of how long we live. Bill Castelli, longtime director of the longest-running epidemiological study in the world—the famous Framingham Heart Study—was once asked what he would do to reverse the coronary artery disease epidemic if he were omnipotent. His answer? "Have the public eat the diet … described by Dr. T. Colin Campbell."[3753] In other words, he told PBS, if Americans ate plant-based enough, the whole heart disease epidemic "would disappear."[3754]

PRESERVING YOUR HAIR

In every grade school class photo, I seemed to have a mess of tousled hair on my head. No matter how much my mom tried to tame my hair, it was a little unruly. (I sported the windblown look without even trying.) Later came my metalhead phase, with headbangable hair down to the middle of

my back. Sadly, though, like many of the men in my family, it started to thin, then disappear. Why do some lose their hair and others don't? Why do some people go gray earlier than others? How can we preserve the looks of our locks?

GRAYING

The graying of hair is one the most obvious signs of aging.[3755] It's also known by a technical term I had never heard before: *canities*.[3756] (The first time I saw the word I misread it, wondering what gray hair had to do with dentistry.) Evidently, gray hair isn't really gray or even white, but the pale yellowish tinge of the constitutive keratin protein that, like polar bears, looks white by the way light reflects off it.[3757]

WHY DO WE GRAY?

I detail the prevailing "free radical theory of graying"[3758] in see.nf/gray. Basically, free radicals naturally produced in the production of pigment[3759] lead to the deaths of pigment-producing cells[3760] as our antioxidant defenses decline as we age.[3761]

REVERSIBLE AND CONTRIBUTORY CAUSES

The age-related "exhaustion of the pigmentary potential"[3762] is thought to be mainly genetic,[3763] with a family history of premature graying present in up to 90 percent of cases.[3764] But if the rate of graying is caused by oxidative damage, what role might be played by antioxidants and systemic oxidative stress outside the hair follicle? Those with premature graying do seem to have higher circulating markers of oxidative damage and lower antioxidant levels in their blood.[3765] The higher prevalence of premature graying among smokers[3766] also supports this possibility that external free radicals may speed up oxidation in the aging hair follicle.[3767] Obese individuals tend to gray early, consistent with the oxidative stress concept, though drinkers do not.[3768] Alcohol consumption clearly causes oxidative stress,[3769] yet it is not significantly associated with premature graying.[3770]

Those trying to maximize their intake of antioxidants by eating plant-based must deal with the Achilles' heel I noted here—the risk of vitamin B_{12}

deficiency for those not actively supplementing their diets with B_{12} or B_{12}-fortified foods.[3771] B_{12} deficiency is one of the rare reversible causes of hair graying through some unknown mechanism.[3772] Thankfully, hair can repigment after B_{12} repletion.[3773] Another reversible cause is hypothyroidism, which can be treated with thyroid hormone replacement.[3774]

Rather than oxidative stress, what about regular stress? In see.nf/hairstress, I cover whether fight or flight can turn hair white, why we evolved to gray in the first place, and whether premature or extensive graying may be a sign of accelerated aging and subsequent risk of age-related diseases.

Do Hair Dyes Cause Cancer?

Since there is typically no way to reverse hair color loss, up to 60 percent of men and women in Western countries choose to use hair colorants, often to cover gray.[3775] Check out see.nf/dye for the entire saga, but basically, in response to FDA-mandated cancer warning labels in 1979, the hair dye industry started reformulating to eliminate its most carcinogenic ingredients.[3776] This led to the drop-off of some cancers[3777,3778,3779] but not others,[3780] leading some scientists to conclude that "exposure to hair colorants should be reduced as much as possible."[3781]

BALDING

Each human head harbors about 100,000 hairs[3782] and normally sheds about 100 a day as old hairs are replaced with new ones.[3783] But, as we age, hair thinning affects at least 50 percent of women by age fifty and 40 percent of men by thirty-five,[3784] rising to a lifetime prevalence of up to 80 percent.[3785] Age-related hair loss is known as androgenic or androgenetic alopecia in the hormone or gynecology literature, or male or female pattern hair loss in

dermatology.[3786] Either way, it's characterized by chronic, progressive hair loss, predominantly of the central scalp.[3787]

CAUSE AND CONSEQUENCES

The word "androgenic" hints at the cause of male pattern hair loss. Derived from the Greek *andro-* for "man," androgens, male hormones like testosterone, exert an inhibitory effect on hair follicles in the scalp.[3788] This is ironic, since those same hormones are the principal *drivers* of hair growth[3789] on other areas of the body, such as the face and armpits.[3790] (Hair follicles in eyelashes appear unaffected either way.[3791]) Some knowledge of the role of male hormones dates back at least to Hippocrates, who noted, "Eunuchs do not … become bald,"[3792] which indeed appears to be the case. Castration can also halt the progression of hair loss in men, though it doesn't reverse it.[3793] The role of testosterone was nailed down when a Yale pathologist noticed that the castrated twin brother of a bald man had a full head of hair. As an experiment, he administered testosterone to the castrated brother, who subsequently went bald, too.[3794]

(If the ethics of that seem questionable, consider why the guy was castrated in the first place. Castration was recommended for the "feeble-minded" to "mitigate aberrant behavior,"[3795] such as the "nameless habit" of masturbation.[3796] Though the original justification[3797] for removing the testicles and ovaries of "idiot children" in the nineteenth century was in part to rein in "confirmed masturbators," under the refinement of the twentieth century, the rationale switched to eugenics.[3798] Due to eugenics laws in the United States—the first in the world[3799]—mentally handicapped persons were routinely sterilized without their consent or knowledge, a practice upheld by the U.S. Supreme Court in 1927.[3800] In the 1930s, a vocal proponent complained, "The Germans are beating us at our own game."[3801])

Is there some sort of evolutionary advantage to going bald? Though bald men may have more direct scalp exposure to sunlight, they do not appear to have higher "sunshine vitamin" D levels,[3802] but with higher levels of circulating testosterone in their blood, might they possess greater virility? [3803] On the contrary, researchers have found that balding men may be found to be less sexually attractive, averaging fewer lifetime sexual partners.[3804] What the elevated testosterone does get them is increased risk for prostate

problems.[3805] While men who are genetically predisposed to have higher lifetime testosterone levels tend to have better bone density and decreased body fat, aside from hair loss, they are also more likely to suffer prostate cancer and high blood pressure.[3806]

The hypertension connection may explain why the brains of balding men are more likely to be littered with traces of ministrokes (white matter hyperintensities) on MRI.[3807] The majority of studies on the question have found that baldness is a risk factor for cardiovascular disease. Researchers suggest signs of balding be used in a clinical setting by doctors as a visible marker to identify men at increased risk of heart disease to target for prevention intervention.[3808] In women, hair loss is associated with a ninefold increased risk of having metabolic syndrome, a cluster of risk factors that include excess body fat around the waist, along with increased blood sugar, pressure, and triglycerides.[3809]

REVERSIBLE HAIR LOSS

The role male hormones play in female hair loss is uncertain,[3810] as only a minority of women with female pattern hair loss exhibit elevated androgen levels in the blood.[3811] Women often thin, predominantly over the top and front, rather than go bald[3812] and, unlike men, may not feel that they have the option of sporting a shaved head.[3813] Female hair loss may also have more varied causes.

Whereas an aging man losing his hair may just be assumed to have male pattern baldness, female hair loss demands a clinical investigation.[3814] For example, as many as one-third of those with hypothyroidism,[3815] an underactive thyroid gland condition that strikes women up to seven times more than men, present with diffuse hair loss.[3816] This is usually irreversible even with thyroid hormone replacement, underscoring the importance of early diagnosis. Oral contraceptive use, crash dieting, and the recent birth of a child can also cause a common type of hair loss called *telogen effluvium*.[3817]

Unlike most of the hair follicles on our body and on our pets, which are in a resting maintenance “telogen” phase, approximately 90 percent of the hair follicles on our scalp are in an active growing “anagen” phase.[3818] In both men and women, stressful events, such as surgery and sickness, can

cause a mass reset of the hair cycle, switching follicles into the telogen phase, which only lasts two to three months before the cycle renews.[3819] (COVID-19 was a major cause of this.[3820]) This reset means that a few months after the traumatic event, your hair can start falling out in clumps as the new hairs that are being born all begin to simultaneously push out the established hair, rather than being staggered over time. People tend not to make the connection with their precipitating event and fear they may go bald, but telogen effluvium tends to be self-limiting. The hair loss resolves as the new hairs start growing out over the subsequent months, but it may take a year or longer to experience cosmetically significant regrowth.[3821]

How do you know what kind of hair loss you have? Pattern hair loss can often be distinguished from telogen effluvium with what's called a pull test.[3822] After not washing your hair for at least twenty-four hours, grasp approximately fifty hairs between the thumb, index finger, and middle finger and, slowly and gently, pull them away from the scalp.[3823] Normally, most of your hairs are in an active growing phase, so less than 10 percent of the hairs should come out. If more than that come out and they have a small white bulb on the scalp end (what's referred to as telogen "club hairs"), then you may be experiencing telogen effluvium.[3824]

MODIFIABLE RISK FACTORS

Balding men tend to have not only higher levels of testosterone but higher levels of testosterone receptors in their scalps,[3825] which appears to be mostly genetically determined.[3826] Identical twins show a concordance rate of about 80 or 90 percent, meaning if one twin is balding, eight or nine times out of ten, the other twin is, too.[3827] But what about the 10 to 20 percent who share the same genetics but have discrepant hair loss? What can we learn from them?

No, hair loss is not caused by washing or brushing your hair too much, two of the many myths out there.[3828] In identical twin women, the sister with higher levels of stress, more marriages, more divorces or separations, and more children was more likely to suffer hair loss.[3829] In both identical twin pairs of brothers[3830] and sisters,[3831] wearing hats appeared to be protective, but the results for exercise and caffeine intake were contradictory. Exercise and caffeine were associated with less hair loss in female identical twins but

more hair loss in male identical twins. Perhaps this is because interventional trials show that aerobic exercise can increase testosterone levels in men.[3832] Interestingly, caffeinated coffee can increase testosterone in men but decrease levels in women.[3833]

The data on tobacco were consistent. Studies of identical twin pairs of men[3834] and women[3835] found that smoking was a common factor associated with a receding hairline, a factor confirmed in studies of the general population.[3836] This is thought to be due to genotoxic compounds in cigarettes that may damage the DNA in hair follicles and cause microvascular poisoning of their blood supply.[3837] Other toxic agents associated with hair loss include[3838] mercury, which seems to concentrate about 250-fold in growing scalp hair.[3839] Mercury poisoning from his syphilis treatment may have been the reason Shakespeare started losing his hair.[3840] Thankfully, doctors don't give their patients mercury anymore. These days, as the Centers for Disease Control and Prevention (CDC) points out, mercury "enters the body mainly from dietary seafood sources."[3841]

Perimenopausal women frequently seek treatment for what is thought to be hormone-related hair loss, but there are case reports of women with high fish intake and correspondingly high blood mercury levels whose hair loss can be reversed with a fish-free diet. For example, within two months of the elimination of dietary tuna, mercury blood levels can drop as much as a third and hair can not only start growing back but it can completely regrow within seven months. The medical director of the Center for Menopause, Hormonal Disorders and Women's Health suggests doctors should consider screening for mercury toxicity in the face of hair loss, since "[i]nstructing patients to reduce fish intake … could offer relief of symptoms" from heavy metal-induced hair loss.[3842] (Though, admittedly, thinking back to glam bands of the 1980s, sometimes heavy metal may lead to too much hair.)

DRUG TREATMENT FOR HAIR LOSS

Historically, recommended treatments for hair loss included sprinkling mouse droppings and the ashes of a donkey's penis on your head.[3843] Julius Caesar reportedly tried a mélange of minced mice, horse teeth, and bear grease.[3844] Treatments today may be less exotic, but apparently no less

desperate, as more than $3 billion is reportedly spent every year in the United States to treat hair loss.[3845] Currently, the only two FDA-approved drugs for hair loss are minoxidil, sold as Rogaine, and finasteride, sold as Propecia.[3846] I cover the efficacy and safety of both in see.nf/hairdrugs.

PULL THE PLUG

There are also surgical options, though punch grafts or "plugs" historically gave hair restoration procedures a bad name.[3847] Developed back in the 1950s, small circles of scalp skin from areas where hair is still growing, like the back of the head, were transplanted to bald areas on the top and front.[3848] This left an unnatural cornrow doll's hair appearance.[3849]

Today, there is "follicular unit transplanting," where a long strip of hairy scalp is surgically excised and divided into much smaller punches for transplantation.[3850] The transplanted follicles then retain the androgen resistance native to their original location. For men who are completely bald, hairs can be transplanted from the chest, abdomen, legs, shoulders, or beard.[3851] Most of the grafted hair follicles tend to survive (on the order of 85 percent), and high rates of patient satisfaction have been recorded.[3852] However, cosmetically desirable results require multiple operations, and each carries up to a 5 percent rate of complications,[3853] which can include necrosis at the excision site, excessive scar tissue, and infections, though serious complications are rare.[3854]

PLASMA AND LASERS

What about nondrug, nonsurgical interventions? Autologous platelet-rich plasma therapy has been tried, a process in which concentrated portions of your own blood are repeatedly injected into your scalp. The efficacy may be similar to the available drugs,[3855] but the evidence thus far is considered to be insufficient to recommend it, and it remains unapproved in the United States and Europe for hair restoration purposes.[3856] Botox in the scalp is also not recommended. The thought was that relaxing scalp muscles might prevent hair loss by improving blood flow,[3857] but when it was actually put to the test, it *caused* hair loss in some pilot study participants.[3858] Then, there are lasers.

The FDA cleared the first low-level laser therapy (LLLT) device for pattern hair loss in 2007,[3859] and now there are clinics advertising lasers for everything from tennis elbow[3860] to "scrotal rejuvenation."[3861] As I go through in see.nf/lasers, there have been at least ten randomized controlled trials of LLLT devices for hair loss,[3862] and though there are statistically significant improvements in hair density and thickness, there may be little *clinically* significant improvement.[3863] If you want to give them a try anyway, in the video I offer some safety tips and advice on how to choose between the dozens of FDA-cleared devices currently on the market.[3864]

SUPPLEMENTS FOR HAIR LOSS

Are there nutrient deficiencies that can cause hair loss? After bariatric surgery, hair loss is the most frequently reported nutrient deficiency symptom, but the surgery often involves anatomy rearrangement to purposefully cause malabsorption.[3865] In general, there is little evidence to suggest that vitamin and mineral supplementation benefits people unless they are actually deficient.[3866] This is the case with vitamin C, zinc, iron, and biotin, which can actually do more harm than good. The details for these studies are in see.nf/hairsupplements. For example, there has not been a single clinical trial demonstrating efficacy of biotin for any kind of hair loss,[3867] unless a deficiency is induced by raw egg white consumption,[3868] and biotin supplements can cause havoc on a bunch of different blood tests.[3869] (See here.)

In terms of poor regulation, sloppiness by supplement manufacturers includes accidentally putting two hundred times the intended selenium dose that ended up *causing* hair loss due to selenium toxicity.[3870] The same can happen when getting too much vitamin A[3871] or vitamin E, yet the best-selling hair supplement on Amazon.com contained both A and E vitamins, and the next most popular one contained vitamin A, vitamin E, and selenium.[3872]

What about all the patented hair-growth supplements on the market these days? A dermatology journal review considered the available evidence and concluded that, at least to date, it should be considered a myth that any increase hair growth.[3873] Ironically, such supplements may actually be more expensive than the current medications—up to more than $1,000 a year,

compared to $100 to $300 a year.[3874] What about treating hair loss from the inside out with food?

FOODS FOR HAIR LOSS

Population studies have found that pattern baldness is associated with poor sleeping habits and the consumption of meat and junk food,[3875] whereas protective associations were found for the consumption of raw vegetables and fresh herbs,[3876] as well as frequent intake of soymilk. Drinking soy beverages on a weekly basis was associated with 62 percent lower odds of moderate to severe hair loss,[3877] raising the possibility that there are compounds in plants that may be protective.[3878]

There is no shortage of Rapunzel-length boasts of different dietary regimens and other alternative treatments to "cure" hair loss,[3879] but a critical review of the literature shows much of the evidence was obtained on shaved rodents.[3880] Even when clinical studies are done on actual people, sometimes there's no placebo control, so you have no idea if the food had anything to do with it.[3881] Check out see.nf/hairfoods for a remarkable case report of a totally bald man receiving a fecal transplant and regrowing a full head of hair, as well as detail on all the foods shown in a randomized, double-blind, placebo-controlled trial to improve hair loss. These include the hot pepper compound[3882] found in a daily one-half of a habanero pepper[3883] or a teaspoon of medium-hot red pepper,[3884] the daily soy isoflavones[3885] found in three-quarters of a cup of tempeh or just straight cooked soybeans, or a half cup of soy "nuts,"[3886] and the pumpkin seed oil found in about four pumpkin seeds a day.[3887] Unfortunately, the supplement they used wasn't straight pumpkin seed oil but an amalgam of vegetable powders and other ingredients, and the study was financially supported by the product's marketing firm.[3888] But it can't hurt to eat a few pumpkin seeds, perhaps encrusted with cayenne on your tempeh wings.

TOPICAL HERBAL TREATMENTS

If pumpkin seed oil is so anti-androgenic, what about just rubbing it on your scalp? It works on mice,[3889] but what about men or, in this case, women? Pumpkin seed oil (about a quarter teaspoon rubbed onto the scalp once a day) was tested head-to-head against minoxidil foam (5 percent once daily)

for three months in women with female pattern hair loss. Both treatments worked, but the minoxidil worked better,[3890] though at about five times the cost.

A similar experiment compared a topical 0.2 percent caffeine solution, which is about five times stronger than coffee, to 5 percent minoxidil, and the researchers found they worked similarly well for balding men.[3891] However, as with the pumpkin seed oil trial, there was no third placebo group to ensure the study participants weren't somehow just improving on their own[3892]—due to seasonal influence, for example, with greater shedding in the fall than in the spring.[3893]

Dripping caffeine on human hair follicles growing in a petri dish enhances hair growth,[3894] and when it was finally put to the test against placebo, it won out for both male[3895] and female[3896] pattern baldness. In the study on men, 85 percent were satisfied after using the caffeine-containing shampoo for six months, compared to only 36 percent in the placebo shampoo group.[3897] EGCG, one of the major constituents of green tea, can also promote human hair growth in vitro,[3898] perhaps via inhibition of 5α-reductase,[3899] and may help balding mice,[3900] but I couldn't find any clinical hair growth trials on green tea.

Pyrithione zinc (1 percent) shampoo, typically used for dandruff, beat out placebo for increasing hair density in balding men after twenty-six weeks, but not enough for the study subjects to notice any difference, and it worked less than half as well as 5 percent minoxidil.[3901]

What about topical herbal treatments used since time immemorial?

Ginger offers a good cautionary tale. Ginger has a long history of traditional use in Asia to halt hair loss and heighten hair growth. Do a quick search for "ginger shampoo" on Amazon.com, and nearly a thousand entries pop up. But when the Natural Science Foundation of China finally put it to the test, researchers were surprised to find that ginger actually *suppressed* human hair growth. Given their results, they suggested that ginger could instead be used for the removal of unwanted body hair.[3902]

Polygonum multiflorum, known in traditional Chinese medicine circles as *heshouwu*, is a flowering plant in the buckwheat family popularized as a hair tonic.[3903] Like green tea, there are promising in vitro[3904] and rodent studies,[3905] but no human clinical trials. Rosemary, however, has been put to the test.

In see.nf/rosemaryoil, I detail a series of experiments on successfully treating a patchy form of hair loss called *alopecia areata* with a mixture of essential oils[3906] or, less pleasantly, topical onion[3907] or garlic juice.[3908] In terms of age-related pattern hair loss, rubbing a quarter teaspoon of your favorite lotion premixed with ten drops of rosemary essential oil for each fluid ounce onto your scalp twice a day appears to work as well as the drug minoxidil in balding men.[3909] That much rosemary oil would cost about a penny a week.

PRESERVING YOUR HEARING

For what we can do to preserve our sense of smell—primarily not smoking[3910]—see my video see.nf/smell. Though this can have serious consequences, such as missing gas leaks[3911] or adding more salt to foods,[3912] most people who are affected don't even seem to be aware their sense of smell is impaired, even when directly asked about it.[3913] Hearing loss, however, is considered a major cause of global disability,[3914] ranking among the top chronic conditions affecting older adults.[3915] Yet, for far too long, as a National Academy of Medicine report put it, hearing loss has been "relegated to the sidelines of health care."[3916]

HEARING AIDS FOR AGE-RELATED HEARING LOSS

Age-related hearing loss, also known as *presbycusis* (from the Greek *presbys* for "old" and *akousis* for "hearing"), affects about a quarter of those in their sixties, more than half in their seventies, and 80 percent of those in their eighties in the United States.[3917] More than 95 percent of centenarians were also found to have profound hearing loss.[3918] Because of impaired communication,[3919] this may lead to social isolation, loneliness,[3920] and depression.[3921] It may even threaten one's life due to an associated increase in motor vehicle accidents.[3922]

Hearing aids can help, though they appear to be vastly underutilized, with fewer than one in six hearing-impaired older adults using them.[3923]

Barriers include comfort, cosmesis, and cost. Unlike countries like the United Kingdom, which have provided hearing aids to their citizens for free for more than half a century,[3924] in the United States the devices have been prohibitively expensive, averaging between $2,000 and $7,000, and are often not covered by health insurance.[3925] Thankfully, the bipartisan Over-the-Counter Hearing Aid Act was passed in 2017, which gave the FDA three years to allow their sale through traditional retail outlets rather than doctor's offices or specialty shops to increase competition and bring down costs.[3926] The FDA understandably missed their statutory deadline due to COVID-19, but with masking and physical distancing making it even more difficult for the hearing impaired to communicate, the need for affordable options had never been greater.[3927] Thanks in part to pressure from a presidential executive order, over-the-counter hearing aids finally hit U.S. shelves on October 17, 2022.[3928]

How well do they work? Unlike "aural rehabilitation," a collection of coping strategies such as lip reading, which has not been shown to be effective in older adults with hearing loss,[3929] hearing aids have been proven to be effective in improving the ability of adults with mild to moderate hearing loss to understand others and take part in everyday situations.[3930] They are considered the first-line clinical management tool for those seeking help for hearing difficulties.[3931]

Some of the complaints people used to have with hearing aids, such as whistling tones from acoustic feedback, have since been digitally reduced or eliminated in modern devices. Other issues that arise from blocking the ear canal, such as changes in the sound of your own voice or hearing yourself chewing, have been more difficult to rectify.[3932] People like to think that correcting hearing problems with sound amplification is as straightforward as correcting vision problems with eyeglasses, but just because sounds are louder doesn't necessarily mean they're clearer.[3933] Insufficient benefit is one of the leading reasons why some people who have hearing aids just don't wear them.[3934] But, are there benefits beyond symptomatic relief that might change the cost-benefit calculus?

HEARING AIDS FOR COGNITIVE DECLINE

If you visit the websites of leading hearing aid brands, you'll see marketing claims implying that their products can prevent or forestall cognitive decline.[3935] I review the science in see.nf/thinkingaids, but sadly, as a recent World Health Organization review concluded, "There is insufficient evidence to recommend use of hearing aids to reduce the risk of cognitive decline and/or dementia."[3936] Hearing aids may not help your brain, but they can still add significant symptomatic relief of hearing difficulty. What about treating the cause of hearing loss in the first place?

HOW TO REVERSE EARWAX-INDUCED HEARING LOSS

One of the most common, reversible causes of hearing loss is earwax buildup. Earwax is normal, and if it's not causing symptoms, it should be left alone. It doesn't start interfering with hearing acuity until it clogs at least 80 percent of the ear canal. Ironically, hearing aids are a risk factor for excessive earwax, as is anything else you put into your ear, like earplugs, since that stimulates the earwax glands.[3937] For further irony, so, too, may the cotton-tipped swabs that as many as two-thirds of people use to clean out their ears.[3938] So, you may think you're making things better by swabbing out your ears, but you may actually be making things worse.[3939] In fact, just the removal of protective wax can leave your canals dry, itchy, and achy or even lead to "Q-tip otalgia," a term coined in the *Journal of the American Medical Association* to refer to an ear pain syndrome caused by cotton-tipped swabs.[3940] You shouldn't need to clean your ear canals at all because the wax should make its way out on its own.

Ears are self-cleaning. The lining of your ear canal grows outward from your eardrum, so secreted earwax and any dirt that's been trapped is eventually conveyor-belted out. However, this self-cleaning mechanism can fail in one in twenty younger adults and as many as one in three older adults, and it may lead to excessive or impacted earwax accumulation, though those affected may not even be aware of it.[3941] Seventy percent of those surveyed who had both ears completely blocked with wax thought their hearing was good, but when their ears were cleared, they were suddenly able to hear better. Clearing out impacted wax can also improve

symptoms of ear irritation, pressure, and fullness,[3942] but what's the best way to do it?

Q-tips and other cotton-tipped swabs are a no-no. Pushing anything into the ear canal can end up making things worse by impacting wax even deeper into the ear or traumatizing the canal, resulting in abrasions,[3943] infections,[3944] or even eardrum perforation in a small percentage of users.[3945] There's even been a case report of a cotton swab causing a brain abscess and fatal meningitis, though the presence of wood splinters suggests the tip had broken off inside the ear.[3946] Cotton swab packaging already cautions users against ear canal insertion, but perhaps warning labels should be made clearer, wrote one clinical medical officer: "[D]o not go near the ear hole or avoid the ear altogether."

What about wax removal ear drops? There are about a dozen different formulations on the market, none of which appears to work any better than any other one or even when compared to just saline (salt water) or even plain tap water. But, five days of treatment does clear earwax in about one in five cases (22 percent) compared to only 5 percent clearing up on their own within that time frame.[3947] At the very least, ear drops may be able to soften wax before bulb syringe irrigation.[3948]

Also called ear syringing, irrigation involves flushing out wax with a low-pressure jet of warm (body temperature) water. It works up to 70 to 90 percent of the time, and if it doesn't, clinicians have fancy devices to manually remove the wax under direct observation.[3949] Irrigation can also be tried at home. Those randomized to use a bulb in the comfort of their own home had about a 50 percent success rate in clearing the obstruction[3950] and, armed with this knowledge, were significantly less likely to subsequently require in-office irrigation.[3951] Significant complications only happen in approximately one in a thousand irrigations.[3952]

You should *not* use an oral water jet. There are scientific papers with titles such as "Catastrophic Otologic Injury from Oral Jet Irrigation of the External Auditory Canal." Even at one-third power, Waterpiks were shown to perforate the eardrums of fresh cadavers. Those who insist on violating this important proscription should, at the very least, choose the lowest setting, use a tip with multiple orifices, and make sure the water stream is directed only against the walls of the ear canal and never straight back toward the eardrum,[3953] but I still strongly caution against it.

What About Ear Candling?

Ear candles (also known as ear cones) are promoted as a low-cost, effective treatment for earwax,[3954] but as I document in see.nf/candling, a series of experiments found that it not only offers no benefit, it can make things worse[3955] and even result in serious injury.[3956]

HEARING LOSS IS NOT INEVITABLE

Earwax is one thing, but what about preventing age-related hearing loss? It's said to be a natural part of the aging process,[3957] but that's what we used to think about pathological conditions like high blood pressure. The vast majority of people eventually develop hypertension, just like the vast majority of people eventually lose their hearing, so it must just be an inevitable consequence of growing old, right?

But then it was discovered that there were rural populations living in Africa,[3958] Asia,[3959] and the Amazon,[3960] who ate and lived more healthfully and did not experience an inexorable rise in blood pressure as they aged. So, it appeared hypertension was a lifestyle choice rather than an aging effect—and the same may be true for hearing loss.

The Mabaan, a tribe living in the Sudanese bush, were found to retain their hearing into old age.[3961] Another study, on the isolated native population on Easter Island, found that exposure to modern environments appeared to undercut their hearing advantages.[3962] What is it about our modern world that seems to lead us to lose our hearing as we grow older?

Age-related hearing loss is a result of the premature death of the sensory hair cells in the inner ear, which turn vibrations into electric signals to the brain.[3963] Once they're lost, they don't grow back, so prevention is critical.[3964] What is killing the sensory hair cells? A study of more than 2,000 twins found that the heritability of age-related hearing impairment was only 25 percent, so most of the risk is due to nongenetic influences.[3965]

Risk factors include smoking, ototoxic (hearing-damaging) medications, and repeated exposure to loud noises.[3966] Noise exposure earlier in life appears to render the inner ear more vulnerable to aging.[3967] Animal studies

suggest exposure to low-level yet constant noise over 60 decibels may also be harmful.[3968] This has not been demonstrated in humans, but if you use a white noise generator to sleep, it can't hurt to make sure it's under 50 decibels.[3969] Aminoglycoside antibiotics, such as streptomycin, amikacin, neomycin, and kanamycin, are among the highest-risk medications for sensory hair cell toxicity,[3970] but loop diuretics (for example, furosemide, sold as Lasix) and NSAIDs (nonsteroidal anti-inflammatory drugs like aspirin, ibuprofen, and naproxen) have also been linked to progressive hearing loss.[3971] The key to the preservation of hearing in older Mabaan tribe members, however, may be their diet.

What About Cell Phone Radiation?

Your inner ear may be the organ most frequently and directly exposed to cell phone radiation. Might that have adverse effects on hearing? Long-term cell phone users have been found to have detectable hearing loss compared to nonusers, though not enough to be noticeable. The impairment was measurable in both ears, which may be more consistent with a radiation effect than simply a constant loud-noise-in-one-ear effect.[3972] I explore all the studies in see.nf/phones, but in short, researchers found no effect at thirty minutes of cell phone use, but sixty minutes did appear to immediately impact hearing threshold levels at specific frequencies.[3973] Bluetooth was found to be safer, presumably because it operates at nearly a thousand times lower strength.[3974]

WHAT TO EAT TO SLOW HEARING LOSS

The reason the researchers concluded that the Mabaan tribe's diet likely accounted for their lack of age-related hearing loss is they also appeared to lack something else: coronary artery disease.[3975] What kills more of us in the industrialized world than anything else doesn't appear to touch them at

all.[3976] Their blood pressures are also perfect their whole lives, at about 110 over 70 into their seventies, while the rest of us, on average, become hypertensive starting as early as our forties.[3977] And, it's no wonder. The Mabaan diet is centered around whole grains (sorghum) and "almost free of animal protein." So, the researchers suggested that atherosclerosis clogging the small blood vessels feeding the inner ear may be the underlying cause of age-related hearing loss in most of the rest of the world.[3978]

Indeed, healthier diets are associated with a significantly lower risk of hearing loss, and for all three diet quality scoring systems they used, avoidance of meat was most strongly linked to lower risk.[3979] The Mabaan also do not eat sugary junk, which explains their almost total absence of dental cavities.[3980] A high glycemic diet of refined carbohydrates is also associated with developing age-related hearing loss,[3981] and elevated blood sugars in general may explain why diabetics and prediabetics are at higher risk, too.[3982] Even among whole grains, sorghum has a particularly low glycemic index due to its resistant starch content,[3983] causing about a 25 percent lower rise in blood sugar response compared to whole wheat.[3984]

Impaired blood circulation may also explain how noise damages the inner ear, since loud noises cause constriction of the accompanying blood vessels.[3985] It may also help clarify the link between obesity and hearing loss. Excess weight may just be a proxy for unhealthier diets, but the pro-inflammatory state of obesity can itself lead to vascular dysfunction.[3986] Measures of systemic inflammation seem to directly correlate with age-related hearing loss, as do measures of oxidative stress.[3987]

Details in see.nf/earfoods, but basically, blueberries can actually reverse hearing deficits in rats,[3988] though adding antioxidants to their food[3989] or water[3990] seems to help prevent age-related hearing loss, whereas antioxidant supplements fail to improve hearing in people.[3991] What has been shown to help is folic acid supplementation,[3992] of which the healthiest sources are dark green leafy vegetables and legumes. (Just one cup of cooked lentils has 90 percent of an adult's daily needs,[3993] for example, and a cup of edamame 120 percent.[3994])

WHAT TO AVOID TO SLOW HEARING LOSS

A 2021 broad overview titled "Role of Nutrition in the Development and Prevention of Age-Related Hearing Loss" screened thousands of papers and concluded: "Diets rich in saturated fats and cholesterol have deleterious effects on hearing that could be prevented by lower consumption."[3995] The case of the Mabaan makes for a compelling story, but what exactly are the reviewers basing that conclusion on? It's true that you can prove it in laboratory animals—randomize rats to added saturated fat[3996] or chinchillas to added dietary cholesterol, and scientists can show that atherosclerosis-inducing diets exacerbate inner ear damage and hearing loss—but that doesn't necessarily mean the same is true in people.[3997]

There are cogent epidemiological data. For example, a study of thousands of twins was able to draw a significant link between a diet high in cholesterol and hearing impairment.[3998] In the Blue Mountains Hearing Study, which enrolled thousands of older men and women, dietary cholesterol was the nutritional component most associated with age-related hearing loss. Those eating about two eggs' worth of cholesterol a day had 34 percent greater odds of hearing loss compared to those only getting about a single egg's worth. Consistent with a vascular cause, people on statins and particularly those at higher doses appeared to be at lower risk. The researchers suggest that atherosclerotic inflammatory changes, caused by the high cholesterol diet, in the tiny arteries feeding the inner ear would explain their findings, but how about actually looking at the arteries to see if this is true?[3999]

The extent and severity of coronary artery disease in the heart, as determined by angiogram, were found to be closely correlated to hearing loss.[4000] Since atherosclerosis is a systemic disease affecting the entire arterial tree, this has relevance for the arteries feeding the inner ear. The same connection was found for the amount of atherosclerotic plaque found in the carotid arteries in the neck. The greater the plaque, the poorer the hearing,[4001] and the greater the risk of further hearing impairment measured over the subsequent five years.[4002] We're getting closer, but how about the arteries that directly supply the inner ear? Early autopsy data suggest[4003] and direct imaging studies show[4004] a direct correlation between the degree of hearing loss and atherosclerotic narrowing of those arteries.

Now all we need is an interventional trial to wrap it all up in a bow. Yes, diets high in cholesterol[4005] and high in saturated fat[4006] have been shown to kill off cochlear hair cells and cause inner ear damage and hearing loss in laboratory animals, but it's not as though you can lock up hundreds of people for a few years, force them to eat different amounts of saturated fat, and see what happens to their hearing. Oh, but you can, and they did. Enter: the Finnish Mental Hospital Study. In 1958, one of two mental hospitals near Helsinki changed its menus to decrease its patients' intake of saturated animal fat.[4007] Then, after a few years, the two hospitals switched their menus. It was one of the first interventional trials of its kind and showed you could decrease heart disease deaths by decreasing saturated fat intake. And their hearing? It followed the exact same pattern.[4008] As their heart disease got worse, so did their hearing.[4009] And, after the hospitals switched their menus, the reverse happened—and not just by a little. Patients in their fifties in the lower saturated fat hospital ended up with significantly better hearing than the group in the control hospital who were ten years younger.[4010] The researchers stated that "our audiological studies lead us to conclude that diet is an important factor in the prevention of hearing loss."[4011]

PRESERVING YOUR HORMONES

The search for a hormonal fountain of youth has a colorful and controversial history. Sigmund Freud recommended that the perimenopausal mother of Prince Philip, Duke of Edinburgh, have her ovaries irradiated with high-intensity X-rays to restore her youthful vitality. During the 1920s and '30s, this was evidently accepted as an energizing "cure" for the symptoms of aging in women.[4012] Mental and physical debilities in men were blamed on "seminal losses" from masturbation, and when injecting semen into the blood of elderly men was deemed too dangerous, an eminent physiologist chose instead to inject the "juice" from freshly crushed dog testicles.[4013] This eventually led to a popular cottage industry of the transplantation of testicular extracts, minced tissues, or entire testicles of goats, guinea pigs, or chimpanzees to "rejuvenate" aging

men.[4014] By 1940, more than 10,000 testicular implantations had taken place in human experimentation trials at San Quentin State Penitentiary in California.[4015]

"ANTI-AGING" HORMONES

Millions are spent on hormone treatments to slow aging, but they may do more harm than good.

HUMAN GROWTH HORMONE

Of all of the anti-aging clinic scams and hucksterisms, the selling and administration of human growth hormone has been called "perhaps the most blatant and organized form of quackery today."[4016] As I detail in see.nf/hgh, not only is there no evidence of anti-aging effects,[4017] if anything, growth hormone may actually accelerate the aging process.[4018] Given the risk of cancer and potential for a *shortened* lifespan, one prominent clinician remarked that growth hormone may be a "true anti-aging drug" in that it may prematurely stop you from growing any older.[4019]

Tired of "Adrenal Fatigue"

Many seeking treatment for common nonspecific symptoms are led to believe that they are suffering from some sort of hormonal deficiency.[4020] "Adrenal fatigue" is the prototypical example. Chiropractor-coined in 1998, the invented diagnosis has since been embraced by naturopaths, functional medicine practitioners, and anti-aging doctors,[4021] but the title of a systematic review in an endocrinology journal says it all: "Adrenal Fatigue Does Not Exist."[4022] I do a deep dive in see.nf/adrenal. In sum, hawking unproven tests and treatments for a made-up malady could delay the diagnosis of an actual, treatable condition.[4023]

Dehydroepiandrosterone (DHEA) is the most abundant steroid hormone circulating in our blood,[4024] though levels drop with age[4025] after a peak at around thirty.[4026] Heralded as an "anti-aging" "superhormone" "panacea,"[4027] U.S. DHEA had sales of more than $50 million a year[4028] on the premise that replenishing youthful levels might have restorative effects. As I document in see.nf/dhea, early enthusiasm has been replaced by a sober skepticism as the "panacea" repeatedly failed to beat out placebo.[4029] Aside from intravaginal DHEA for vaginal atrophy,[4030] which I'll cover in the Preserving Your Sex Life chapter, the only convincing benefit is the improvement of birth rates of women in their late thirties undergoing in vitro fertilization.[4031,4032] As with any supplement, there are concerns about quality control issues. Some "DHEA" supplements just blatantly lie and contain no DHEA whatsoever,[4033] but there are natural ways to boost DHEA.

Lower protein intake is associated with higher levels of DHEA,[4034] and an interventional trial found that increasing fiber intake actively raised levels,[4035] so what about putting them together? Researchers found that after only five days on an egg-free vegetarian diet, levels of DHEA in the blood increased by nearly 20 percent.[4036] It can also be tested the other way: When study participants already eating a plant-based diet were switched to a conventional diet, their DHEA levels dropped by up to 20 percent.[4037,4038] It seems the bodies of those eating plant-based hold on to the hormone better, excreting less in their urine, which is normally something seen only when fasting.[4039]

Holding On to Eggs by Letting Go of Dairy

What can women do to preserve their fertility in the first place? We used to think that women's ovarian reserve of eggs stayed relatively stable until a rapid decline at around age twenty-seven,[4040] but we now know it appears to be a more steady and gradual loss of eggs over time, starting at peak fertility in one's early twenties.[4041] As I review in

see.nf/ovarianreserve, Harvard researchers suggest that the increased dairy consumption corresponding with as much as a decade's worth of accelerated ovarian aging is either because of contamination of milk products by endocrine-disrupting chemicals or the presence of natural reproductive hormones.[4042] Around 60 to 80 percent of dietary exposure to estrogens, progesterone, and other placental hormones comes from dairy products.[4043] (Cows are typically milked while they're pregnant.[4044]) Once inside the human body, these bovine hormones get converted into estrone and estradiol, the main active human estrogens,[4045] which could end up altering the speed of ovarian decline.[4046]

MENOPAUSE

Life after menopause is unusual in the animal kingdom. Females of most species die soon after their reproductive capacity drops off,[4047] which was true even for humans until the last century or so. (The average life expectancy of women in the United States in 1900 was forty-eight.[4048]) These days, though, women may live more than a third of their lives after menopause, so the question becomes, *how can women thrive through this transition and beyond?*

MENOPAUSE ON PAUSE

Since 1970, the proportion of women having their first child after age thirty-five increased nearly tenfold.[4049] This may introduce a "longevity penalty" on their children, as those born to older mothers don't tend to live as long, but women having children later tend to live longer themselves.[4050] I explore this phenomenon in my video see.nf/delaymenopause, along with the diet and lifestyle factors that affect the timing of menopause, including smoking,[4051] marital history,[4052] and plant protein intake.[4053]

MEDICALIZING MENOPAUSE

A woman is considered to be postmenopausal after twelve consecutive months without a menstrual period.[4054] In the United States, the average age

at menopause is 51.5. About 20 percent of women escape symptom-free, whereas 20 percent at the other end of the spectrum face severe symptoms from the accompanying hormonal changes. Some get better over time, like hot flashes, but others tend to get worse, like vaginal dryness.[4055] Hot flashes and night sweats typically last about five to seven years[4056] but may exceed a decade in 10 to 15 percent of individuals.[4057] The medical establishment's answer was hormone replacement therapy.

Even the name, hormone replacement, speaks to the medicalization of menopause as a disease. Taking thyroid hormone for an underactive thyroid gland or insulin for type 1 diabetics who don't make any of their own is hormone replacement therapy. In contrast, the drop in hormones like estrogen during menopause is the normal and natural state, so the name for this treatment has since been changed to simply *hormone therapy* or *menopausal hormone therapy*.[4058] It was originally marketed not merely for symptom relief but as a fountain-of-youth formula, preying on older women's self-esteem, vanity, and fear of aging,[4059] as popularized in the cringeworthy 1968 bestseller *Feminine Forever*, written by a Manhattan gynecologist named Robert Wilson.

"The unpalatable truth must be faced that all postmenopausal women are castrates," Wilson wrote. He recommended hormones be prescribed to lift women from their "vapid cow-like" state[4060] and make them "much more pleasant to live with."[4061] It's a little-known fact that Wilson's work promoting the drugs was funded by—you guessed it—the Big Pharma hormone manufacturers themselves,[4062] who ponied up more than a million dollars.[4063] He dismissed the suggestion that hormones like estrogen and progesterone might cause breast cancer as "against all logic," suggesting that, if anything, it would *protect* women from breast cancer. By the 1990s, up to 40 percent of menopausal women in the United States were on these drugs,[4064] raking in billions of dollars a year for the pharmaceutical industry.[4065] But then the revelations of the Women's Health Initiative and the Million Women Study were published, indicating elevated risk for breast cancer, blood clots, and endometrial cancer.[4066] The use of menopausal hormone therapy plummeted by 80 percent,[4067] along with a subsequent sharp and significant reduction in breast cancer rates.[4068]

MORE BREAST CANCER *AND* MORE CARDIOVASCULAR DISEASE

As far back as the 1940s, concerns were being raised that dosing women with estrogens might cause breast cancer,[4069] but it took the bulk of a century before it was decided to definitively study the safety of something prescribed to millions.[4070] I describe the whole saga in my video see.nf/premarin, but basically, the bombshell landed in the summer of 2002. The Women's Health Initiative study found so much more invasive breast cancer in the estrogen and progesterone (PremPro) users that they were forced to stop the study prematurely. Researchers expected that lowered cardiovascular risk would balance this out,[4071] but the women didn't just have more breast cancer; they had more heart attacks, too, as well as more strokes and more blood clots to their lungs.[4072] In 2003, the Million Women Study was published in Europe, confirming breast cancer fears,[4073] and in 2004, the estrogens-only (Premarin) wing of the Women's Health Initiative was also halted prematurely due to elevated stroke rates.[4074]

The news that women treated with hormone therapy experienced more breast cancer, cardiovascular disease, and overall harm "rocked women and physicians across the country."[4075] Before the study, estrogen had been the most prescribed drug in the United States,[4076] but after its publication, the number of prescriptions dropped immediately[4077] and, within a year, so did the incidence of breast cancer[4078] around the world.[4079] The Women's Health Initiative hormone trial cost about a quarter billion dollars to run, but given the number of lives the drop in hormone usage subsequently saved (including more than 100,000 fewer cases of breast cancer alone over the subsequent decade), the net economic return was estimated at $37 billion, a 140-fold return on investment.[4080]

Big Pharma did not go gently into that good night. Even after the findings were published, millions of prescriptions continued to be dispensed.[4081] Mortified at all the cancer his colleagues were causing, one doctor wrote, "How long will it take us to discard the financial gains, to admit that we are harming many of our patients, and to start changing our prescription habits?"[4082] Many physicians continue to cling to the "non-evidence-based perception"[4083] that hormone therapy carries net health benefit despite overwhelming evidence to the contrary,[4084] and that has been blamed on "decades of carefully orchestrated corporate influence on

medical literature."[4085] Lawsuits from breast cancer victims unearthed internal documents showing that the drug companies hired PR firms to ghostwrite dozens of skewed reviews and commentaries in medical journals.[4086] It's been said that the "current culture of gynecology encourages the dissemination of health advice based on advertising rather than science."[4087]

After the truth came out, Big Pharma continued to try to distort the medical record by paying to have editorials appear in medical journals to downplay the risks and promote unproven benefits. Of the 110 partisan polemics that were published, only 6 disclosed their financial relationship with the hormone manufacturers.[4088] As pharmacology professor Adriane Fugh-Berman put it, "Women were placed in the way of harm by their physicians, who acted as unsuspecting patsies for the pharmaceutical companies."[4089] If we really wanted to prevent heart attacks in women, instead of being drug industry pawns, doctors could recommend simple lifestyle behaviors that may eliminate more than 90 percent of heart attack risk.[4090]

THE RISKS AND BENEFITS OF MENOPAUSAL HORMONE THERAPY

Where do things stand now with menopause hormone therapy? The U.S. Preventive Services Task Force, echoing other authorities, such as the American Academy of Family Physicians,[4091] American Geriatrics Society,[4092] and American Heart Association,[4093] now recommends against the use of hormone therapy for the prevention of chronic conditions in postmenopausal women with or without a uterus.[4094] Note that the guidance is separate from hormone therapy for the treatment of severe menopausal symptoms for which the American College of Obstetricians and Gynecologists advises "the gynecologist should help the patient to weigh the risks against the benefits."[4095] To make an informed decision, let's run the numbers.

Estrogen is very effective in reducing hot flash frequency and severity, by about 80 percent compared to placebo,[4096] with no difference noted between pills or patches.[4097] Hormone therapy can also decrease the risk of osteoporotic fractures. For women with an intact uterus, if two hundred took hormones for ten years, that would be expected to result in nine fewer

fractures. Those are the upsides: symptom relief and fewer fractures.[4098] In the same scenario, those benefits would have to be weighed against four additional heart attacks (fatal or not), two extra strokes, four more cases of dementia,[4099] two more cases of breast cancer, one more case of fatal lung cancer, four extra cases of gallbladder disease, and ten extra blood clots[4100] (though not a single partridge nor pear tree). Unless the menopausal symptoms were debilitating and everything else was tried and failed, it's hard for me to imagine a woman choosing to accept that risk-benefit balance were she given all the facts.

The safety profile is better for younger (recently menopausal) women, those at reduced risk of cardiovascular disease, blood clots, and breast cancer, and those who lack a uterus and can therefore take estrogen-only preparations.[4101] (Otherwise, the risk of uterine cancer is too great.[4102]) Just the estrogen gives the same symptomatic relief,[4103] but eleven fractures would be prevented in two hundred women over a decade and there were no extra heart attacks or dementia and two *fewer* cases of breast cancer up against six extra cases of gallbladder disease, only one extra blood clot case, and those same two extra strokes.[4104] In either case, the FDA recommends estrogens only be prescribed "at the lowest effective doses and for the shortest duration,"[4105] though it's not clear whether lower doses are actually safer or not.[4106]

WHAT ABOUT "BIOIDENTICAL" HORMONES?

The Women's Health Initiative used Premarin because it was the most commonly prescribed form of estrogen; in fact, more than a million prescriptions are still written for it every year in the United States.[4107,4108] It's a mixture of more than fifty different estrogens from horse pee.[4109] ("Premarin" comes from the words "pregnant mare urine." If you're skeptical, try crushing a pill and sniffing it.) The dour findings of the Women's Health Initiative (combined with some high-profile celebrity endorsements) saw interest shift to *bioidentical hormones* made from plants rather than a horse source. As I explore in see.nf/bioidentical, there are now pee-free and FDA-approved bioidentical hormones, but they are expected to carry the same risks.[4110]

So, how can you safely treat menopausal symptoms like hot flashes? The American College of Obstetricians and Gynecologists suggests palliative measures, such as "consuming cool drinks."[4111] Turning down the thermostat, layering clothing, and using fans can offer some relief,[4112] but is there really no way to treat hot flashes without the cancer, clots, and coronaries? Thankfully, there is.

The Risks and Benefits of Mammograms

Speaking of making informed choices about your own body in the face of the confusion generated by the corrupting commercial interests of multibillion-dollar industries, what about mammograms? Contradictory recommendations have been published—for example, getting mammograms from age forty versus fifty, screening annually versus every other year,[4113] or not getting them routinely at all.[4114] Nine out of ten women surveyed vastly overestimated the benefits of mammograms or had no idea how beneficial they are. One survey found that "if women knew how small the real effectiveness of breast cancer screening in preventing breast cancer deaths is, 70 % said they would not submit to it."[4115] You may be in that 30 percent, though, and you have every right to decide for yourself.

Decisions with completely one-sided consequences—all risk or all benefit—are easy. For example, should doctors teach women to do breast self-exams? The answer is no. It was put to the test. Hundreds of thousands of women were randomized to perform self-exams or not. Researchers not only didn't find any benefit to doing them, they found harms, including double the number of women who had to get biopsies taken. Self-exams were not shown to decrease the risk of getting breast cancer, dying from it, or catching tumors in earlier stages. That's why the U.S. Preventive Services Task Force came out explicitly recommending against teaching women to do breast self-exams in 2015.[4116]

To be clear, the USPSTF didn't come out against breast self-examination—only against teaching women to do them. That's because reminding women to perform self-exams only appeared to cause harm with no benefit. If you do discover an abnormality, then definitely tell your doctor, but being told to get in the practice of looking seems to do more harm than good. Yet, most doctors continue to teach women to perform self-exams. If self-exams haven't been shown to help and, in fact, have been shown to harm, why do physicians keep calling for them? Because that's just what they've been telling women forever. Medical inertia may trump women's health, even without a multibillion-dollar industry tipping the scales to push for the practice to continue, which brings us to mammograms.

Over the last half century, more than half a million women have participated in ten randomized trials of mammography, each with about a decade of follow-up.[4117] What does the science have to say? Let's imagine that one thousand asymptomatic women at average risk were randomized to either skip mammograms or get screened following the USPSTF recommendations to get mammograms every other year starting at age fifty. Over the next twenty years, we would expect two hundred false alarms (though resulting in only thirty biopsies) and three cancers would be missed, but fifteen gratuitous cases would be found, meaning women would be diagnosed with—and treated for—breast cancer unnecessarily. (A third potential harm, getting radiation-induced breast cancer from the mammogram X-rays, is not included in the model because only rough indirect estimates exist, on the order of one to five cancer cases per ten thousand women.[4118]) On the other side of the scale, thanks to mammograms, two breast cancer deaths would be averted, though no lives would apparently be saved overall.

When surveyed, women think mammograms cut the risk of dying from breast cancer in half, saving the lives of about

one in twelve. In reality, about five women in a thousand die per decade from breast cancer without regular mammogram screening compared to four in a thousand dying with screening. Doesn't saving the life of even a single woman in a thousand make it all worth it? But even that may not even be true. None of the ten randomized trials have ever shown an overall mortality benefit, meaning it appears that no lives are actually saved.[4119] How does that make any sense? If a decade of mammograms prevents one in a thousand women from dying from breast cancer, then the only way for no lives to be saved is if mammograms somehow led to the deaths of one in a thousand *healthy* women. This is where the overdiagnosis may come in.

The fact is that some of the tiny tumors picked up on mammograms may have never progressed[4120] and some might have even disappeared on their own.[4121] Autopsy studies of accident victims show that 7 to 39 percent of women aged forty to seventy are walking around with tiny breast cancers, 96 percent of which will never go on to spread or kill them. So, had those tumors not been picked up during screening, the women may have been none the wiser, may have never been affected by them or even known they had them. But, once cancer is detected on a mammogram, you have to treat it because you don't know what it's going to do.[4122] And this treatment comes with all the attendant harms of unnecessary surgery, chemotherapy, and radiation.[4123]

Unnecessary radiation treatments to the chest increase the risk of dying from heart disease and lung cancer,[4124] which could explain why mammograms may kill as many as are saved.[4125] Those who survive become mammography's biggest cheerleaders, thinking mammograms saved their lives.[4126] In actuality, the more likely scenario—in fact, the two to ten times more likely scenario—is that the treatment didn't do anything because the cancer wouldn't have hurt you anyway.[4127] So, you went through all that pain and

suffering for nothing. That's the irony about mammograms: The people who are harmed the most are the ones who claim the greatest benefit.

I am not opposed to mammograms. I *am* opposed to the patronizing attitude that women should be pressured into getting them without being fully informed about the benefits and risks. Some women will still choose to get them, but others will not. It's for you to decide.

RELIEVING YOURSELF OF EXCESS ESTROGEN

The general public is so confused about mammograms that most people believe they prevent or reduce the risk of developing cancer.[4128] Of course, getting screened for cancer doesn't change the risk of getting cancer in the first place. The good news is that the same diet and lifestyle changes that can protect against breast cancer can also protect against the leading cause of death, cardiovascular disease, which kills ten times more women in the United States—about 400,000 women dead each year[4129] versus 40,000 for breast cancer.[4130]

In the Harvard Nurses' Health studies that followed more than 150,000 women and their diets for decades, researchers found that those who ate more plant foods and fewer animal foods were significantly less likely to cultivate breast cancer—and that was even after controlling for factors such as body weight, family history, alcohol use, and exercise habits. Furthermore, plant-based eating appeared particularly protective against the deadliest[4131] types of tumors.[4132] The California Teachers Study, with more than 90,000 women, found similar results, including significantly reduced breast cancer risk associated with a plant-based dietary pattern, particularly for the hardest-to-treat tumors.[4133]

Circulating estrogen levels in both pre-[4134] and postmenopausal[4135] women are strongly associated with breast cancer risk, potentially explaining virtually the entire relationship between excess body fat and breast cancer.[4136] (Estrogen produced by fatty tissue spills over into the bloodstream.[4137]) Does that explain why plant-based eaters, who tend to be thinner on average, have lower breast cancer risk? There are studies finding lower average estrogen levels in pre-[4138] and postmenopausal vegetarians

that don't appear be explained solely by their slimmer frames. That may be due to greater fiber intake.[4139]

Our body gets rid of excess estrogen the same way we evolved to get rid of excess cholesterol—by dumping it into the digestive tract, where it expects that there will be a lot of fiber to grab it, hold on to it, and flush it out.[4140] Without fiber, excess hormones (and cholesterol) can just wind up getting reabsorbed into the bloodstream,[4141] but our body just assumes our intestines are going to be packed with fiber all day long because that's the context in which we evolved. We did start eating meat once we developed tools, but plants don't tend to run as fast, so the bulk of our diets was made up of a lot of bulk. Our ancient ancestors got an estimated seven times more fiber than we're getting now.[4142]

Researchers at my medical alma mater published a study in *The New England Journal of Medicine* in which vegetarian and nonvegetarian women were "provided with plastic bags and insulated boxes filled with dry ice for three 24-hour fecal collections." (You've heard of popsicles; these were more like poopsicles.) Vegetarians excrete two to three times more estrogens every day, because they produce two[4143] to three[4144] times greater "fecal output." So, passing on hormone pills is just one way to reduce breast cancer risk. The other is to rid yourself of estrogen excess the way nature intended.

THE BEST AND WORST FOODS FOR MENOPAUSE SYMPTOMS

The lower estrogen levels of plant-based women may protect them from breast cancer, but might they suffer worse menopausal symptoms? It turns out the opposite may be the case, granting them the best of both worlds. Those eating strictly plant-based diets report significantly fewer bothersome symptoms around menopause. This included the vasomotor symptoms, such as hot flashes and night sweats, as well as other physical symptoms of menopause, like muscle and joint aches, fatigue, sleep difficulties, reduced strength and stamina, lethargy, skin changes, weight gain, facial hair, bloating, and urinary frequency or incontinence. The researchers concluded: "Eating a plant-based diet may be helpful for women in menopausal transition who prefer a natural means to manage their symptoms."[4145]

Which foods may account for the difference in symptoms? Fruits, vegetables, soy, and plant-based omega-3-rich foods, such as flaxseeds, correlated with lesser symptom severity, whereas "total flesh food" (meat), dairy, and fish-based omega-3s were associated with more severe menopausal symptoms. What appeared to be the deciding factors, though, were berries, leafy greens, and vegetable intake more broadly.[4146] In general, according to a 2020 review of dietary intake and menopausal symptoms, those eating higher-quality diets, including more fruits, vegetables, and whole grains, tend to suffer less—not only from vasomotor and physical symptoms but also from psychological symptoms, sleep disorders, and bladder and genital issues. On the other hand, diets high in processed foods, sweets, meats, and saturated fat were linked to more severe symptoms.[4147]

As I note in see.nf/menopausal, both oxidative stress[4148] and inflammation[4149] are associated with menopausal symptoms, but correlation doesn't necessarily mean causation. Interventional studies with control groups are necessary, especially since studies on hot flashes show such a large placebo effect (at least 35 percent relief),[4150] such that some have suggested surreptitiously giving women sugar pills as a treatment.[4151]

The largest dietary interventional trial for menopausal symptoms was within the Women's Health Initiative umbrella. Instead of randomizing women to take hormones, the researchers randomized them to advice to eat a low-fat diet. Adherence was poor, so the women in the low-fat group never actually achieved a low-fat diet,[4152] but they did cut back a bit on meat[4153] and ate at least one more serving a day of fruits or vegetables.[4154] The result? They ended up significantly more likely to eliminate their hot flashes or night sweats. They also lost more weight, but the benefits on vasomotor symptoms of menopause appeared to extend beyond just the weight loss.[4155]

Within a more plant-based diet, those randomized to a vegetarian diet plus daily walnuts, almonds, and flaxseed oil did better than those randomized to the same diet but with the addition of extra-virgin olive oil instead. After sixteen weeks, the meat-free diet rich in plant-based omega-3s reduced hot flash frequency significantly better than the olive oil group.[4156] In fact, even just two daily teaspoons' worth of ground flaxseeds alone can significantly decrease menopausal symptoms. In a head-to-head trial of flaxseeds versus hormone therapy (typically bioidentical estrogen

plus a form of progesterone), the flaxseeds reduced menopausal symptoms to about the same extent as the hormone pills.[4157] This may have been due to the phytoestrogens in flaxseeds, though, rather than the omega-3s.

WHY THERE ISN'T A WORD FOR HOT FLASH IN JAPANESE

Hot flashes, also known as hot flushes, are the most common menopausal symptom for which women seek treatment.[4158] They afflict up to 80 to 85 percent of American and European menopausal women[4159] and, along with night sweats, last more than seven years on average.[4160] But as I explore in see.nf/hotflash, these symptoms are not universal nor inevitable.[4161] In Japan, for example, only 15 percent of women may be affected.[4162] In fact, there isn't even a term for *hot flash* in the Japanese language.[4163]

The absence of a Japanese term is all the more remarkable because the language is said to be "infinitely more sensitive" in describing body states than English,[4164] with all sorts of extremely subtle distinctions for somatic sensations.[4165] In Japanese, there are twenty or more words just to describe the state of one's stomach and intestines, but hot flashes appear to be so unusual there that researchers had to come up with ways to describe them in Japanese surveys.[4166] They hypothesized it might be the soy.[4167]

I review the interventional trials on soy foods and isoflavone supplements in see.nf/isoflavones. Dozens of such clinical trials have been performed, and, indeed, the equivalent of about two servings of soy foods a day has been found to reduce hot flash frequency by about 20 percent more than placebo and hot flash severity by around 25 percent more than placebo, compared to more like a 30 to 40 percent net reduction from estrogen hormone therapy.[4168] Soy isoflavones have also been shown to improve other menopause concerns, including vaginal dryness,[4169] bone density,[4170] depression,[4171] memory, and cognitive function more generally.[4172]

The bottom line, wrote one consensus panel of experts, is that soy can be considered a first-line treatment for symptoms of menopausal hot flashes and night sweats.[4173] One convenient whole-food source of soy are soy "nuts" (dry roasted soybeans). Harvard Medical School's Center of Excellence in Women's Health funded a randomized crossover study of a half cup of unsalted soy nuts a day (divided into three or four portions and spaced throughout the day) and achieved a 50 percent reduction in hot

flashes within two weeks.[4174] But, what's inconvenient about soy nuts is the formation of AGEs (see the Glycation chapter) in the roasting process, so incorporating canned soybeans into meals would be better.

What if you combined a plant-based diet and soybeans? Two randomized controlled trials found that reduced-fat plant-based diets with a daily half-cup serving of cooked whole soybeans can reduce the number of serious hot flashes by 84 to 88 percent within twelve weeks. Overall, most randomized to the plant-based group ended up free of moderate-to-severe hot flashes, compared to 95 percent still suffering in the control group.[4175,4176]

Soy and Breast Cancer

Contrary to rampant misinformation online, the best available evidence consistently shows a protective effect of soy consumption in the prevention of breast cancer.[4177,4178] Each daily 5 g increase in soy protein consumption—less than a cup of soymilk—is associated with a 12 percent reduction in the risk of dying from breast cancer.[4179] This may help explain why women living in Connecticut, for example, can end up with ten times more breast cancer than women living in Japan.[4180] Review see.nf/soybreast for a discussion of the mechanism and source of the controversy.

It is estimated that one in eight U.S. women will develop invasive breast cancer during her lifetime.[4181] Switching from dairy milk to soymilk would be expected to reduce breast cancer risk by about a third, though this may say more about the breast cancer–promoting effects of dairy milk than the breast cancer–preventing effects of soy. Postmenopausal or premenopausal, women drinking a cup of dairy milk a day appear to have about 50 percent greater breast cancer risk than those averaging less than a cup every two months or so. Researchers suggest that this may be due to the estrogen levels in dairy milk (particularly since about 75 percent of cows in dairy production are pregnant) or the

IGF-1 in the milk or provoked by milk protein consumption.[4182]

Are the anti-estrogenic effects of soy foods in the breast enough to actually change the course of the disease? The first human study on soy food intake and breast cancer survival was published in 2009 in the *Journal of the American Medical Association*, suggesting that "[a]mong women with breast cancer, soy food consumption was significantly associated with decreased risk of death and [breast cancer] recurrence."[4183] That study was followed by another one,[4184] then another one,[4185] each with similar findings. That was enough for a wide range of cancer experts offering nutrition guidelines for cancer survivors to conclude that, if anything, soy foods should be beneficial.[4186] Since then, two additional studies have been published,[4187,4188] for a total of five out of five studies that tracked more than 10,000 breast cancer patients, and they all point in the same direction.[4189]

Pooling all the results, soy food intake after breast cancer diagnosis was associated with both reduced mortality and reduced recurrence—that is, a longer lifespan and less likelihood that the cancer comes back. This improved survival was for women with either estrogen receptor–negative tumors or estrogen receptor–positive tumors, and for both younger and older women.[4190] In one study, for example, 90 percent of the breast cancer patients who ate the most soy phytoestrogens after diagnosis were still alive five years later, while half of those who ate little to no soy had died.[4191] Pass the edamame.

IS THERE HOPE FOR HOPS?

Flaxseeds also have phytoestrogens (called *lignans*) that are associated with breast cancer prevention[4192] and survival.[4193] Interventional trials involving before and after biopsies have shown beneficial effects in breast cancer patients randomized to muffins containing flaxseeds versus flax-free

placebo muffins.[4194] Higher lignan exposure may reduce breast cancer mortality between 33 and 70 percent.[4195]

Also, like soy, flaxseeds have been shown to improve LDL cholesterol,[4196] artery function,[4197] and blood pressure.[4198] Flaxseeds also lower other cardiovascular risk factors, including C-reactive protein[4199] and Lp(a),[4200] and can improve blood sugar and weight control.[4201] Unfortunately, they do not appear as effective as soy for improving symptoms of menopause.[4202] Meta-analyses of red clover or black cohosh, other sources of phytoestrogens, also proved disappointing.[4203]

The most potent phytoestrogen is found in beer.[4204] Hopein, also known as 8-prenylnaringenin or 8-PN,[4205] is the reason that handling hops causes women to start menstruating.[4206] It may also contribute to feminized features in alcoholic men, like gynecomastia (man boobs) and a "female escutcheon."[4207] (I had to look that one up. "Escutcheon" derives from the Latin word for "shield." It's medical lingo for the shape of one's pubic hair—diamond-shaped for men or triangle-shaped for women.) The pro-estrogenic effects could also help explain why beer drinkers appear to have better bone density.[4208]

What about hops for hot flashes? As I explore in see.nf/hops, a daily teaspoon of dried hop flowers can significantly reduce hot flash symptoms,[4209] but unfortunately, the estrogenic compounds in hops act more like the breast cancer–promoting compounds in pregnant horse urine than the breast cancer–preventing compounds in soy.[4210] That explains why hops are such a common ingredient in so-called breast-enhancing supplements—that is, because they act more like animal estrogen.[4211] That also helps explain why beer may be more carcinogenic to the breast than some other forms of alcohol.[4212]

LAVENDER FLOWERS

Lavender is widely used to help alleviate menopausal symptoms. To my surprise, there were sixteen interventional trials involving more than a thousand women putting it to the test.[4213] One supposedly double-blinded, crossover, clinical trial, for instance, randomized a hundred menopausal women to lavender aromatherapy in which they smelled lavender for twenty minutes twice a day for a few weeks and then switched to sniffing

the “placebo” control, which was diluted milk. I don’t know how the women could have been effectively blinded given the fragrance (or lack thereof), so the placebo effect can’t be discounted, but the hot flash frequency remained about the same during the control weeks yet was cut in half during the weeks sniffing lavender.[4214] Other physical menopause symptoms, along with decreased sexual desire and feelings of anxiety and depression, also improved during the lavender exposure.[4215]

The scent of lavender essential oil did not appear to help postmenopausal women with insomnia, a common complaint.[4216] What about just eating lavender flowers? More than a dozen randomized controlled trials have found that smelling lavender can help with anxiety, and that appears to extend to eating lavender, too.[4217] Eighty-three percent of postmenopausal women randomized to capsules containing 500 mg of lavender flower powder (which I measure out as one teaspoon of dried flowers) twice a day reported a good or very good improvement in anxiety, compared to only 44 percent in the placebo capsule group.[4218] The same team of researchers tried the same dose on postmenopausal women having difficulty sleeping. Seventy-four percent of those unknowingly taking the lavender reported satisfactory improvements on subjective sleep quality compared to only 31 percent of the control group.[4219] It’s not clear if the active component(s) are water soluble, so the same effect may or may not be achieved drinking the same amount in the form of lavender tea.

FENNEL SEEDS AND FENUGREEK

The nice thing about studying herbs and spices is that entire servings can be stuffed into pills to perform randomized, double-blind, placebo-controlled trials. In this way, a half teaspoon of ground black cumin powder was found to significantly improve menopausal symptoms compared to placebo, but the effects may be limited to the psychological aspects, such as decreased anxiety, more vitality, and improved mental health.[4220]

Fennel seeds, which aren’t actually seeds but the whole little fruits of the fennel plant, can more broadly improve symptoms, including improvements in hot flashes and night sweats, as well as other physical, psychological, and sexual symptoms.[4221] Details in see.nf/fennelfenugreek, along with fenugreek, another galactagogue spice. No, not another sci-fi

reboot, a *galactagogue* is something that increases breast milk production in lactating women.[4222] Fenugreek can also, at one and a half teaspoons a day, improve symptoms of early menopause.[4223]

"ANDROPAUSE"

Today, testosterone is mass marketed to aging men for nonspecific symptoms supposedly related to what's been called "andropause," the decline in testosterone levels as men age. Also known as male menopause,[4224] penopause,[4225] viropause, androgen deficiency in aging males (ADAM),[4226] late-onset hypogonadism, or simply "low T syndrome,"[4227] it is considered a classic example of disease-mongering,[4228] a "template" for how to hawk a disease.[4229] Disease-mongering is the selling of sickness by widening the boundary of illness to encompass ordinary life experiences.[4230] The medicalization of menopause made billions for Big Pharma. Why not extend that to the other half of the aging population?

THE "LOW T" TSUNAMI

In 1889, physiologist Charles-Édouard Brown-Séquard, one of the first to postulate the existence of hormones, claimed to have "rejuvenated" himself with injections of extracts of testicles from dogs and guinea pigs. The rejuvenation must not have worked that well, as he died a few years later,[4231] but not before thousands of physicians administered his "Brown-Séquard Elixir."[4232] Recipients included Hall of Fame pitcher Jim "Pud" Galvin, the first to use a purported performance-enhancing substance in Major League Baseball.[4233] This was followed by rich old men opting for testicular transplants from humans, monkeys, and goats before testosterone was finally discovered in the 1930s.[4234]

Testosterone levels do tend to drop, on average, about 0.5 percent a year, but this may be due more to obesity and coexisting medical conditions than to age per se.[4235] In the Healthy Man Study, for example, men reporting excellent health appeared to experience no drop in testosterone between the ages of forty and ninety-seven.[4236] So, it's not inevitable,[4237] but rather mostly a consequence of chronic conditions like hypertension, diabetes, depression, heart disease, liver disease, lung disease, kidney disease,[4238] or simply deconditioning or excess body fat.[4239] Of course, you could try to

treat the underlying cause with diet and lifestyle changes, but where's the profit in that?

Big Pharma marketers of "low T" ran a sophisticated, direct-to-consumer ad campaign to lead men to believe that testosterone deficiency could be a cause of generic symptoms such as "low energy, feeling sad, sleep problems, decreased physical performance, or increased fat."[4240] Take the quiz! They came up with consumer tests, encouraging men to ask their doctors about testosterone if they exhibited nonspecific symptoms such as "falling asleep after dinner."[4241] There was so little correlation between the answers and testosterone levels[4242] that the questionnaires had up to a 70 percent false-positive rate,[4243] so 70 percent of those who were found to have testosterone deficiency—according to the quiz, that is—actually did not.

Only two industrialized countries, the United States and New Zealand, even allow predatory direct-to-consumer drug ads, but testosterone hawkers sidestep these prohibitions by running "disease awareness" campaigns that don't mention brands by name.[4244] Anti-aging clinics started touting testosterone replacement therapy,[4245] and regular clinicians were convinced en masse by sponsored CME (continuing medical education, or often more accurately *commercial* medical education)[4246] to an "irrational exuberance in testosterone prescribing."[4247] It worked. The billions spent on advertising[4248] translated into billions in annual sales,[4249] a "global tsunami of testosterone prescriptions"[4250] resulting in a hundredfold increase in testosterone sales.[4251]

TESTOSTERONE "REPLACEMENT" PUT TO THE TEST

There are legitimate reasons to prescribe testosterone, but since the Nobel Prize–winning isolation of testosterone in 1935, there has been only one FDA-approved indication: "classic hypogonadism."[4252] That's low testosterone due to conditions such as missing or damaged testicles or certain genetic anomalies.[4253] In contrast, 25 percent of men prescribed testosterone these days may not have even had their testosterone levels tested.[4254] Or, they may have gotten tested and their levels were normal or even high, but they still got prescriptions.[4255] Why even bother getting a test, though? Most of the "hypogonadal" symptoms bear no relation to

testosterone levels in the blood. The exception are a few sexual symptoms, such as “low frequency of sexual thoughts,” which do seem to be tied to testosterone levels under 320 nanograms per deciliter (ng/dL), though more than a quarter of men with normal testosterone levels had similar symptoms.[4256]

There are no generally accepted lower limits for healthy testosterone levels in the blood.[4257] Suggested reasonable thresholds range from less than 200 ng/dL (from the American Association of Clinical Endocrinology) to as high as 350 ng/dL (from the European Association of Urology).[4258] When put to the test, though, by first chemically castrating men, then adding back more and more testosterone, researchers only saw definitive changes in sexual desire and function when men’s levels sank below 100 ng/dL.[4259] Regardless of the cutoff used, for a hypogonadism diagnosis, the Endocrine Society guidelines require two low-testosterone measurements taken in the morning, preferably four weeks apart,[4260] in the context of consistent symptoms.[4261] (Testosterone levels naturally fluctuate season to season, week to week, day to day, and even hour to hour,[4262] with levels higher in the morning and dropping as much as 30 to 40 percent by midafternoon.[4263])

These guidelines are often ignored.[4264] In the United States, a study of hundreds of thousands of men starting testosterone found that only 10 percent got the recommended second test.[4265] Fifty percent only got one test, and the remaining 40 percent didn’t appear to get tested at all. As many as 77 percent of older men may see testosterone levels lower than 300 ng/dL on the first test, but after running a confirmatory second test, that number can drop down to 18 percent and further fall to just 3 percent when other recommended criteria are included, such as a morning blood draw.[4266]

So, the vast majority of men treated with testosterone “replacement” therapy don’t actually need it.[4267] But that doesn’t necessarily mean that they wouldn’t benefit from it. Maybe men have different set points and taking extra testosterone might help even if they don’t test as being deficient. You can imagine men feeling better taking testosterone just from the placebo effect, which is why it’s so important to put it to the test.[4268] Researchers intercepted older men lining up for testosterone treatment because they or their doctors thought it would help with symptoms, such as reduced energy or libido, and randomized them to a testosterone gel or a

placebo gel. The results? Testosterone worked—but so did the placebo, such that there were no significant differences in the end.

Testosterone flopped even for sexual symptoms. But weren't those the one set of symptoms actually correlated with low testosterone? Yes, but that doesn't mean low testosterone is the cause.[4269] Rather than low testosterone leading to sexual disinterest, perhaps sexual disinterest leads to less testosterone. When men have sex, they can get a spike in testosterone levels in their blood,[4270] so much so that their beards may actually grow faster on days they have sex.[4271] Men resuming sex after nonhormonal treatment of their erectile dysfunction—via penile pumps or prostheses, for example—bump up their testosterone level by a whopping average of 450 ng/dL.[4272] (In contrast, interestingly, men don't get a testosterone boost when they masturbate. This may be because testosterone increases with "competitive success," like winning at sports. While sex "is not usually regarded as a competitive event," psychology researchers note, "one's mental state following coitus could nevertheless be something like that of a winner," as opposed to the mental state after masturbation.[4273])

Though the study participants tended to have testosterone levels on the low side, the inclusion criteria for the study were symptoms, not specific blood level cutoffs.[4274] No wonder, perhaps, that testosterone was found to be effectively useless. The researchers were giving testosterone to men who may have already had enough. How about a randomized, double-blind, placebo-controlled trial of symptomatic men filling strict criteria for testosterone deficiency? Enter the Testosterone Trials, funded by the NIH.

THE TESTOSTERONE TRIALS

In 2004, an authoritative report from the National Academy of Medicine concluded that testosterone therapy offered no clear evidence of benefit for any health outcome examined and larger, longer, better studies were necessary to know for sure. In response to this mandate, the NIH funded not one, not two, but seven clinical trials across a dozen academic centers randomizing men to testosterone or placebo for twelve months. The men had to be at least sixty-five with measured and confirmed low testosterone levels (< 275 ng/dL) and exhibiting a symptom like diminished vitality or libido.[4275] What would "correcting" testosterone levels back up to that of

young healthy men do for seven clinical endpoints: cognition, vitality, physical function, sexual function, anemia, bone health, and cardiovascular health?

There was great hope testosterone replacement would improve brain function. Population studies had shown a correlation between lower testosterone levels and higher risk of cognitive impairment[4276] and dementia.[4277] Prostate cancer patients receiving long-term androgen deprivation therapy (surgical or chemical castration) seemed to be at higher risk of dementia later on.[4278] But, in the Testosterone Trials, "correcting" testosterone levels failed to improve memory or other cognitive functions,[4279] and the same failure was noted in a meta-analysis of more than a dozen other randomized controlled testosterone studies.[4280] An editorial in the *Journal of the American Medical Association* concluded that these "convincing, unequivocal findings affirm that testosterone treatment does not improve cognitive function in older men."[4281]

Testosterone also failed to improve both physical function and vitality scores.[4282] This is consistent with dozens of other randomized controlled trials that found little to no effect on physical functioning, depressive symptoms, energy, or vitality.[4283] It's no wonder that, within a year, 80 to 85 percent of men who had started testosterone stop taking it. In fact, based on a study of nearly 16,000 patients, about 50 percent stop taking topical testosterone and about 70 percent stop getting injections within three months.[4284] The lack of noticeable benefits makes sense if indeed lower testosterone is a consequence, rather than a cause, of obesity, lack of exercise, and chronic disease.[4285]

However, the Testosterone Trials did find that testosterone improved bone mineral density.[4286] Unfortunately, if you put together all ten of the randomized controlled trials on testosterone therapy and bone health to date, no overall bone benefit was found.[4287] The opposite may be the case, though, for sexual symptoms.

There was a transient increase in sexual function, but by the end of the year, there was no significant difference between the placebo group and those who got the real thing.[4288] In contrast, most high-quality trials (ten out of thirteen) have found that testosterone therapy in men with low levels increases their sex drive, and seven out of twelve firmly found it to improve erectile function.[4289] The size of the effect, however, is small, described as

"marginal."[4290] Testosterone replacement may help with mild cases of erectile dysfunction but is only a fraction as effective as drugs like Viagra.[4291] My mind was blown to learn that eunuchs had active sex lives even though they had been castrated when they were boys.[4292] Experimentally, severely hypogonadal men (including bilateral surgical castration) with testosterone levels as low as 25 ng/dL not only got erections when exposed to an erotic film but had longer-lasting erections than men with intact testicles in the control group![4293]

A low libido does, however, seem to be a genuine symptom of low testosterone.[4294] So, men with documented low levels of testosterone who suffer from reduced sexual desire and want to improve their sex drive may be candidates for testosterone after consideration of the associated risks.[4295] There are testosterone pills, patches, topical gels, injections, implanted pellets, and even mucoadhesive tablets you stick to your gums.[4296] The different routes appear to work comparably,[4297] though injections are likely cheapest, costing about $150 a year instead of more than $2,000 for some of the topical preparations.[4298] It's worth noting that it may take weeks for testosterone levels to rise and months for symptoms to reverse, though the placebo effect can kick in immediately.[4299] What are the downsides?

THE RISKS OF TESTOSTERONE THERAPY

I do a deep dive into potential problems in see.nf/trisks, which include sexual infidelity,[4300] an increase in "tit-for-tat" provoked aggression,[4301] and the most ironic side effect: developing low testosterone. The reason bodybuilders develop shrunken testicles is that taking supplemental testosterone instructs the feedback loop in the brain to downregulate natural production, leaving the body in an even greater state of deficiency should the testosterone therapy ever stop.[4302] This creates a vicious but profitable cycle of dependency.[4303]

Testosterone can also stimulate our bone marrow to generate more red blood cells,[4304] which is good if you're anemic,[4305] but sludging up your blood with too many red cells can put you at risk for heart attacks and strokes.[4306] Indeed, the Testosterone in Older Men (TOM) trial had to be cut short because the testosterone group was having ten times more cardiac events than the placebo group.[4307] Since black box warnings have been

issued that testosterone presents "a risk of serious and possibly life-threatening cardiovascular (heart and blood vessel) problems,"[4308] prescriptions for testosterone have declined sharply.[4309]

One leading anti-aging journal carried a commentary comparing testosterone replacement therapy to the emperor's new clothes, noting that the topic remains "astonishingly controversial."[4310] What do you expect when there's a billion-dollar industry at stake? An analysis of popular YouTube videos on the subject suggests that mass misinformation persists,[4311] yet a systematic review of more than 150 randomized controlled trials concluded, "We identified no population of normal men for whom the benefits of testosterone use outweigh its risk."[4312]

The Risks and Benefits of PSA Prostate Cancer Screening

Testosterone therapy surprisingly does not seem to worsen symptoms of prostate enlargement,[4313] but what about prostate cancer? We've known about testosterone's role in prostate cancer since the 1940s, when surgical castration was shown to cause a dramatic regression of tumors.[4314] To this day, testosterone suppression is universally accepted as the first-line treatment for symptomatic metastatic disease.[4315] Whether or not testosterone causes prostate cancer or merely accelerates it,[4316] the question is moot since autopsy studies show that as many as about one-third of men in their thirties and two-thirds of men by their sixties already have tiny prostate cancers growing inside them—whether they know it or not.[4317] That's why guidelines recommend rectal exams and PSA screening before starting testosterone.[4318] What about prostate cancer screening in general?

While 64 percent of men develop hidden prostate cancers by their sixties,[4319] the lifetime risk of being *diagnosed* with prostate cancer is only about 11 percent and the risk of dying from it is 2.5 percent.[4320] So, most men die

with their prostate tumors rather than *from* them. Indeed, most men with prostate cancer spend their whole lives never even knowing they had it. That's one of the problems with screening: Many prostate cancers that are detected during screening may never have led to harm even if they'd continued to go undiscovered.[4321] Nonetheless, not all men are so lucky. Nearly 28,000 die from prostate cancer every year[4322] (at the average age of eighty).[4323] So, should you get a PSA prostate screening test or not?

The U.S. Preventive Services Task Force recommends against routine PSA screening,[4324] as do the American College of Preventive Medicine,[4325] the American Academy of Family Physicians,[4326] and the majority of professional medical societies in developed countries around the world (thirty-six out of forty-two).[4327] In 2018, though, the USPSTF shifted from a summary judgment against routine screening to stating that "the decision about whether to be screened for prostate cancer should be an individual one" for men aged fifty-five to sixty-nine,[4328] which is more in line with the "shared decision making" stance of the American Urological Association,[4329] American College of Physicians,[4330] and American Cancer Society.[4331] In other words, men should be informed about the risks and benefits and decide for themselves. However, men who are on the fence and don't express a clear preference in favor of screening should not be screened, according to the latest USPSTF recommendations.[4332]

More recently, an international panel of experts concluded that clinicians need not feel obligated to systematically bring it up, judging that most men would decide to decline PSA screening given the clear harms and small and uncertain benefits.[4333] That, however, is up to each individual. Let's run the numbers.

Similar to the 92 percent of women who either overestimated the mortality reduction from mammograms by tenfold or more or simply didn't know, 89 percent of

men vastly overestimated the benefits of prostate cancer screening or had no idea. Most thought fifty prostate cancer deaths could be prevented out of one thousand men regularly screened,[4334] when in reality it's more like one.[4335] But doesn't even a one-in-a-thousand chance of not dying from cancer make a few blood tests worth it? The downsides are more than inconvenience.

About 1 in 7 men who undergo PSA screening will test positive, yet, in two-thirds of the cases, the subsequent biopsy results will be normal.[4336] So, out of 1,000 regularly screened men, about 150 will have a false alarm and be biopsied unnecessarily, which can cause minor complications like pain and bloody ejaculate, or, in approximately 1 percent of cases, more serious complications, like blood-borne infections that require hospitalization.[4337] The greatest harm, however, is overdiagnosis. Unnecessary biopsies are bad enough, but nothing compared to unnecessary cancer treatment.

Large-scale randomized trials suggest that 20 to 50 percent of men diagnosed with prostate cancer would have never become symptomatic in their lifetime. They never would have been the wiser had they not been screened, but now they may be needlessly heading to the operating table. About three in a thousand men die during radical prostatectomy or soon after the surgery. That may help explain why there appears to be no overall mortality benefit to prostate cancer screening.[4338] For every life saved, another one may be extinguished for a cancer they would never have even known about.[4339]

Another fifty in a thousand end up with serious surgical complications. Even if the surgery goes smoothly, about one in five men develop long-term urinary incontinence requiring use of pads, and most—two out of three—will experience long-term erectile dysfunction. Most men who receive radiation therapy also experience long-term sexual erectile dysfunction, and up to one in six experience long-

term bowel issues, such as fecal incontinence. If this treatment was saving your life, it would be worth it, but it may be fifty times more likely that you were instead overdiagnosed with a cancer that would never have bothered you. In that much more likely case, you would be suffering all harms, no benefit.[4340] Yet, it's like with mammograms—the people who have been harmed the most feel as though they've been helped the most.

NATURAL WAYS TO BOOST TESTOSTERONE

To treat low testosterone, the American Urological Association, the European Association of Urology, and the Endocrine Society, the oldest association devoted to hormone research (so old they used to be called the Association for the Study of Internal Secretions),[4341] all recommend lifestyle modifications as the first-line treatment.[4342] In other words, treat the underlying cause.

Obesity and comorbidities underlie most cases of low testosterone in older men,[4343] which is frequently reversible with weight loss.[4344] An enzyme in body fat actually converts testosterone into estrogen.[4345] Even just losing 5 percent of your weight is associated with a significant increase in testosterone levels. Men losing more than 15 percent of their weight bumped up their testosterone by more than 150 points (ng/dL) on average,[4346] and those losing about 30 percent of their weight (through bariatric surgery) experienced around a 250-point increase.[4347]

Exercise may raise testosterone levels,[4348] but it depends on which kind. Despite the popular belief that resistance exercises, such as weight lifting, increase testosterone, a systematic review of training trials of older men found that only aerobic and interval training made a difference.[4349] Interestingly, listening to music while you work out may cause testosterone levels to drop. Within thirty minutes of listening to music, testosterone levels in men decline by 14 percent.[4350] Do all kinds of music have this effect or just some genres? While a half hour of silence had no effect, listening to thirty minutes of Mozart, jazz, pop, or Gregorian chants (no relation) had similar suppressive effects. What about a half hour of people's personal favorites? Testosterone levels were cut in half! What's going on?

Since testosterone in men is related to dominance and aggression, we may have evolved using music as a way to soothe the savage beast, like a melodious cold shower to keep everyone chill.[4351]

What else may decrease testosterone? Sleep deprivation. Experimentally restricting men's sleep to five hours a night for one week lowered testosterone levels by 10 to 15 percent.[4352] Alcohol can do it, too. While two or three alcoholic drinks can cause an acute transient increase in testosterone that peaks after about two hours,[4353] randomizing men to three beers a day for three weeks reduced testosterone blood levels by about 7 percent (compared to nonalcoholic control drinks).[4354] Heavy coffee–drinking men appear to have higher testosterone levels,[4355] but when put to the test, those randomized to five small (6 oz) cups a day for eight weeks saw an increase in testosterone at the end of one month, but the effect seemed to disappear by month two.[4356]

What about "testosterone boosting" supplements? An analysis of the top "T-Boosters" sold on Amazon.com found that 70 percent contained components that had either no effect, an indeterminant effect, or even *decreased* testosterone[4357] in as many as 10 percent of such supplements.[4358] One of the few constituents that would be expected to increase levels, however, is fenugreek.

Fenugreek seed has been used historically as an aphrodisiac and for male reproductive issues.[4359] It can increase the testicular weight and testosterone production in rats, but what about people?[4360] Clinical trials of fenugreek with daily dose equivalents as low as a quarter teaspoon[4361] to two-thirds of a teaspoon[4362] were found to raise testosterone levels[4363] by about 10 percent within three months, accompanied by a rise in sex drive and arousal.[4364] Side benefits include an improvement in LDL cholesterol, triglycerides,[4365] and short- and long-term blood sugar control (with actual fenugreek powder working better than fenugreek extract supplements).[4366] It can also make your armpits smell like maple syrup.[4367] (Really!)

TESTOSTERONE LEVELS AND DIET

What about broader dietary changes that might increase testosterone for those who are low and suffering from diminished libido? I do a deep dive in see.nf/tdiet. Acutely, high-fat meals can have a dramatic effect on

testosterone levels.[4368] When men ate a McDonald's Sausage & Egg McMuffin breakfast, their testosterone levels plummeted by 25 percent within an hour and stayed down for up to four hours.[4369] It's not just the inflammation,[4370] because the drop in testosterone was found to precede the bump in inflammation from the saturated fat. Testosterone can significantly drop within fifteen minutes of eating a ham and cheese sandwich, which is hardly even time for it to be digested.[4371] This led scientists to focus on digestive hormones like GLP-1,[4372] which is released within fifteen minutes of consuming a high-fat meal[4373] and appears to have a suppressive effect on testicular function.[4374] The researchers suggest that "men should minimise their fat intake … in order to optimise testicular function."[4375]

High-protein diets can also suppress testosterone,[4376] contrary to the "flagrant misuse of scientific information" in *Men's Health* magazine.[4377] When overweight men were randomized to a few scoops of whey (dairy) protein powder, their testosterone dropped one hundred points within an hour,[4378] explaining why high-protein, low-carbohydrate diets may cause large decreases in testosterone levels.[4379] That doesn't mean junky carbs are any better, though. Drinking two soda cans' worth of sugar water can also cause testosterone to plummet.[4380]

Can Phytoestrogens Be Feminizing?

I cover the evidence in see.nf/phyto, but even considerably higher doses than the one or two daily servings of soy phytoestrogens that Asian men typically eat do not exert feminizing effects on men,[4381] nor do they affect testosterone levels in people.[4382] What about the phytoestrogens in flaxseeds? Men fed six daily slices of flaxseed-enriched bread containing two tablespoons of ground flaxseed experienced no change in testosterone levels over a period of six weeks, compared to weeks avoiding flaxseed.[4383] There was a case of a man who developed gynecomastia (breast enlargement) after starting a tablespoon of flaxseed

oil a day, but he was also on a statin drug, which on its own increases gynecomastia risk.[4384]

TESTOSTERONE AND MORTALITY

Big Pharma framed low testosterone as a serious health problem. "It is one thing to tell men that Low T can make them grumpy," read a commentary in *JAMA Internal Medicine*, but "it is another to say that it can kill them."[4385] Most observational studies have reported associations between low testosterone and increased mortality, which isn't surprising because obesity and chronic illness—even acute ailments like heart attacks or infections—decrease testosterone levels, whereas healthy older men are able to maintain their levels. So, low testosterone can act as a barometer of health[4386] and is much more likely a consequence, rather than a cause, of disease.[4387]

In the largest observational trial of men at high cardiovascular risk who had been given testosterone replacement,[4388] when researchers controlled for these other confounding factors, testosterone takers were found to be at significantly higher risk of heart attack, stroke, or premature death.[4389] Testosterone may help explain why women outlive men by an average of seven years.[4390] This might be expected given that testosterone is a powerful immune suppressant.[4391]

Men have a reduced capacity to fight infections and don't respond as well to vaccinations compared to women. That said, less immune activation may have the advantage of less autoimmune disease. Testosterone may be the reason women have higher rates of diseases like lupus, rheumatoid arthritis, and multiple sclerosis,[4392] but the reason men have more infectious disease morbidity and mortality. Lower infection risk is one reason why neutered cats live years longer than "intact" males.[4393] In fact, there are rare mammals who evolved "semelparous" reproductive strategies in which the males engage in a single, "out with a bang" mating frenzy fueled by surging testosterone before dying shortly thereafter from a total collapse of their immune system.[4394] So, might human eunuchs actually live longer?

Castration does extend the lifespan of rodents.[4395] (Then again, giving them hundreds of 10,000-volt electric shocks can, too, so I'm not being prescriptive.[4396]) A historical study of Korean eunuchs suggested they lived fourteen to nineteen years longer than uncastrated men of similar

socioeconomic status, with a centenarian rate more than a hundred times higher than present-day populations.[4397] However, the existence of one eunuch purported to have lived 109 years, close to the longest lifespan ever recorded in men, cast aspersions on the accuracy of the records.[4398] A similar analysis dating back as far as the 1500s of castrati—male singers castrated before puberty to maintain their pitch—found no survival advantage compared to "intact" male singers during the same period.[4399]

More contemporary records can be drawn from the history of American eugenics in which the developmentally disabled were sterilized en masse through the 1930s,[4400] a practice that was sanctioned by the U.S. Supreme Court.[4401] At one Kansas mental institution, the hundreds who were castrated were found to live, on average, thirteen years longer than their uncastrated colleagues. The fact that death from infection constituted the chief difference between the two groups is consistent with the testosterone hypothesis.[4402] Regardless, testosterone replacement therapy is not a viable anti-aging strategy. Sadly, as an editorial published in the *Journal of the American Medical Association* lamented, "Testosterone misuse will not simply disappear for lack of logic or evidence as none was needed to get it started—rejuvenation fantasies thrive on hope without needing facts.…"[4403]

PRESERVING YOUR IMMUNE SYSTEM

A decline in immune function is one of the most well-recognized consequences of aging. We see this in increased vulnerability to acute viral and bacterial infections, such as the flu and pneumococcal pneumonia.[4404] In the developed world, infectious diseases are the fourth leading cause of death among the elderly, who suffer triple the mortality rate of acute infections compared to younger adults.[4405] This is exacerbated by a relatively poor response to vaccination, a phenomenon that's been recognized since the dawn of vaccine development.[4406] For example, while flu shots can build up sufficient antibody protection in 50 to 75 percent of younger individuals, that proportion falls to as few as 10 to 30 percent of older adults, who are among those who need the protection the most.[4407]

At the same time, we've known for nearly thirty years that the immune cells of eighty-year-olds produce significantly more pro-inflammatory signals.[4408] As I discuss in the Inflammation chapter, this suggests the worst of both worlds—a decline in the part of the immune system that fights specific infections and an aggravation of nonspecific overreactions that can lead to inflammation.[4409] We saw this play out with COVID-19. Certainly, older adults are more likely to be in tinderboxes like nursing homes and carry comorbidities that make infection more likely and serious, but part of their vulnerability may lie in both declining immune function and the potential for a hyperinflammatory "cytokine storm" immune reaction linked to poorer outcomes.[4410] Since I already covered the inflammaging dimension, I'll concentrate here on immunosenescence, the decline in immune defense with aging, and what we can do about it. (For the too-fantastical-to-be-believed overview on how the immune system actually works, see my Infections chapter in *How Not to Die*.)

LIFESTYLE

How can our daily habits influence our immune function?

WEIGHT LOSS

Obesity can weigh down the efficacy of vaccination,[4411] such that despite flu shots, individuals who are obese can have double the risk of coming down with the flu or flu-like infections compared to healthy-weight, vaccinated individuals.[4412] In fact, one of the reasons obese persons have higher cancer rates may be an impairment of antitumor immunity.

The Swedish Obese Subjects (SOS) trial was the first long-term controlled study to assess the outcomes of thousands of bariatric surgery patients against matched control subjects who began the trial the same weight but then followed a nonsurgical route. Over the next ten to twenty years, the control group's weights remained about the same, while the surgical group maintained about a 20 percent weight loss and also suffered significantly fewer heart attacks and strokes, developed 80 percent less diabetes, and, not surprisingly, had lower overall mortality. They also got less cancer.[4413]

Obesity severely impairs the function of our natural killer cells, critical members of our immune system's rapid-response force, fighting against cancerous and virus-infected cells. But when obese individuals were randomized to a weight-loss program, researchers saw a significant reactivation of natural killer cell function within only ninety days.[4414] An exercise component was included in the program, though, so it's difficult to tease out the impact of just the weight loss since physical activity on its own can boost natural killer cell activity.[4415]

EXERCISE

Exercise can ramp up our immune system by so much that we can reduce the number of sick days we have to take by 25 to 50 percent.[4416] Natural killer cells taken after thirty minutes of cycling killed off 60 percent more cancer cells in a petri dish.[4417] This may be one of the reasons exercise seems to both help prevent cancer and improve cancer survival.[4418] Men and women aged sixty-four and older who were randomized to twenty-five to thirty minutes of vigorous exercise three days a week for ten months before they got flu shots achieved significantly better protection,[4419] though you can't just slouch on the couch all year and jump up for a brisk walk right before your flu[4420] or pneumonia[4421] shot and expect additional protection. For more on what exercise can do to bolster your immunity, and for which infections interventional studies have shown exercise can help prevent, watch see.nf/exerciseimmunity.

Breathing in the Forest

Another way to lower cortisol levels is by forest bathing, surrounding yourself with trees,[4422] which may also elevate natural killer cell activity, as shown in a series of randomized controlled trials I document in see.nf/forestbathing. It turns out, as I explain in my follow-up video see.nf/treefragrance, trees produce aromatic volatile compounds called *phytoncides*,[4423] like pinene, that

you breathe into your lungs in the forest.[4424] They enter your bloodstream[4425] and boost natural killer cell activity.[4426]

A combination of wood aromas improved the recovery of mice from stress-induced immune suppression,[4427] but is it really just the fragrance of the forest? Researchers investigated whether that same boost in natural killer cell activity could be achieved by just vaporizing some essential oil from one of the trees into a hotel room overnight—and it worked![4428] Ironically, these phytoncide compounds are part of the tree's *own* immune system, which we may be able to commandeer.[4429] Researchers speculate these compounds may be playing some role in the fact that more heavily forested regions in Japan appeared to have lower death rates from breast cancer and prostate cancer.[4430] Being out in nature has been found to be an important coping strategy among cancer patients.[4431] It turns out this could potentially help more than just with coping, thanks to the fragrance of trees.

SLEEP

In mice, sleep deprivation has alternatively been found to undermine vaccine efficacy,[4432] have no effect,[4433] or even bolster protection,[4434] but, consonant with popular wisdom, there is "surprisingly strong evidence"[4435] that sleep enhances immune defenses in human beings. Individuals getting inadequate sleep on the days immediately before and after getting a hepatitis B[4436] or flu vaccine[4437]—for example, fewer than six hours compared to more than seven—tended to end up with significantly fewer protective antibodies. This was confirmed in interventional trials of imposed sleep loss.

In one study, half the participants had to pull an all-nighter after getting a hepatitis A vaccine. The individuals who had been allowed to sleep normally that night after getting the exact same vaccination ended up with twice the antibodies in their bloodstream a month later.[4438] Even one year later, they were significantly more protected—all because of one night's sleep.[4439] Can't you try to make up for it by sleeping longer on subsequent

nights? Even then, the die may have already been cast. Those getting a flu shot during a week in which they were restricted to four hours of sleep a night ended up with less than half the antibodies ten days later compared to the regular sleeping group, despite sleep getting extended to twelve hours a night in the sleep-debt group the subsequent week.[4440] Sleep deprivation—whether going to bed too late[4441] or getting up too early[4442]—has also been shown to impair natural killer cell activity.

What about infection rates? In the Harvard Nurses' Health Study II, those averaging no more than five hours of sleep a night appeared to have about a 40 percent greater chance of coming down with pneumonia, relative to those sleeping for eight hours. Those who were both overweight and not sleeping enough were at more than 80 percent higher risk.[4443] In a more direct demonstration, researchers at the Mayo Clinic dripped cold viruses right into people's noses, and those self-reporting sleeping fewer than seven hours a night were about three times more likely to come down with a cold than those who slept for eight hours or more.[4444] Self-reported sleep tends to underestimate duration, so the study was repeated using a wrist accelerometer for objective measurements. Those sleeping no more than six hours a night were four times as likely to fall ill compared to those getting seven hours or more.[4445] Note that infection rates were the same. After all, they had virus instilled directly in their nose. The well-rested group was just able to clear the virus so quickly that they were four times less likely to become symptomatic.[4446]

FOODS

As you can imagine, the upkeep of our immune system takes a tremendous amount of energy.[4447] We churn out millions of new immune cells every day.[4448] This may be why our immune function contracts as we age, paralleling the shrinkage of other energy-demanding organs, such as our muscles. This isn't inevitable, though. Some are able to maintain a fully functional immune system into old age.[4449] Part of the deterioration may be a function of the tendency for dietary quality to decline as we get older.

PRODUCE AISLE PROTECTION

Do people who eat well stay well? Those who eat more fruits and vegetables do appear to have a lower risk of getting an upper-respiratory-tract infection like the common cold. Even just one added apple a day may indeed help keep the doctor away.[4450] In terms of more serious respiratory infections, such as influenza, on a community-wide level, a 5 percent increase in obesity prevalence is associated with a 6 percent increase in flu-related hospitalizations.[4451] The same increase in physical inactivity rates was linked to a 7 percent increase in hospitalizations, and low rates of fruit and vegetable consumption may increase flu-related hospitalizations by 8 percent. Fruit and veggie intake is also linked to all sorts of other healthy behaviors, though. The only way to know if shopping the produce aisle can boost immunity is to put it to the test.

To assess the theory that inadequate nutrition could help explain the loss in immune function as you age, researchers split eighty-three volunteers aged sixty-five and older into two groups. The experimental group ate at least five servings of fruits and vegetables a day, while the control group ate fewer than three. All the participants were then vaccinated against pneumonia, a practice recommended for everyone over the age of sixty-five.[4452] The goal of vaccination is to prime our immune system to produce antibodies against that particular pathogen in case we ever get infected. Compared with those in the control group, the study subjects eating five or more servings of fruits and vegetables had an 82 percent greater protective antibody response to the vaccine. This was after just a single month of eating a few extra servings of fruits and veggies a day.[4453] That is how much control our forks may exert over immune function.

KIWIFRUIT, ECHINACEA, AND ELDERBERRY

Certain fruits and vegetables may give the immune function an extra boost. One that's been put to the test is kiwifruit. Preschoolers were randomized to eat either bananas or gold kiwifruits every day. Compared to the banana group, the kiwi-eating kids appeared to nearly halve their risk of contracting a flu-like illness or cold. (Why *gold* kiwifruits? The study was funded by the company that owns the patent on gold kiwifruits.)[4454] However, about 1 in 130 children may be allergic to kiwifruit,[4455] which may make kiwis the

third-most-common food allergen (after milk and eggs),[4456] so they are not for everyone.

A similar experiment was tried on another high-risk group, the elderly. Those in the control group who ate bananas and got an upper-respiratory-tract infection suffered with congestion and a sore throat for about five days, compared to the kiwifruit eaters, who felt better after one or two days.[4457] In contrast, anti-flu drugs like oseltamivir (Tamiflu) may only shorten symptom duration in adults by an average of about seventeen hours.[4458] A 2020 review titled "Food or Medication? The Therapeutic Effects of Food on the Duration and Incidence of Upper Respiratory Tract Infections" noted another advantage: The price of kiwifruit is "much lower."[4459]

Kiwis are technically berries. (They were known originally as Chinese gooseberries before some innovative New Zealand exporters named the fuzzy brown fruit after their fuzzy brown bird.) What about other berries? I cover all the studies on elderberries in see.nf/elderberries. In short, four studies seemed to show positive results, but they were also all funded by elderberry product companies.[4460] Finally, in 2020, an independent (philanthropy-funded) study was published—a randomized, double-blind, placebo-controlled trial of an elderberry extract for the treatment of influenza. In contrast to the industry-funded studies, those randomized to the elderberry seemed to do *worse*, experiencing more aches and pains. Among those not taking Tamiflu, the participants randomized to the elderberry placebo were sick for five days, whereas those randomized to the *real* elderberry were sick for *seven* days.[4461] The accompanying editorial concluded that, based on these results, "we can confidently advise patients not to take elderberry."[4462] As I show in the video, similarly disappointing results have been reported for the herb echinacea.[4463]

Elderberry supplements may not even be safe.[4464] A case report was published about a man taking an elderberry extract suffering an attack of acute pancreatitis (a sudden painful inflammation of the pancreas). What makes the case is that it went away when he stopped the supplement and then reappeared again years later when he tried taking it again, which suggests cause and effect. Why take elderberry extracts, though, when you can just eat the elderberries themselves? Because consuming raw elderberries can cause you to puke your guts out,[4465] as I found out the hard

way after foraging a backyard bush for breakfast. Turns out raw elderberry fruit forms cyanide.[4466] Only after recovering did I discover CDC reports like "Poisoning from Elderberry Juice—California" about eight people having to be medevacked out by helicopter after someone brought freshly squeezed elderberry juice to a gathering.[4467] All I can say is, I'm glad my body rejected it. What would they have put on the headstone? *Author of* How Not to Die *killed by a smoothie*.

OTHER BERRIES

What other berries might help us? In see.nf/immuneberries, I go through the whole rundown. Interventional studies show, for example, that blueberries can increase the numbers of natural killer cells,[4468] the aromatic spice cardamom can increase their activity,[4469] and black raspberries appear to do both,[4470,4471] but does this translate into fewer infections? Sea buckthorn berries boost the activity of another type of "first responder" immune cell[4472] but fail to help prevent respiratory, digestive, or urinary tract infections compared to placebo.[4473]

Goji berries do actually appear to have relevant, real-world, beneficial effects on immune function. Older men and women aged sixty-five to seventy were randomized to eat four teaspoons[4474] of powdered goji berries or an identical-appearing placebo powder every day for 90 days. On day 30, everyone received a flu shot. By day 60, the goji group already had a significantly better antibody response such that, by day 90, three times more of the goji group achieved seroconversion (a sufficiently protective antibody threshold): 28 percent versus only 9 percent in the placebo group.[4475]

Do They Need to Be Organic?

In a review updating the evidence of the implications of pesticides on human health, the body of evidence linking pesticide exposure and cancer is said to be "so huge that the role of pesticides in cancer development can no longer be doubted."[4476] However, most of the data showing DNA

damage from pesticides are limited to occupational exposure: among farmers and workers in fields, within the pesticides industry itself, or among those living in high-spray areas.[4477] What about the residues left on conventional produce? I explore that body of literature in my video see.nf/pesticides. In short, those who choose organic produce seem to have lower cancer rates after controlling for confounding factors,[4478] but even if it is cause and effect, the benefits of consuming conventionally grown produce are likely to outweigh any possible risks from pesticide exposure.[4479] So, concerns over pesticide risks should never discourage us from eating as many fruits and vegetables as possible. The potential lifelong damage of any pesticides on produce is estimated to cut only a few minutes off a person's life on average, which is nothing compared to benefits we get from eating fruits and veggies.[4480]

VEGETABLES

A series of experiments involving fruit and vegetable deprivation dramatically demonstrated the impact that healthy foods can have on our immune function. Figuring that their carotenoid pigments may be responsible for the immune-actuating effects, researchers advised volunteers to try to avoid all brightly colored fruits and vegetables. It didn't take more than two weeks for measures of their immune function to plummet. White blood cells taken from the participants became sluggish to proliferate in the face of immune activation. To see how quickly this activity could be recovered, they tried three potential rescue treatments each day: one and a half cups of tomato juice, one and a half cups of carrot juice, or a serving of powdered spinach. Within a week of starting the tomato juice, white blood cell activity started to significantly perk up, but neither the carrot juice nor the spinach seemed sufficient to salvage immune function.[4481] This tells us two things: Remarkably, we can affect our immune function with simple dietary decisions, and not all veggies are alike.

When this study was repeated to look at other immune markers, tomato and carrot appeared more evenly matched. (Spinach was skipped this time.)

Both the post-deprivation tomato and carrot juice periods saw a significant increase in natural killer cell activity, for example.[4482] In contrast, tomato extract supplements (Lycomato) failed to result in any improvements in immune defense.[4483] Could something as simple as tomato juice improve immune protection even in those who hadn't been deprived of carotenoid-rich fruits and vegetables? Well-nourished elderly men and women were randomized to a cup and a half of tomato juice or mineral water for eight weeks, and no difference in immune function was found.[4484] So, if you're stuck in a rut of beige food like white potatoes, it doesn't take much to recoup some of your lost immune function, but if you're eating a minimum threshold of healthy produce, it's going to take more than a glass of tomato juice. Either add multiple daily servings of fruits and vegetables like in that flu shot study, or level up your veggies to include some at the top of the heap, like broccoli.

CRUCIFEROUS VEGETABLES

Here, I explore how crucifers are critical for intestinal immune function. Broccoli can also boost our natural killers.[4485] Researchers drew blood from study participants before and after they ate broccoli sprouts for just a few days and found that the ability of their natural killer cells to produce *granzyme B* went up. That's an enzyme used to activate what are called "execution caspases" in target cells to initiate a self-destruct protocol and wipe out virus-infected and cancerous cells.[4486] Does this translate into helping us actually fight off infection? Researchers dripped flu viruses into the noses of volunteers to find out.

In a randomized study, compared to the placebo (alfalfa sprouts), about 4 oz of broccoli sprouts eaten on the day before and the day of infection significantly reduced the viral load as well as virus-induced inflammation in the nose in smokers. The researchers concluded that cruciferous vegetables like broccoli may present a "low-cost and low-risk measure for reducing the impact of influenza."[4487] The same was found for reducing respiratory syncytial virus disease in mice[4488] and blocking Epstein-Barr virus in vitro.[4489] Sulforaphane, the purported active component in broccoli and other crucifers, has also been found to restore bacteria recognition and engulfment in macrophages extracted from the lungs of patients with

pulmonary diseases like emphysema (COPD).[4490] However, the concentration they used might only be reached in the bloodstream by eating around five cups of broccoli at one sitting,[4491] so we won't know clinical relevance until it's been studied at more modest doses.

NO NEWS IS GOOD NEWS

Nitric oxide—not to be confused with nitrous oxide, aka laughing gas—is best known as the "open sesame" molecule our artery lining releases to enable our blood vessels to dilate, but it also has broad-spectrum antiviral, antibacterial, and antifungal properties. It's secreted into our airways as a first line of defense against respiratory infection,[4492] shooting up more than 500 percent over baseline.[4493] Nitrate-rich vegetables can improve athletic performance,[4494] but what about immune performance? Infusions of spinach leaves have been used since ancient times to treat respiratory symptoms,[4495] but as I explore in see.nf/noimmune, the evidence that this translates into lower infections rates still remains suggestive.[4496]

SEAWEED

What about underwater greens? Billions of pounds of sea vegetables are harvested each year.[4497] Japan has among the highest per capita intake of seaweed, and its consumption is associated with lower disease rates and even lower all-cause mortality,[4498] though it may just be an indicator of following more traditional Japanese dietary customs.[4499] In terms of immune function, wakame, which is the kind you find in seaweed salad, can double[4500] or quadruple[4501] the replication potential of T cells, an important part of our immune defense against viruses like herpes. See my video see.nf/wakame to learn what eating just 2 g a day of wakame can do for those suffering from various herpes infections and how wakame can significantly boost protective antibody responses to flu vaccination.

Soy foods can also boost antibody-producing B cells. Those randomized to three daily cups of soymilk increased B cell populations in the blood by about 35 percent more than those receiving dairy milk.[4502] Japan also has among the highest per capita soy consumption,[4503] so the speculation that seaweed intake may help explain the relatively low rates of HIV[4504] and

COVID-19[4505] in the country could also be extended to other traditional Japanese foods.

What about nori, probably the most accessible seaweed? They're the sheets used for making sushi rolls,[4506] but they can also make quick and easy snacks, one of my go-to favorites. It's hard to beat the nutrient density; each sheet has as little as a single calorie.[4507] Study participants randomized to a nori extract for eight weeks experienced an increase in natural killer cell activity.[4508] The dose they were given was equivalent to about seven sheets of nori a day,[4509] though, so it's not clear what the effects of smaller doses might be.

CHLORELLA

About 95 percent of all infections begin in our mucosal surfaces, the moist linings of our eyes, nostrils, and mouth.[4510] To protect these surfaces, our body covers them with a special antibody called *immunoglobulin A* (IgA), which it pumps out to the tune of ten thousand million billion a day ($1x10^{19}$).[4511,4512] This provides an immunological barrier that neutralizes and prevents viruses from penetrating the body. The IgA in saliva, for example, is a first-line defense against pneumonia, influenza, and other respiratory-tract infections.[4513]

Researchers in Japan found that IgA concentrations in breast milk could be increased by giving mothers chlorella, a unicellular freshwater green algae (essentially, a single-celled plant) sold as powder or compressed into tablets.[4514] What about other parts of the body? Chlorella didn't convincingly improve the immune response to flu vaccination,[4515] but it did increase IgA secretion into the mouth.[4516] Unfortunately, as I cover in see.nf/igachlorella, it's not clear if this translates into fewer illnesses.

Chlorella can also significantly improve natural killer cell activity.[4517] This may play a role in reducing liver damage in chronic hepatitis C virus infection,[4518] with benefits for cholesterol, blood pressure, and blood sugar control,[4519] but as I note in my video see.nf/nkchlorella, there was a concerning case report of apparent chlorella-induced psychosis that makes me wary.[4520]

GARLIC

In World War II, garlic was called "Russian Penicillin" because, after running out of antibiotics, that's what the Soviet government turned to.[4521] Does it actually work? Eating garlic appears to offer the best of both worlds, dampening the overreactive face of the immune system by suppressing inflammation,[4522] while boosting protective immunity, such as natural killer cell activity. Check out see.nf/coldsandcancer for double-blind, placebo-controlled trials of garlic for the prevention of the common cold and cancer. (Garlic supplement users did not appear to be protected from COVID,[4523] but it may take up to fifty-four capsules of garlic extract supplements to obtain the same amount of garlicky goodness found in just one clove of crushed raw garlic.[4524])

What happens if you cook it? If you compare raw chopped garlic to garlic that's been cooked in various methods, you can see dramatic drops in one of the purported active ingredients. You can get a 66 percent drop when you boil it for six minutes, 94 percent less when you simmer it for fifteen minutes, and a full 100 percent wipeout from just one minute of stir-frying it.[4525] What about roasted garlic? Surprisingly, even though roasting is done at temperatures hotter than boiling water, it preserves about twice as much. Raw garlic has the most, but it may be easier for some to eat two or three cloves of cooked garlic than the equivalent (half a clove) of raw.[4526]

In *How Not to Die*, I suggested that the only major caveat against consuming garlic (besides a potential decrease in kissability) is that garlic can have blood-thinning effects, so maybe you shouldn't have any a week before elective surgery.[4527] That was based on a study in which subjects were fed 10 g of garlic every day for two months, which is about three daily cloves.[4528] However, at a more "socially acceptable" dose of one to two cloves a day for a week, no changes in clotting function were noted.[4529] What about garlic breath? Raw apple, raw lettuce, and mint leaves have all been shown to be at least partially effective.[4530]

MUSHROOMS

As I show in my video see.nf/mushrooms, cooked white button mushrooms can also boost IgA production[4531] while potentially tamping down immune overactivity. A randomized, double-blind, placebo-controlled clinical study

confirmed an apparent anti-allergy effect of an oyster mushroom component in kids who had a history of recurrent upper-respiratory-tract infections.[4532]

Shiitake mushrooms have also been shown to improve human immune function. Just eating two or three large dried shiitake mushrooms a day for a month resulted in an increase in the proliferation of two types of first-line immune defenders, all while lowering markers of systemic inflammation.[4533] What we care about most, though, is actually preventing infections.

White button mushroom supplementation enhances natural killer cell activity in aged mice, for example, but it doesn't actually protect them against subsequent influenza infection.[4534] Oyster mushrooms seem to work—at least in athletes. After intensive exercise, elite athletes can suffer a 28 percent reduction in natural killer cell activity during recovery.[4535] When they were given about one daily oyster mushroom's worth[4536] of the special beta-glucan fiber found in fungi (sourced from oyster mushrooms), not only did their natural killer cell counts buoy up, but they suffered fewer upper-respiratory-tract symptoms over three months. In the placebo group, 84 percent suffered four or more symptoms, compared to only 12 percent in the mushroom group.[4537]

NUTRITIONAL YEAST

That same immune-activating beta-glucan fiber is found in brewer's, baker's, and nutritional yeasts. Details in see.nf/nooch, but basically, the IgA-boosting effects[4538] of the beta-glucan from a daily heaping teaspoon or so of nutritional yeast can reduce the incidence, duration, and severity of upper-respiratory-tract infections compared to placebo.[4539] And what's the downside—tastier popcorn? Randomized controlled trials have also found it has anti-inflammatory effects[4540] sufficient to improve wound healing,[4541] reduce the severity of canker sores,[4542] and alleviate symptoms in ragweed sufferers, as well as benefit weight loss.[4543,4544] None of the studies reported treatment-related adverse effects,[4545] but I would caution against the use of any kind of yeast for those with two specific autoimmune diseases: Crohn's disease[4546] (see.nf/crohns) and a skin condition known as *hidradenitis suppurativa*[4547] (see.nf/hidradenitis).

Our body is always on the lookout for *PAMPs*, pathogen-associated molecular patterns. These are molecules foreign to our body that are associated with infection, such as components of bacterial cell walls. We have immune cells with pattern-recognition receptors that recognize these "nonself" signatures. Not all bacteria are pathogenic, though, so, in order to be more accurate, the name was changed to *MAMPs*, microbe-associated molecular patterns. The beta-glucans in yeast and mushrooms are major MAMPs.[4548] They make up the cell walls of fungi, so they act as nonspecific immunostimulants (as opposed to a specific immunostimulant like a vaccine).[4549] Essentially, when our body detects beta-glucans in our system, to err on the side of caution, it immediately thinks *fungal infection*, not shiitake stir-fry.[4550] We can then benefit from that increased vigilance.

There are also MAMP mimickers in certain plants. Bacteria, fungi, parasites, and tumor cells all release a class of MAMP compounds called *alkylamines*.[4551] Theanine, the unique amino acid that gives tea its savory (umami) taste, is broken down in our gut into an alkylamine called *ethylamine*, which then circulates throughout the body. You can tell if someone is a tea drinker by testing their urine for ethylamine.[4552] There are also preexisting alkylamines in apple peels (*n*-Butylamine),[4553] wine (iso-amylamine),[4554] and healthy vaginal secretions (isobutylamine).[4555]

Alkylamines enhance the proliferation and activity of gamma-delta T cells, a type of first-line defender.[4556] The "priming" of these cells by ethylamine may explain why gamma-delta T cells taken from tea drinkers are more active than those taken from coffee drinkers. Take white blood cells before and after just one week of tea drinking, and you get two to four times the defensive interferon release upon exposure to bacteria in vitro. The day-to-day low-level exposure to ethylamine seemed to maintain their immune cells in a constant ready state. There has even been speculation that primate immune systems evolved to take immune-boosting advantage of the alkylamines and their precursors in plant foods.[4557]

Tea drinkers have been documented to have lower rates of influenza[4558] and as little as half the risk of dying from pneumonia.[4559] A randomized, double-blind, placebo-controlled trial found that those taking concentrated green tea capsules had about one-third fewer days of cold and flu symptoms

compared to those randomized to placebo capsules, but the dose equivalent was comparable to drinking ten cups of tea a day.[4560] Subsequently, a similar trial on healthcare workers found that those participants randomized to the equivalent of just one and a quarter cups of green tea a day[4561] for five months were about three times less likely to come down with the flu (4 percent versus 13 percent in the placebo group).[4562] How low can you go? In 2020, researchers tried to push the envelope and found that even the equivalent of half a cup of green tea a day (about one typical teacup's worth)[4563] cut the risk of upper respiratory infection in half, but less than a quarter cup a day did not.[4564]

What About Gargling with Green Tea?

A study that involved swabbing the mouths of volunteers ten, forty, and sixty minutes after they drank some tea found that antiviral concentrations[4565] of tea compounds were retained in the oral cavity even an hour after ingestion.[4566] The studies that I mentioned earlier found a reduction in infection risk even with swallowed green tea extract capsules; they show that direct contact with our throat is not necessary. What about the opposite? What about gargling green tea and spitting it out so there's *only* oral contact?

As I note in see.nf/gargling, acrobatic attempts have been made to present purported tea gargling benefits as statistically significant for upper-respiratory-tract infections[4567] or influenza,[4568] either by folding them in with tea ingestion trials or combining them with observational gargling studies. However, that doesn't change the fact that none of the randomized controlled trials of tea gargling has been found to significantly lower infection risk.[4569] The evidence for water gargling to prevent upper-respiratory-tract infections is also disappointing.[4570]

So, although gargling may work wonders to soothe a sore throat, it may not prevent the sore throat in the first place—unless it's caused by gonorrhea. A single one-minute

gargle with an antiseptic mouthwash (Listerine diluted up to 1:4 with water in this case) can significantly reduce the amount of any gonorrhea bacteria you may have in your oral cavity.[4571] Gargling has been found to be superior to simply rinsing out your mouth in terms of reaching the back of your throat. At least twenty seconds is recommended,[4572] but in a study of female sex workers, the average gargle time was only four seconds.[4573]

FIBER-RICH FOODS

In my High in Fiber-Rich Foods chapter in *How Not to Diet*, I relayed the detective story of the search for the keys that fit into two mysterious locks in the body, vital receptors expressed heavily throughout our body—on our nerves, in our gut, and in our immune, muscle, and fat cells.[4574] Spoiler alert: They were the short-chain fatty acids our gut bacteria make when we eat fiber,[4575] constituting a critical line of communication between our gut bacteria and the rest of our body.[4576]

This may explain how fiber is so anti-inflammatory.[4577] For instance, how is it possible that just one high-fiber meal can improve lung function in asthmatics within a matter of hours? We now know that our good gut bacteria turn the fiber we eat into short-chain fatty acids, which then are absorbed into our bloodstreams. They are then free to dock in these receptors found on the inflammatory immune cells in our airways and turn them off.[4578]

Does that mean that people who eat more fiber have better immune systems? How might we determine that? Well, most people have gotten an MMR shot, the measles-mumps-rubella vaccination that's been routinely given to children since the 1970s. Are there measurably more antibodies against pathogens in different dietary groups? Yes, for mumps. All participants had received the same MMR vaccine, but those eating more fiber had significantly higher levels of antibodies against mumps, though not against any of the other bugs.[4579]

To help prove cause and effect, researchers gave volunteers a cocktail of antibiotics to wipe out much of their gut flora as they were getting their annual flu vaccine. Those starting out with low preexisting immunity

suffered a striking impairment of their antibody response.[4580] They had much weaker reactions to the vaccine. Conversely, by randomizing people to prebiotics, like fiber, which is what our good bacteria eat, or probiotics, the good bacteria themselves, antibody responses to flu shots can be enhanced.[4581] Does this translate into lower infection risk?

Those with higher levels of fiber-feeding bacteria in their gut were found to be five times less likely to develop viral pneumonia or bronchitis.[4582] Establishing cause and effect, a meta-analysis of randomized controlled trials found that *pre*biotics can reduce the incidence of respiratory tract infections in general.[4583] For probiotics, in children, those randomized to probiotic dairy yogurt, soy yogurt, or supplements experienced both fewer and shorter-lasting upper-respiratory-tract infections,[4584] though, in older adults, only the duration of symptoms appears to be lessened.[4585,4586,4587] Given the potentially negative impacts of probiotics I note in the Prebiotics and Postbiotics chapter, I would suggest instead focusing on feeding the good bacteria we already have, by eating foods naturally rich in dietary fiber.

DO VEGETARIANS MAKE BETTER KILLERS?

As we get older, our natural killer cells tend to lose some of their proliferative capacity and killing power.[4588] What can we do to maintain their function? I reviewed a few plants that appear protective, but what about an entire diet centered around plants? The natural killer cells of vegetarians were pitted head-to-head against those of omnivores in a test to see which could wipe out more leukemia cells, and the vegetarian killer cells were victorious. They were more than twice as effective in killing off cancer. On average, each natural killer cell drawn from the blood of a vegetarian knocked off two cancer cells for every one the nonvegetarian killers succeeded in overtaking. The researchers suggested that "the reduced cancer risk of vegetarians is possibly partially related to the better natural defense system which they seem to have."[4589]

Having more effective immunity doesn't just help protect against cancer by targeting tumors directly. Sometimes infections cause cancers. Take HPV (human papilloma virus). Cervical cancer is now considered a sexually transmitted disease.[4590] It was originally suspected as such, based

on cancer rates in "nuns versus prostitutes,"[4591] but we now have DNA fingerprinting proof that virtually all cervical cancer is caused by HPV,[4592] a sexually transmitted virus that also causes cancers of the penis, vagina, vulva, and throat.

HPV is considered a necessary but insufficient cause of cancer. HPV is so common that most young women will contract it, yet most don't get cervical cancer because their immune systems are able to wipe out the virus. Within one year, 70 percent of women clear the infection and more than 90 percent clear it within two years—before the virus can cause cancer.[4593]

Might those with particularly strong immune systems clear the virus even faster? That may explain the finding that vegetarian women had significantly lower HPV infection rates, one of many studies reporting lower risk of HPV infection among those eating plant-based diets.[4594] Greater vegetable consumption alone may even help.

Researchers followed women with cancer-causing strains of HPV infecting their cervix and retested them at three months and nine months, while analyzing their diets. Higher levels of vegetable consumption appeared to cut their risk of HPV persistence in half, doubling their likelihood of clearing this potentially cancer-causing infection.[4595] This may help explain why vegan women have significantly lower rates of all female cancers combined, including cancer of the cervix.[4596] However, a comparison of the natural killer cell activity between vegans and nonvegetarians failed to replicate the earlier study, so other cancer-fighting components or nonimmunological mechanisms may be responsible for the lower cancer rates.[4597]

Plant-Based Pandemic Protection

The COVID-19 pandemic offered a good opportunity to see if eating more healthfully could help stave off infection. Details in see.nf/plantdemic, but basically, Harvard researchers collected data from nearly 600,000 participants and found that those who ate the most healthful plant foods and the least meat, eggs, dairy, and junk not only had a

significantly lower risk of suffering a severe course of COVID-19 but they also had a significantly lower risk of getting infected in the first place, even after taking into account comorbidities and other nondietary lifestyle risk factors, such as exercise, smoking, and socioeconomic status.[4598]

SUPPLEMENTS

Are there any supplements that can help protect against infection?

GINSENG

Ginseng is notable for its Latin name, *Panax*, which comes from the word *panacea*, meaning "cure-all."[4599] It can extend the lives of fruit flies[4600] and roundworms[4601] but not mice.[4602] The two main species are American ginseng (*Panax quinquefolius*) and Asian ginseng (*Panax ginseng*), which can be further divided up by processing method. White ginseng is Asian ginseng root that's simply been washed and dried. Red ginseng is Asian ginseng root that undergoes an additional step of steaming before drying.[4603] Various ginseng preparations have been shown to boost populations of B and T cells[4604] and natural killer cell activity,[4605] but what about disease endpoints?

A meta-analysis of randomized, double-blind, placebo-controlled trials found that ginseng appeared to reduce the risk of developing acute upper respiratory infections, but it did not appear to significantly affect the duration of illness. A subgroup analysis, however, suggests that the preventive benefit is limited to Asian ginseng, which cuts infection risk in half compared to placebo, as opposed to American ginseng, which reduced risk by only 14 percent, not reaching statistical significance.[4606]

I cover the downsides in see.nf/ginsengabuse. Aside from the symptoms of "ginseng abuse syndrome" and tissue swelling,[4607] there have been case reports of manic psychosis,[4608] estrogenic effects,[4609] and increased surgical bleeding.[4610] So, some recommend that those with hypertension, hyperthyroidism, a predisposition to mania, estrogen-dependent disease, or upcoming surgery avoid ginseng.[4611]

MULTIVITAMINS

All nutrients play some role in the functioning of the immune system. If you have a nutrient deficiency, then supplementation could certainly improve immunity, but we shouldn't expect that adding extra on top of nutrient sufficiency would necessarily further amplify immune function.[4612] However, many apparently healthy elderly people have been found to have micronutrient deficits,[4613] so what about taking a multivitamin and mineral supplement?

Extraordinary benefits were published in some of the most prestigious journals,[4614] leading reviewers to conclude, "All these reports confirm that immune responses may be enhanced in elderly individuals by the use of micronutrient supplements."[4615] Then, most of the papers were retracted,[4616] one after another.[4617] An earlier paper published by one of the principal authors tipped off investigators. "Impossible" results from a study purporting to show cognitive benefits of multivitamin and mineral supplements[4618] led to a formal investigation that confirmed the impropriety,[4619] which then led to the cascade of retractions.

Since the debacle, there have been three large randomized controlled trials of multivitamin and mineral supplements for the prevention of infections.[4620] One such study, on noninstitutionalized elders and acute respiratory infections, found no effect on incidence or severity.[4621] Another, on nursing home residents and infections in general, found no fewer cases of infections, though those randomized to the multivitamin and mineral supplements did end up spending fewer days on antibiotics over the eighteen-month-long study.[4622] The third study looked at multivitamin and multimineral supplements separately and found the antibody response to flu vaccines improved on the minerals compared to placebo, while the antibody response to flu vaccines on the vitamins was worse than on placebo.[4623] Neither, however, led to a significant drop in infection rates.

VITAMIN C

Vitamin C has been proposed as a treatment for respiratory infections since its discovery nearly a century ago.[4624] In 1970, Nobel Prize laureate Linus Pauling published an influential book titled *Vitamin C and the Common Cold* that generated tremendous public interest and no doubt helped inspire

the dozens of randomized, double-blind, placebo-controlled trials that were to follow to put his endorsement to the test.[4625] Check out see.nf/c4colds for details on what they found, but basically, those under extreme physical stress, such as marathon runners or soldiers on subarctic maneuvers, do appear to benefit from regularly taking vitamin C supplements, cutting their risk of coming down with a cold in half. However, for the general population, daily vitamin C supplementation does not appear to significantly reduce the incidence of infection, though when regular users do get sick, they don't get *as* sick and get better about 10 percent faster. Unfortunately, just starting vitamin C after the onset of cold symptoms doesn't seem to help cut down on cold severity or duration.[4626]

The downside is that vitamin C supplements appear to favor kidney stone formation,[4627,4628] as much as doubling risk. Those taking 1,000 mg or so of vitamin C a day may have a one-in-three-hundred chance of getting a kidney stone every year, instead of a one-in-six-hundred chance, which is not an insignificant risk, given how painful they can be.[4629]

VITAMINS D AND E

Daily vitamin D supplementation appears to reduce the risk of acute respiratory infections in children and adolescents, but it does not seem to make a difference in adults, nor is D effective for boosting antibody responses to influenza vaccination.[4630,4631] Vitamin E, on the other hand, was able to significantly boost immunity to hepatitis B and tetanus vaccinations, though not to diphtheria or pneumonia.[4632] As I detail in see.nf/immunevitamins, the data on vitamin E and infections are mixed, with some studies showing a worsening of infections.[4633] The question appears moot, since randomized controlled trials show vitamin E increases the risk of cancer[4634] and overall mortality.[4635] In other words, those who buy vitamin E supplements may in effect be paying to live a shorter life.

ZINC

In February 2020, a noted virologist told his friends and family, "Stock up now with zinc lozenges" for the coming pandemic.[4636] He based his supposition on the efficacy of zinc for common colds, up to 29 percent of which are caused by coronaviruses.[4637] There's actually a heartwarming

backstory to that discovery that I detail in see.nf/zinc, involving a three-year-old girl with cancer who inspired her father to conduct the first randomized, double-blind, placebo-controlled trial on zinc lozenges for the common cold.[4638]

I run through all the studies in the video, but basically, zinc lozenges appear to shorten colds by about three days,[4639] with significant reductions in nasal discharge (by 34 percent), nasal congestion (by 37 percent), hoarseness (by 43 percent), and cough (by 46 percent).[4640] The best way to take zinc for the common cold is lozenges containing around 10 to 15 mg of zinc taken every two waking hours for a few days, starting immediately upon symptom onset as either zinc acetate or zinc gluconate[4641] *without* binders such as citric acid, tartaric acid, glycine, sorbitol, or mannitol.[4642]

Efficacy against more serious infections such as pneumonia may only be present among those with preexisting zinc deficiency.[4643] I was surprised to learn that the essentiality of zinc in humans wasn't established until the 1960s and wasn't formally recognized until 1974.[4644] About 40 percent of men and women in the United States aged sixty and older may not reach the recommended daily intake through their diet.[4645] Unlike some other minerals, such as iron, you can't just get a blood test to tell if you're deficient because zinc levels in the blood aren't a good reflection of overall zinc status in the body.[4646] The best we can do is make sure we get enough in our diet. The healthiest sources are probably legumes, nuts, and seeds, though oysters may be the most concentrated source by far.[4647] (A single oyster has more zinc than a cup of baked beans.[4648])

Zinc supplementation doesn't appear to reduce the risk of getting sick in the first place,[4649] though, and supplementing long-term may actually impair certain aspects of immunity in the elderly. This is perhaps because, at high doses, zinc can interfere with the absorption of other nutrients important to immune function, such as copper and folate.[4650] A month of zinc supplementation did appear to boost the antibody response to tetanus vaccination,[4651] but even two months of zinc supplementation before flu shots didn't appear to have any effect.[4652] Short-term use is considered to be safe, but zinc supplements and lozenges can cause nausea, especially when taken on an empty stomach, and other gastrointestinal symptoms.[4653] You should *never* put zinc in your nose. In the drugstore, you'll find all sorts of

intranasal zinc gels, sprays, and swabs, but these have been linked to the potentially permanent loss of one's sense of smell.[4654]

Note there was a happy ending: That three-year-old beat her cancer, never relapsed, and grew up to become a scientist herself.[4655]

VACCINES

Vaccines are considered one of the greatest public health achievements of the last century,[4656] having eradicated smallpox, a scourge that killed hundreds of millions of people, and greatly reducing other major diseases, such as measles and polio.[4657] To this day, vaccines are estimated to save millions of lives each year.[4658]

More than 90 percent of U.S. children get common childhood vaccinations, such as polio and MMR shots, but most adults fail to get their full complement of recommended adult vaccinations. Assuming you got all your childhood vaccinations (and aside from any emergent pandemic needs), the CDC recommends that all adults get annual flu shots, tetanus boosters every ten years (though the World Health Organization doesn't think this is necessary),[4659] shingles vaccination at age fifty, and pneumonia vaccination at age sixty-five. Certain groups need others, such as hepatitis A vaccination for those experiencing homelessness, people with chronic liver disease, or men who have sex with men; or a hepatitis B series for healthcare workers and those who are incarcerated.[4660] Ask your medical professional for a personalized schedule.

How safe are vaccines? In a 2021 systematic review and meta-analysis, the RAND Corporation screened more than 50,000 citations and concluded that routine vaccinations can be considered safe, with only rare serious adverse effects,[4661] such as severe allergic reactions in one to ten individuals in a million. Transient autoimmune syndromes (Guillain-Barré and immune thrombocytopenic purpura) occur in about one to three in a million and ten to thirty in a million for flu shots and MMR vaccines, respectively.[4662]

FLU VACCINE

Each year, influenza typically kills between 4,000 and 20,000 Americans,[4663] though the death toll for the 2017–18 flu season was estimated at 80,000, making it one of the deadliest in the last half

century.[4664] Most hospitalizations and 90 percent of flu-related mortality occur in those sixty-five and older.[4665] Mortality rates for the flu at ages seventy-five and older are fifty times higher than for those younger than sixty-five. Nonetheless, the CDC recommends that everyone over the age of six months get a routine flu shot every year,[4666] if for no other reason than to help prevent transmission to the more vulnerable.[4667] As I've discussed, the cruel irony is that older adults—the ones who need protection the most—acquire less robust protection from flu shots due to waning immunity with age.[4668]

Depending on the season, vaccination typically reduces the risk of getting the flu by about 40 to 50 percent.[4669] So, in healthy younger adults, we can say with moderate certainty that we can decrease the risk of getting the flu from about 2 percent each year down to just under 1 percent.[4670] Among older adults, there may be a similar relative risk reduction—from 6 percent down to 2.4 percent—but since the risk is higher and the consequences greater, the absolute benefits are greater, too.[4671]

In the Northern Hemisphere, the flu season can start as early as September and run as late as March.[4672] The problem with getting vaccinated too early is that immunity might wane before the season is over, especially in older adults.[4673] The CDC recommends trying to get vaccinated by the end of October, but getting it at any time throughout flu season is preferable to not getting vaccinated at all.[4674]

Yes, the influenza vaccine can cause Guillain-Barré syndrome, an autoimmune attack on your nerves that can leave you paralyzed for weeks, but so, too, can getting the flu.[4675] As I mentioned, there are only one to three additional individual cases of Guillain-Barré per one million vaccinations versus about seventeen extra cases per million flu episodes.[4676] So, you're much more likely to be temporarily paralyzed by the flu than the flu shot, but since it takes vaccinating about thirty older people to prevent one case of the flu,[4677] getting vaccinated would still be expected to raise your overall Guillain-Barré risk. However, the reason flu shots are recommended is not to lower risk of a rare autoimmune syndrome but to reduce the common—and potentially devastating—impacts of the flu that extend beyond just the respiratory infection.

In the week following a confirmed flu infection, the risk of having a heart attack shoots up to six times higher.[4678] The inflammation of infection

can destabilize atherosclerotic plaques, constrict arteries, and make the blood more liable to clot.[4679] So, might flu vaccinations save lives in more ways than one? Those who get their flu shots are indeed less likely to die from cardiovascular disease in a given year as well as all causes put together.[4680] In other words, those who get regular flu shots live longer lives on average. But, who disproportionally gets flu shots? White, married nonsmokers of a higher social class with higher levels of education, higher incomes, and health insurance.[4681] You can't tell if it's truly cause and effect until you put it to the test.

There have been four randomized controlled trials—flu shots versus placebo shots—in those with preexisting heart disease, and, overall, those who got the real shots had a 56 percent lower chance of dying from cardiovascular disease and a 47 percent lower chance of dying from all causes put together. So, flu shots really can be an *extraordinary* lifesaver. Whether the observational data showing fewer deaths across the board—even including those without preexisting heart disease[4682]—similarly pan out is, as of yet, unknown.[4683]

Given the benefits, overcoming vaccine hesitancy should be as simple as correcting misinformation, but, sadly, debunking vaccine myths can actually backfire. Busting the myth that inactivated flu shots (the type given to older adults) can give you the flu surprisingly makes people even less likely to get it.[4684] Similarly, correcting the falsehoods that MMR vaccines cause autism[4685] or that pertussis vaccination causes as many side effects as people think, paradoxically, makes people less inclined to vaccinate.[4686] The researchers conclude that "correcting vaccine myths may not be an effective approach to promoting vaccination."[4687]

PNEUMONIA VACCINE

"Pneumonia may well be called the friend of the aged," wrote Sir William Osler, the "Father of Modern Medicine,"[4688] in 1898. "Taken off by it in an acute, short, not often painful illness, the old man escapes those 'cold gradations of decay' so distressing to himself and to his friends."[4689] The thought was that pneumonia mercifully killed those who would soon die anyway from a potentially more protracted and painful illness. But these days, healthy older adults hospitalized with pneumonia are not significantly

more likely to die in the subsequent two years than younger adults in the same situation. Because of comorbidities at older ages, though, pneumonia is the fourth leading cause of death in the world[4690] and the ninth leading cause in the United States.[4691]

The most common cause of community-acquired pneumonia (as opposed to hospital-acquired) is a bacteria known as pneumococcus (*Streptococcus pneumoniae*).[4692] In addition to pneumonia, pneumococcus can cause inner ear infections, sinusitis, and pink eye. It gets serious when it starts to invade the bloodstream, which can result in meningitis (infection of the brain), endocarditis (infection of the heart valves), or sepsis (a life-threatening organ dysfunction caused by blood poisoning).

Thankfully, we have vaccines against pneumococcus. The first was developed more than a century ago, but it fell out of favor after penicillin was discovered and it was thought that antibiotics would eliminate the threat.[4693] Unfortunately, these days, up to 40 percent of pneumococcal infections are resistant to at least one antibiotic,[4694] and, despite our miracle drugs, mortality rates of invasive pneumococcus in the elderly stand at around 15 to 30 percent.[4695] According to randomized controlled trials, pneumococcus vaccines can reduce the risk of those sixty-five and older getting pneumococcal pneumonia by 64 percent and, even more important, the risk of *invasive* pneumococcal disease by 73 percent.[4696] Like the flu vaccine, population studies have found that pneumonia vaccines appear to reduce both the risk of heart attacks and the overall risk of dying, but unlike the flu vaccine, there aren't randomized controlled trials to confirm these bonus benefits.[4697]

SHINGLES VACCINE

A major issue hampering the uptake of shingles vaccination is the lack of awareness of the disease.[4698] Shingles is caused by a reactivation of the chicken pox virus later in life. After your body beats back chicken pox, the virus hides in your spinal cord, waiting for an opportunity to strike again.[4699] When your defenses are down, the virus can surge forth, traveling along the path of a nerve branching off the spinal cord and wrapping around one side of the body to the front, producing skin blisters in a characteristic belt-like

pattern that does not cross the midline.[4700] (Both *shingles* and the name of the virus, *zoster*, are from the Latin and Greek, respectively, for "belt."[4701])

The blistering rash can be intensely painful and leave behind scarring or discoloration, but it usually disappears on its own in a few weeks. However, approximately 30 to 50 percent of those with shingles suffer "postherpetic neuralgia," persistent pain that can last for a year or more and sometimes be debilitating. It usually affects nerves around the trunk, but, in 10 to 25 percent of cases, it can erupt across your face and lead to permanent facial muscle weakness, hearing loss, or blindness.[4702] As if all that isn't bad enough, having shingles as much as quintuples your odds of having a stroke over the subsequent few weeks,[4703] a risk that gradually declines over the following six to twelve months.[4704]

It's surprising that more people don't know about this, since the lifetime risk of getting shingles is 30 percent, meaning nearly one in three of us will get it sometime in our lives. Young adults only have about a one-in-a-thousand chance of getting it every year, whereas it climbs to closer to one in a hundred per year for older adults. That comes out to a million cases of shingles annually in the United States.[4705] Thankfully, there is a shingles vaccine.

The first (Zostavax) became available in 2006, using a live, weakened strain of the virus. The efficacy was only about 50 percent, though, and it couldn't be administered to immunocompromised individuals, such as those with HIV or on immunosuppressive drugs, such as chemotherapy. In 2017, however, a recombinant shingles vaccine was approved (Shingrix) with a 90 to 97 percent efficacy for preventing an outbreak. It requires two separate injections two to six months apart[4706] and is expensive ($280), but it's covered by Medicare Part D and most private insurance plans. It can also cause transient systemic symptoms, such as muscle aches, fatigue, headache, fever, and chills, about 10 percent of the time,[4707] but Shingrix is considered to be so much more effective that it's recommended for everyone starting at age fifty, even if you were previously immunized with Zostavax.[4708] Given that the new vaccine is only about five years old, we don't yet have longer-term safety and efficacy data—they're still coming in[4709]—but so far, so good.[4710] I recently turned fifty and lined right up for mine.

PRESERVING YOUR JOINTS

Osteoarthritis, the most common joint disease in the world,[4711] develops when the cartilage that cushions the lining of our joints breaks down faster than our body is able to build it back up.[4712] Affecting more than twenty million Americans, osteoarthritis is the most frequent cause of physical disability among older adults. The average age of diagnosis is fifty-five,[4713] and the most common presenting symptom is pain, most often in the knees, hands, hips, and spine.[4714] In the United States, 40 percent of men and 47 percent of women will develop osteoarthritis within their lifetime.[4715]

PILLS

Acetaminophen (Tylenol) is widely recommended as the first-line painkiller for osteoarthritis,[4716] but it shouldn't be.[4717] Why not? Because it doesn't work. Although acetaminophen can provide *statistically* significant improvements in pain and physical function over placebo, the benefits are not *clinically* significant—the equivalent of just three points better on a hundred-point pain scale compared to placebo.[4718] The minimum change that is deemed clinically relevant is ten points.[4719] Now, this is not to say that Tylenol doesn't *appear* to work; it can drop pain scores by twenty-six points. But it just doesn't work compared to placebo, a sugar pill, which on its own drops pain scores by twenty-three points.

Acetaminophen overdose is the leading cause of sudden liver failure,[4720] but, even at recommended doses, it can still cause liver damage. While acetaminophen is definitely safer than most over-the-counter or prescription pain pills,[4721] those taking it for conditions like osteoarthritis were found to be nearly fourfold more likely to develop liver function abnormalities compared to placebo.[4722]

Traditionally, osteoarthritis was considered to be a prototypical "wear and tear" disorder,[4723] but we now know that inflammation plays an integral role in the disease's process.[4724] So, what about using anti-inflammatory drugs? Most patients with osteoarthritis in the United States are prescribed nonsteroidal anti-inflammatory drugs (NSAIDs), such as over-the-counter ibuprofen (Advil) or naproxen (Aleve), or prescription-only celecoxib (Celebrex).[4725] Unfortunately, primary care practitioners often lack

sufficient awareness of the gastrointestinal, cardiovascular, and kidney risks associated with these drugs.[4726]

Side effects from NSAIDs may be one reason why those with osteoarthritis tend to live shorter lives. The drugs do work for osteoarthritis pain,[4727] but 10 to 30 percent of people who regularly take NSAIDs develop stomach ulcers.[4728] NSAIDs also increase the odds of a heart attack by about 50 percent,[4729] which translates into one extra heart attack per one hundred to two hundred users every year[4730] and appears to double the risk of sudden kidney injury in those over fifty.[4731] The risks are considered so great at older ages that the American Geriatrics Society recommends opioid drugs over NSAIDs for chronic pain in those older than seventy-five.[4732]

The cardiovascular, kidney, and gastrointestinal risks are similar for ibuprofen and naproxen.[4733] Prescription-only celecoxib has similar cardiovascular risk to both, but it seems to cause fewer kidney problems than ibuprofen and has significantly lower gastrointestinal risk than either of the over-the-counter drugs.[4734] Given the risks associated with this class of drugs, the consensus is that, if their use is deemed necessary, the lowest effective dose should be taken for the shortest possible duration.[4735]

GELS

The best pharmacological option may be topical NSAIDs,[4736] which just became available over the counter in the United States in 2020.[4737] They appear to have a similar efficacy to oral NSAIDs in terms of pain management[4738] and have a better safety profile since they have lower systemic absorption.[4739] They can cause (mostly) mild skin reactions, but they don't seem to raise the risk of gastrointestinal issues any more than placebo.[4740] They also appear safer in terms of kidney[4741] and cardiovascular risk.[4742]

INJECTIONS

The "nonsteroidal" in NSAID is to differentiate them from anti-inflammatory steroids, like cortisone, which can be injected directly into the joint. A Medicare sample of a half-million patients with osteoarthritis in their knees found that about a third were treated with at least one

corticosteroid injection.[4743] This can help with pain in the short term,[4744] but it makes the condition worse in the long term.[4745]

Those getting steroid injections can end up with a worsening of pain, stiffness, and disability with accelerated joint deterioration and progression to total knee replacement surgery.[4746] This is in addition to complications that include osteonecrosis (bone rot) and rapid joint destruction.[4747] In a randomized controlled trial, two years of steroid injections for knee osteoarthritis sufferers led to a significantly greater loss of cartilage volume—and, ironically, no better pain relief—than a placebo injection of saline (basically water).[4748] The study may have been the "final nail in the coffin" for the practice.[4749]

See see.nf/injections to learn about other injections, but in sum, both hyaluronic acid and PRP (platelet-rich plasma—or, perhaps more accurately, *profit-rich placebo*) "cannot be recommended."[4750]

SURGERY

In 2003, a courageous study was published in *The New England Journal of Medicine*, putting the most common orthopedic surgery—arthroscopic surgery of the knee—to the test. Billions of dollars are spent sticking scopes into knee joints and cutting away damaged tissue in osteoarthritis and knee injuries, but does the procedure actually work? Knee pain sufferers were randomized to get the actual surgery versus a sham surgery in which doctors actually sliced into people's knees and pretended to perform the procedure, complete with splashing saline, but never actually did anything within the joint.[4751]

The trial caused an uproar. How could you randomize people to fake surgery? Professional medical associations questioned the ethics of the surgeons and the sanity of the patients who agreed to be part of the trial.[4752] But, guess what happened? The surgical patients got better, but so did the placebo patients who had undergone sham surgery.[4753] Indeed, the surgeries had no actual effect. Currently, rotator cuff shoulder surgery is facing the same crisis of confidence.[4754]

Surgical research has long been ridiculed as a "comic opera,"[4755] as most peer-reviewed surgery publications were just filled with presentations of series of individual cases or airings of professional opinions. Unlike drugs,

which must be demonstrated to have a certain safety and efficacy, there is no such requirement for new surgical procedures, which can be introduced without regulatory oversight. Only about one in five surgical procedures performed in all of orthopedics is supported by at least one good randomized controlled trial showing it to be superior to a nonsurgical alternative.[4756] In the fifty-three trials in which surgeries of all stripes were put to the test against sham operations, the majority of surgeries were themselves the shams, unable to beat out the placebo procedures.[4757]

A subsequent systematic review and meta-analysis of arthroscopic surgery for middle-aged or older patients with knee pain, with or without osteoarthritis, concluded that, although there may be a small, transient "inconsequential" benefit, the surgery does not outweigh the harms. Complications of arthroscopic surgery include blood clots (deep venous thromboses) in 1 in 250 procedures, which can travel to the lung, cause an infection, and, extremely rarely, result in death.[4758] What is especially tragically ironic is that those with osteoarthritis who underwent arthroscopic surgery appeared to be three times more likely to end up having to undergo total knee replacement surgery in that same knee within the ensuing nine years.[4759]

PLACEBOS

To be clear, arthroscopic surgery works. It just doesn't work better than fake surgery.[4760] People tend to feel better either way, which may help explain why surgery has been referred to as the "ultimate placebo." So, arthroscopic surgery works like going to a witch doctor works. It even has many of the same components—the journey to the healing place, fasting, and anointment with a purifying liquid (skin prep) before your audience with the masked healer.[4761]

It's been estimated that, across different therapies for osteoarthritis, about 75 percent of pain relief, 71 percent of improvement in function, and 83 percent of stiffness improvement are due to the placebo effect.[4762] This has led to the proliferation of all manner of bogus treatments, such as "low-dose" radiation therapy involving pulsing the joint with 60,000 chest X-rays' worth of radiation.[4763] That treatment does work, but only as well as it

does when the equipment is covertly turned off and a recording is played of the *sound* of the machine working.[4764]

A rich literature explores the placebo effect. It's hard enough to believe that a sugar pill could have a clinical effect, but that's just the beginning. Taking two sugar pills has a stronger effect than taking just one,[4765] and green and blue sugar pills have a different effect than red and orange ones.[4766] Sugar pills labeled *Bayer aspirin* help headaches more than sugar pills labeled *generic aspirin*,[4767] which isn't so surprising since patients who were told their tablets were obtained at full cost felt they worked better than those who were told theirs were obtained at a discount.[4768] And a needle is better than a pill.[4769]

The placebo power of administering a shot is so potent that, unbelievably, giving osteoarthritis sufferers placebo injections offers clinically important pain relief that lasts for three months and clinically significant improvements in function and stiffness that last for six months.[4770] This introduces the so-called efficacy paradox. Hyaluronic acid injections are not administered because they don't beat out placebo injections, whereas NSAIDs *are* given because they do have a real effect beyond just the placebo effect. That makes sense, but ready to have your mind blown? Because needles have a greater placebo effect than pills, injecting joints with hyaluronic acid—the treatment that is *not* recommended—works better than the recommended treatment of taking NSAID pills[4771] and would probably be safer, too! So, why not just stick needles into people if that works so well? We do. It's called acupuncture.

There's actually a way to test acupuncture against a placebo. There are "sham acupuncture devices" that look and feel exactly like real acupuncture needles. In actuality, though, the needle tip is blunted and retracts into the hollow shaft like a magic trick. Then, when it's bandaged in place and sticking out, you can't tell if you're getting real acupuncture or fake acupuncture, where there's no "puncture" at all.[4772]

So, what happens when you test acupuncture on knee osteoarthritis? It works! But the fake acupuncture works, too. That's why the American Academy of Orthopaedic Surgeons makes a strong recommendation against it.[4773] Nevertheless, if acupuncture "works" and is relatively safe, why not do it?

Adverse side effects from prescription drugs alone are estimated to kill more than 100,000 Americans every year, making medications a leading cause of death.[4774] Whatever you may think of doctors prescribing placebos, at least they aren't killing people. If there are conditions like osteoarthritis where placebos have been proven to be effective, why don't doctors actively deceive patients by prescribing them?

They do.

Different surveys of medical professionals have found that 17 to 80 percent of physicians and 51 to 100 percent of nurses have given patients "pure" placebos, meaning they didn't just uselessly prescribe antibiotics for the common cold, for instance, but actually gave people an intentionally bogus treatment, like an injection of saline.[4775] There are all sorts of placebos on the market you can even buy for yourself, with brand names like Obecalp[4776] ("placebo" backward), Magic Bullet, and Fukitol. (I'm not kidding!)

Defense of the occasional indispensable medical lie dates back to Plato, who wrote in the *Republic*, "[A] lie is … useful only as a medicine to men.…"[4777] Thomas Jefferson called it the "pious fraud."[4778] In the medical literature, it's been referred to as the "humble humbug." While some doctors decry giving placebos as quackery,[4779] others, specifically in regards to osteoarthritis, ask, "Why not use it to our advantage?"[4780] *The American Journal of Medicine* published a review on the "Ethics and Practice of Placebo Therapy," which argued that "deception is completely moral when it is used for the welfare of the patient," questioning why the "dwellers in ivory towers decry the use of placebos." Some patients can be sensitive, though, the review warns, so they "should never be told that their precious medicine was a hoax."[4781]

WEIGHT LOSS

Twin studies suggest that about half of osteoarthritis risk is genetic.[4782] What can we do about the other half? Thankfully, there are successful treatments that don't involve capsules, needles, scalpels, or falsehoods.

Obesity may be the main modifiable risk factor for osteoarthritis,[4783] offering an explanation why a study of thousands of skeletal remains from prehistoric hunter-gatherers to modern-day city dwellers found a dramatic

rise in incidence over the last half century or so. Compared to healthy-weight individuals (BMI < 25), the incidence of knee osteoarthritis is three times as high among obese individuals (BMI ≥ 30) and five times as high among those with class II obesity (BMI ≥ 35).[4784] Fatty tissue in general[4785] and even right inside our joints—like in the fat pad under the kneecap—can be a source of pro-inflammatory chemicals that have been shown to increase cartilage degradation.[4786]

Losing around just one pound a year over a ten-year period may reduce our odds of developing osteoarthritis by more than 50 percent.[4787] Once you have it, MRI studies show that even just a 5 percent weight loss in overweight sufferers can significantly lower the degree of cartilage degeneration.[4788] As I detail in see.nf/kneereplacement, obese osteoarthritis sufferers who had been randomized to lose weight went on to improve their knee function as much as those undergoing knee surgery, and they did so within just eight weeks. Researchers concluded that losing twenty or so pounds of fat "might be regarded as an alternative to knee replacement."[4789]

This is especially important considering that nearly one in two hundred knee replacement patients dies within three months of surgery. About 700,000 of these procedures are performed every year in the United States. Given its widespread popularity, an editor of an orthopedics journal suggested that "people considering this operation are inadequately attuned to the possibility that it may kill them."[4790]

EXERCISE

Smokers tend to be leaner than nonsmokers,[4791] so that may explain why some studies have found a protective association between osteoarthritis and tobacco use.[4792] Smokers with osteoarthritis, though, tend to have more severe pain and sustain greater cartilage loss than nonsmokers.[4793] Ironically, another potential explanation for lower rates of osteoarthritis among smokers is that they're less likely to play sports.[4794]

Athletic injuries to the knees are a well-established risk factor for osteoarthritis later in life.[4795] At the same time, physical inactivity can put your knees at risk, not only because weakened muscles make for less stable joints but because cartilage also has a "use it or lose it" characteristic. People with paralyzed legs exhibit marked cartilage thinning in their

knees,[4796] whereas people who do weight-bearing exercise may have thicker cartilage.[4797] Both extremes of inactivity and excessive activity may be detrimental.[4798]

What about exercise as treatment? There have been four dozen randomized controlled trials of exercise for knee osteoarthritis, involving a total of thousands of patients.[4799] Exercise was found to be so consistently effective for pain relief that some researchers have suggested that no future studies of the question are deemed necessary.[4800] Direct comparisons in trials comparing high and low intensity of aerobic or resistance exercise conclude that intensity doesn't seem to matter, but frequency does. Exercise programs requiring at least three sessions a week were most effective, as were regimens that concentrated on the quadriceps muscles.[4801] Although most were short-term trials,[4802] there have been some showing clinically significant improvements at least one year out with no adverse effects reported.[4803] National and international best-practice guidelines for osteoarthritis emphasize the importance of both weight control and exercise.[4804] What about diet?

DIET

The best-practice management of osteoarthritis is said to include "optimal nutrition" as a first-line intervention. As a prime example, reviewers in the journal *Arthritis* cite the "China Study," which is shorthand for the China-Cornell-Oxford Project, which in turn is short for the "China-Oxford-Cornell Study on Dietary, Lifestyle and Disease Mortality Characteristics in 65 Rural Chinese Counties," a large study summarized by principal investigator T. Colin Campbell, the same Dr. Campbell who coined the term *whole food, plant-based diet*, and his son in the lay book *The China Study*.[4805] What evidence do we have that a plant-based diet might help?

The National Institutes of Health Osteoarthritis Initiative, the largest-ever prospective study of osteoarthritis patients over time, found that higher fat intake was associated with accelerated progression of the disease (as determined by cartilage loss on X-ray).[4806] Upon further analysis, though, it was only the saturated fat that appeared to increase risk. That's the kind of fat found mostly in meat, dairy, and junk, not the monounsaturated or polyunsaturated fats concentrated in nuts, seeds, and vegetable oils.[4807] Just

dripping saturated fat on human cartilage cells in a petri dish can increase cartilage matrix degradation.[4808] Cholesterol has the same in vitro effect.[4809]

Both saturated fat[4810] and dietary cholesterol[4811] accelerate the progression of trauma-induced osteoarthritis in mice. Even without trauma, though, animal fat can produce typical osteoarthritis-like lesions in the knee joints of rats.[4812] What about people? Osteoarthritis sufferers tend to have higher cholesterol levels in the blood[4813] and also within their joints, both in aspirated joint fluid[4814] and in the cartilage itself.[4815] Exposing human cartilage to cholesterol has been shown to worsen the inflammatory degeneration,[4816] helping, perhaps, to explain why the higher people's cholesterol, the worse their disease.[4817]

So, might lowering cholesterol with statin drugs help? The data are mixed.[4818] Some studies suggest that statins help,[4819,4820] some found no relationship,[4821,4822] and others indicate that statins could make things worse.[4823,4824] Meta-analysis reviewers suggest that the side effects of statins, in terms of muscle weakness and pain, may mask any protective effects of cholesterol-lowering on reducing osteoarthritis symptoms.[4825] In contrast, a healthy enough plant-based diet may offer the best of both worlds, dropping cholesterol as much as a starting dose of a statin drug within a single week,[4826] while lowering blood pressure and facilitating weight loss.[4827] But, what about direct effects on osteoarthritis?

In a study at Michigan State University, men and women with osteoarthritis were randomized to follow a whole food, plant-based diet or continue their conventional lifestyle. Compared to the control group, the plant-based group experienced a significant improvement in physical function and energy/vitality within one week and a significant reduction in pain within two weeks. Of course, they also lost significantly more weight, but improvements were noted even in some who didn't. Because the control group didn't do anything special, one can't disentangle any placebo effects, but, given the ancillary benefits, eating plant-based may be worth a try.[4828]

The researchers suggest that the plant-based pain benefits may be due to the reduced intake of arachidonic acid, a pro-inflammatory omega-6 fat[4829] found primarily in eggs and chicken.[4830] NSAIDs like aspirin reduce pain by blocking the cascade of inflammatory mediators our body makes from arachidonic acid.[4831] By cutting down on consumption of chicken and eggs, the thinking goes, less of the pain-inducing compounds may be produced in

the first place.[4832] (The poultry industry has proposed genetically manipulating chickens to have less arachidonic acid in their muscles to decrease human health risk, but this has yet to be implemented.[4833])

Or maybe the anti-inflammatory nature of plant foods was responsible for the rapid pain relief.[4834] Pro-inflammatory diets are associated with higher osteoarthritis pain intensity,[4835] as well as increased risk of developing the disease in the first place.[4836] So, what about fiber, the most anti-inflammatory dietary component?[4837] As we know, when we eat whole-grain barley for dinner, for instance, our good gut bacteria have it for breakfast the next morning and the short-chain fatty acid butyrate is released into our bloodstream,[4838] which exerts a wide range of anti-inflammatory effects.[4839] Dripping butyrate on cartilage carvings taken from the leg bones of those undergoing joint replacement surgery has been shown to significantly suppress inflammatory cartilage loss in vitro.[4840]

In a study titled "Dietary Fiber Intake in Relation to Knee Pain Trajectory," nearly 5,000 men and women were followed for an average of eight years. Researchers found that those getting at least the recommended minimum fiber intake of about 25 g a day were at significantly lower risk of developing moderate or severe knee pain over time."[4841] What's more, two Framingham cohorts found that a higher intake of fiber was associated with a lower risk of having symptomatic osteoarthritis in the first place.[4842] The provision of extra fiber protects mice from osteoarthritis,[4843] but it has yet to be interventionally tested in people.[4844]

BEVERAGES

Free radicals may also play a role in joint-lining inflammation and cartilage loss.[4845] Observational studies have correlated higher intake of certain antioxidants with a lower prevalence of cartilage deficits or osteoarthritis progression,[4846] but, when antioxidant supplements were put to the test, the results have been largely disappointing.[4847] (They didn't make things worse, though, as did vitamin C in an animal experiment of osteoarthritis.[4848])

On the other hand, when green tea was added to the drinking water of mice, it was found to reduce the incidence of arthritis[4849] and slow the progression of osteoarthritis.[4850] It can also protect human cartilage explants in vitro.[4851] The first and only clinical trial to date was published in 2016.

Knee osteoarthritis patients were randomized to either the equivalent of about three cups' worth of green tea a day plus an NSAID or just the drug on its own.[4852] Within four weeks, there was significant improvement in osteoarthritis symptoms in the green tea group, especially with regards to improved physical function. Unfortunately, it was an open-label study, meaning that the participants knew which group they were in, so placebo effects can't be discounted.[4853] Similarly, those drinking two cups a day of spearmint tea for sixteen weeks reported improved osteoarthritis symptoms, but, again, with no placebo control, we can't be confident that the effect was real.[4854]

Other beverages that have been studied in relation to osteoarthritis include soft drinks and milk. Independent of body weight, soda intake has been associated with increased progression of knee osteoarthritis, but only in men, which calls the relationship into question.[4855] Similarly, milk was associated with less disease progression, but only in women, while cheese was linked to greater progression in a U.S. study.[4856] In a Dutch study, though, cheese (but not milk) was found to be cross-sectionally associated with less osteoarthritis.[4857]

One interventional study comparing soy protein to dairy protein reported that soy edged out dairy, suggesting soymilk might be preferable for osteoarthritis sufferers, though we don't know if this arose from superior soy benefits or potential dairy harms.[4858] A study in Iran sought to answer this question. Half the dairy-drinking, osteoarthritis-suffering participants were randomized to try to stop their dairy intake, and those who were successful experienced a significant reduction of pain within three weeks. (A more rigorous study design would have involved switching to an indistinguishable nondairy milk control, though.)[4859]

STRAWBERRIES

If antioxidants play a protective role, what about berries? Strawberries decrease the levels circulating in the blood of an inflammatory mediator known as *tumor necrosis factor*, but that doesn't necessarily translate into clinical improvement.[4860] For example, drinking cherry juice can lower C-reactive protein, another sign of inflammation, but failed to help with osteoarthritis.[4861] Tart cherry juice "provided symptoms relief," but not

significantly more so than a cherry-free placebo drink (Kool-Aid). Cherries may help with gout, another kind of arthritis, but failed when it came to osteoarthritis.[4862] Similarly, pomegranates may help with rheumatoid arthritis,[4863] but pomegranate *juice* failed to even beat a do-nothing control group for osteoarthritis[4864] even though pomegranate extracts appeared to protect cartilage in a petri dish.[4865]

Pomegranate juice doesn't lower C-reactive protein levels in the bloodstream, though,[4866] and strawberries do. When people with diabetes were given strawberries for six weeks, not only did their diabetes get better, but their C-reactive protein levels dropped by 18 percent.[4867] Strawberries can even downregulate pro-inflammatory genes to the point of reversing precancerous growth.[4868] Even just a single meal can help.[4869] So, can strawberries improve pain and inflammation in confirmed knee osteoarthritis? Yes.

Obese men and women with osteoarthritis were randomized to the equivalent of a pint and a half of strawberries a day (in the form of freeze-dried strawberry powder) or a control group getting a placebo powder matched for the color and flavor of strawberries for twelve weeks. Inflammatory markers plummeted in the real strawberry group *and* they experienced significant reductions in constant pain, intermittent pain, and total pain. Concluded the researchers, "[O]ur study suggests that simple dietary intervention, i.e., the addition of berries, may have a significant impact on pain, inflammation, and overall quality of life in obese adults with OA [osteoarthritis]."[4870]

The strawberries cut the levels of the inflammatory mediator tumor necrosis factor (TNF) in half,[4871] but strawberry efficacy may not be an anti-TNF effect, since blueberries may also suppress TNF[4872] but failed to beat out placebo when put to the test in a similar randomized, double-blind, placebo-controlled osteoarthritis trial.[4873]

ROSE HIPS

When you think about what fruits may be beneficial for osteoarthritis, you probably don't think of rose hips, the fruits of the rose bush. Commonly steeped into tangy tea, rose hips are sold dried and often in bulk at natural foods stores.

There have been three randomized, double-blind, placebo-controlled trials of rose hips for osteoarthritis. Hundreds of men and women suffering mostly from osteoarthritis of the knee were randomized to three to four months of 5 g a day of rose hip powder, which is about one and a third teaspoon, or a look-alike placebo powder. Those unknowingly taking the real rose hips experienced a significant reduction in pain over placebo,[4874] close to that seen with NSAIDs,[4875] but without any reported side effects.[4876]

BROCCOLI

What about vegetables? Broccoli holds some promise. Sulforaphane, the cruciferous compound thought to play a key role in the benefits we can get from broccoli family vegetables, protects human cartilage from destruction in vitro, but how do we know if sulforaphane even makes it into our joints? [4877] We didn't—until a group of British researchers had knee replacement patients eat broccoli for two weeks before surgery and, during the operation, found it in their synovial (joint) fluid (compared to surgical patients told to avoid cruciferous vegetables).[4878]

Sulforaphane has been shown to decrease the severity of osteoarthritis in mice, but it is only now being tested in people.[4879] The Broccoli in Osteoarthritis (BRIO) study is randomizing participants to broccoli soup as we speak, and we should have the results soon.[4880] Even just ten days of broccoli consumption can cut C-reactive protein levels in smokers by 40 percent, but we don't yet know if this translates into decreased knee pain and dysfunction.[4881] However, there are some foods that have been shown to get at the root: ginger and turmeric.

GINGER

In see.nf/ginger, I review the randomized controlled trials showing that as little as an eighth of a teaspoon of ginger powder can reduce knee osteoarthritis pain,[4882] working as well as ibuprofen[4883] but with gastrointestinal lining protection[4884] rather than damage.[4885] Ginger has evidently been applied externally to painful joints for a thousand years,[4886] though the only controlled study of topical ginger to date involved men applying slices to their scrotum. But the researchers were on the ball: Inflamed testicles healed three times faster in the ginger group.[4887]

TURMERIC

After study participants consumed a daily teaspoon and a half of ginger powder for seven days, researchers drew their blood and dripped it onto cells in a petri dish. They found that the release of inflammatory mediators like TNF is suppressed, compared to when blood taken before the week of ginger was used. The same anti-inflammatory effects can be had with the spice turmeric, but at a small fraction of the dose—less than a tenth of a teaspoon per day.[4888]

There have been sixteen randomized controlled trials of various turmeric formulations for knee osteoarthritis, starting at the equivalent of about half a teaspoon a day for up to sixteen weeks. Eleven of the studies compared turmeric to placebo, and the other five pitted the spice head-to-head against NSAIDs. The turmeric extracts significantly reduced knee pain and improved physical function compared to placebo and had similar effects to the NSAIDs, but with a better safety profile.[4889] In 2020, a study published on topical treatment involving the application of a turmeric extract mixed with Vaseline reported a significant reduction in pain. It was purported to be a double-blind trial, but the placebo was straight Vaseline, so the color difference alone likely tipped off both the participants and the assessors as to which subject was in which group.[4890] So if you're going to make some kind of turmeric-y pumpkin pie smoothie like my Okinawa-inspired concoction here (maybe with a little ground ginger thrown in), I'd suggest drinking it rather than rubbing it in.

TOPICAL TREATMENTS

We've covered how to help preserve our joints from the inside out, but what about from the outside in?

SESAME SEEDS

With only good side effects—improving blood pressure,[4891] cholesterol, and antioxidant status—sesame seeds are certainly worth a try.[4892] Refer back to here for the randomized controlled trial of a quarter cup of sesame seed for osteoarthritis.

What about topical sesame oil? In a double-blind, placebo-controlled clinical trial, a hospital in Iran randomized patients with traumatic limb injuries to rub the oil drained off tahini (sesame seed paste) onto their affected limbs. Compared to the placebo control of conventional cooking oil, the sesame group experienced prompt pain relief that was significant within forty-eight hours, and the sesame oil even helped prevent skin discoloration from bruising. So, what about rubbing sesame oil onto osteoarthritic knees?

When topical sesame oil was tested head-to-head against the leading topical NSAID, a 1% diclofenac sodium gel, such as Voltaren, the sesame oil was found to work similarly for pain and some measures of function, but the NSAID gel did better at reducing stiffness.[4893]

FLAXSEEDS

What about other topical treatments? Researchers in Turkey tried randomizing people with osteoarthritis of the hands to a warm flaxseed poultice. A warm mixture of flaxseeds and water was applied to participants' hands, which were then wrapped snugly with gauze and covered with a towel and hot water bottle for twenty to thirty minutes once a day for a week. Compared to those in the control group who did nothing, the flax group experienced a significant improvement in pain and function. How do we know the benefit was from the flax and not just the heat and compression? There was a third arm to the study. Sufferers were randomized to the flax compress, a hot compress without any flax, or a control group, and the flax group experienced a significant improvement in pain and function compared to the hot compress group as well.[4894]

What about flaxseed oil, which has been used medicinally for more than a millennium? One hundred patients with mild to moderate carpal tunnel syndrome were randomized in a double-blinded manner to rub five drops of flaxseed oil or placebo onto the front of their wrists twice a day. Compared to those who got the placebo, the flaxseed oil group experienced significant improvements—not only in pain and functional status but also in nerve conduction velocity, indicating an alleviation of nerve damage. This was at a cost of perhaps a dollar a month.[4895] Time to rub flaxseed oil on some arthritic knees!

In another double-blind, randomized, placebo-controlled clinical trial, participants rubbed twenty drops of flaxseed oil or a paraffin-oil placebo onto their knees three times a day for six weeks. Once again, the flax beat out the placebo on every measure—total symptoms, pain, quality of life, and daily life activities as well as sports and recreation function. The topical use of flaxseed oil for soothing joint pain was recommended in traditional Persian medical texts, such as the *Canon of Medicine*,[4896] which was completed around the year 1012.[4897] It just took a thousand years for it to finally be put to the test.

EXTRA-VIRGIN OLIVE OIL

The ascription of "remarkable anti-inflammatory activity" to olive oil is based on laboratory rodents,[4898] but a systematic review and meta-analysis failed to find any anti-inflammatory effects for olive oil.[4899] In people, as I review in see.nf/oliveoil, extra-virgin olive oil may be no better than butter when it comes to inflammation, and even worse than coconut oil.[4900] But, that's for olive oil taken orally. Topically, it may be a different matter.

Knee osteoarthritis sufferers were randomized to topical virgin olive oil versus an NSAID gel for a month. The olive oil group was instructed to apply just 1 g of oil, which is less than a quarter teaspoon, three times a day. So, that would cost less than three cents a day, and it worked![4901] The virgin olive oil rub worked significantly better than the drug in reducing pain. A similar conclusion was reached in a trial for rheumatoid arthritis, where topical extra-virgin olive oil seemed to beat out rubbing on an NSAID gel or nothing at all (a "dry massage" control).[4902]

Low Back Pain

Low back pain became one of the biggest problems for public health systems in the Western world during the second half of the twentieth century.[4903] The lifetime prevalence of low back pain is reported to be as high as 84 percent, and chronic low back pain is present in about one

in five, with one in ten being disabled. It's an epidemic fueled, in part, by the obesity epidemic.

Carrying excess weight is a risk factor not only for low back pain[4904] but also for sciatica[4905] and lumbar disc degeneration[4906] and herniation.[4907] As with arthritis, it may be due to the combined effects of heavy loads on our joints and the inflammation and cholesterol associated with being heavier.[4908] Autopsy studies show that the lumbar arteries feeding our spine can become clogged with atherosclerosis and then starve the discs in the lower back of oxygen and nutrients.[4909]

In see.nf/backpain, I cover the topic in depth, complete with visuals of the cholesterol-laden plaques obliterating the openings to the spinal arteries.[4910] To get you back into circulation, it may help to get circulation into your back. Unfortunately, it's never been put to the test. Clinical trials have demonstrated the dietary reversal of the progression of coronary artery disease in the heart,[4911] peripheral arteries in the legs,[4912] and pelvic arteries for erectile dysfunction,[4913] but, unfortunately, there has yet to be a randomized controlled trial on the reversal of disc degeneration or back pain with diet and lifestyle changes.

SUPPLEMENTS

There has been a dramatic increase in cannabis use among older adults in recent years.[4914] So far, there don't appear to be any signs of adverse cognitive or mental health effects in the population for low-dose, short-term medical cannabis use.[4915] Certainly the evidence for the harms of alcohol use is much stronger.[4916] But is cannabis effective? Can a joint help your joints?

There was a small, transient effect of oral cannabidiol (CBD) oil noted in a case report of osteoarthritic pain that might have just been a placebo effect.[4917] There were no randomized controlled trials of CBD for osteoarthritis until 2021. Unfortunately, researchers found that it offered no

benefit for pain, compared to placebo, nor for sleep quality, depression, or anxiety.[4918]

Fish oil is another common supplement that fails to move the needle. A systematic review and meta-analysis of the five randomized controlled trials concluded that it had no statistically significant effect.[4919] However, the most commonly used supplement for osteoarthritis is glucosamine.[4920]

GLUCOSAMINE

I do a deep dive into glucosamine supplements in see.nf/glucosamine. Basically, there are marked inconsistencies in the clinical research literature as to whether it works at all,[4921] with industry funding the most potent predictor of trial outcomes, leading the current American College of Rheumatology guidelines to strongly recommend *against* the use of glucosamine.[4922]

CHONDROITIN

As I note in see.nf/chondroitin, the American College of Rheumatology also strongly recommends against the use of chondroitin,[4923] with the best studies showing "minimal or nonexistent" benefit.[4924] The only trial ever published of pharmaceutical-grade, prescription-only preparations of both chondroitin and glucosamine found that they made the pain of osteoporosis significantly *worse* compared to placebo.[4925]

COLLAGEN

Nearly a millennium ago, a medieval nun suggested eating gelatin to reduce joint pain.[4926] Unfortunately, when collagen was put to the test in multicenter, randomized, double-blind, placebo-controlled trials, it didn't seem to work.[4927] (Gelatin is basically just cooked collagen.[4928]) I review all the studies in see.nf/collagenjoints. The few that have shown benefits[4929] have come under fire from critics.[4930]

A comprehensive systematic review published in 2022 suggested that the reason there haven't been more studies done may be the high incidence of adverse side effects attributed to collagen supplements.[4931]

Randomizing people to even a single meal of a gelatin-based protein drink can lead to memory impairments within hours due to "acute

tryptophan deletion." This is presumably due to a drop in the brain of serotonin, which is made from tryptophan.[4932] (As I note here, collagen is an incomplete protein, missing the essential amino acid tryptophan entirely.) Another reason more studies haven't been done is simply that the collagen companies may not be confident they'd get positive results.[4933]

But, since then, the biggest study yet, with more than 150 people, has been published. Collagen company–funded researchers found a significant drop in knee pain and a significant improvement in knee function among those randomized to collagen supplements.[4934] However, they also found a significant drop in knee pain and improvement in knee function in those randomized to the placebo, with no real difference between them. So, the fact that a sugar pill effectively worked as well as the collagen supplements suggests that collagen doesn't work at all.

PRESERVING YOUR MIND

In *How Not to Die*, the exhilaration of my paternal grandma Greger's miraculous recovery from heart disease was counterbalanced by the horror story that was my mom's mother's descent into Alzheimer's disease. When our own mom first started to show the same symptoms, my brother and I steeled ourselves for the inevitable years of heartbreak and loss. The cruel irony of my father's battle with Parkinson's—hand tremors in a photojournalist—was matched by the mockery of my mother losing her mind. She had double-majored in English and chemistry, earned straight A's throughout nursing school, and was always surrounded by stacks and stacks of library books. Then she lost the ability to read, then to write, and eventually she lost her *self*. Given the family history, the neurologist we first took her to lazily diagnosed Alzheimer's. As did the second opinion and the third. But the fourth neurologist—eliciting an early symptom that I had missed, urinary incontinence—suggested a rare condition known as normal pressure hydrocephalus, an abnormal buildup of fluid within the brain.

There are only a few types of *reversible* dementia. Vitamin B_{12} deficiency is one, medication side effects are another, and normal pressure

hydrocephalus is a third. Could it be? I took her in for a diagnostic spinal tap where a few tablespoons of cerebrospinal fluid would be drawn to see if any of the symptoms would change. When I placed her down on the table, she couldn't walk, she could hardly talk, and she didn't know who I was. The fluid dripped out of the needle in her back into a cup, then, incredibly, the lights came back on. Within a span of minutes, my mom was back, walking and talking and hugging. She had been there all along, but the excess fluid had been bearing down on her brain. It was and will likely forever be the happiest moment of my life. But then, in the ensuing hours as the fluid built back up, her mind retreated back into the darkness, like Charlie's in *Flowers for Algernon*. With the diagnosis confirmed, she was scheduled for surgery, a drain was inserted into her brain to permanently siphon off excess fluid, and, just like that, she was back in our lives (and the library).

The moral of the story is to seek out every possible treatable, reversible cause before accepting a terminal diagnosis.

OUT OF MIND

Dementia is one of the most pressing public health challenges of our time.[4935] The single most common keyword in the healthy aging research literature is *Alzheimer's disease*.[4936] Dementia is one of our fastest-growing epidemics, affecting one in ten individuals older than sixty-five and up to 40 percent of individuals older than eighty-five.[4937] "Benign forgetfulness," like frequently misplacing your keys, is even more common. Dementia is much more serious, of course, as it affects daily function. You don't just forget about appointments you have that day; you forget about appointments you *had* that day.[4938]

Alzheimer's is the most common type of dementia and perhaps the most feared disease associated with getting older.[4939] In my clinical practice, I dreaded giving that diagnosis even more than cancer. What weighed so heavily on me wasn't just knowing the psychological toll that was to come for the patient but also the emotional toll that would be placed on their family. The Alzheimer's Foundation of America estimates that more than fifteen billion unpaid hours are supplied annually by more than ten million friends and family members who care for loved ones who may not even

recognize them.[4940] Alzheimer's is the single most expensive disease in the United States and around much of the industrialized world.[4941]

We still have neither a cure nor an effective treatment for this disease that invariably progresses to death, despite billions of dollars spent on research. More than 100,000 research articles have been published on Alzheimer's over just the past decades. Nevertheless, very little clinical progress has been made in treating or even understanding the disease. And a total cure? That's likely impossible, since patients with Alzheimer's may never be able to regain lost cognitive function because of fatal damage to their neuronal networks. Nerve cells, once they are dead, cannot be brought back to life. Even if drug companies could manage to figure out how to halt the progression of the disease, the damage has already been done for many patients, and their personality may be forever lost.[4942]

Alzheimer's disease cannot be diagnosed definitively until after death,[4943] when characteristic brain pathology involving microscopic plaques and tangles can be picked up on autopsy.[4944] Some who die with dementia have pristine brains, though, and others who die with normal cognition have all the distinguishing marks of Alzheimer's. In fact, 39 percent of the brains of nonagenarians and centenarians without dementia fulfilled Alzheimer's pathology criteria, so murkiness can remain even after death.[4945] About 30 percent of people who are clinically diagnosed with Alzheimer's are actually misdiagnosed.[4946]

After Alzheimer's dementia, the second most common type is vascular dementia, representing 15 to 20 percent of all dementia cases.[4947] It can develop after a full-blown stroke or a lot of little ministrokes. Sometimes, blood clots only clog a tiny artery for a moment—not long enough to notice, but still long enough to kill off a tiny portion of your brain. These "silent strokes" can multiply and slowly reduce our cognitive function until full-blown dementia develops.[4948] However, despite medicine's attempt to fit different dementias into discrete categories, most brain autopsies of dementia patients reveal multiple pathologies—for example, evidence of both Alzheimer's and vascular lesions.[4949]

THE MYTH OF THE MYTH OF THE MYTH OF SENILITY

Before COVID-19 knocked it down to killer number seven in 2020,[4950] Alzheimer's disease was the sixth leading cause of death.[4951] The average time between a dementia diagnosis and dying is about five years.[4952] While people may not die of dementia per se, it can directly lead to life-threatening complications, such as aspiration pneumonia due to swallowing difficulties that the family may eventually decide not to treat.[4953] The good news is that dementia is not an inevitable consequence of aging.[4954]

The "myth of senility" is echoed across geriatric textbooks: Dementia is a disease, not a normal part of growing old. This is countered in the medical literature by papers about the "myth of the myth of senility."[4955] With the prevalence of dementia reaching 45 percent by the time we're in our late nineties, it's nearing becoming more likely than not. Indeed, various centenarian studies peg the prevalence of dementia anywhere from 27 to 79 percent, yet there are those who reach extreme ages with their cognition intact.[4956] In the autopsy report "No Disease in the Brain of a 115-Year-Old Woman," Hendrikje van Andel-Schipper, who was the oldest person in the world at the time of her death, had almost no atherosclerosis throughout her body, including her brain, and almost no brain plaques or tangles. When she was tested at age 113, her cognitive performance was above average for those nearly half her age.[4957] Had she had not died from stomach cancer, she could have kept on thriving.

We may have about eighty-five billion neurons, or nerve cells, in our brain.[4958] Autopsy studies in the 1970s and 1980s estimated that we lose about 1 percent of them a year, ending up with as few as half as many when we hit old age. The discovery of this apparent inexorable decline was even suggested to play a role in the spike in suicidality among the elderly around that time. But it turns out it was all a mistake, a technical artifact of different patterns of shrinkage upon brain fixation at different ages. In old age, our brains have about 96 to 98 percent as many neurons as we had when we were young.[4959] How can we keep them healthy?

BRAIN DRUGS

"Successful cognitive agers" are considered a product of a healthy lifestyle.[4960] A commonly held misconception is that we have no control over whether or not we develop dementia.[4961] To underscore the primacy of prevention, allow me to first run through the currently available treatment options. I think it will offer new appreciation for the importance of averting the disease in the first place.

ARICEPT AND NAMENDA

Until recently, there were two main types of treatment: the most common, cholinesterase inhibitors like the drug donepezil (Aricept),[4962] as well as memantine (Namenda).[4963] One of the changes seen in Alzheimer's brains is the destruction of nerve cells that use a neurotransmitter called *acetylcholine* to communicate with one another. By inhibiting cholinesterase, which is the enzyme that breaks down this messenger molecule, the drop in acetylcholine levels can be mediated. This can help with some of the symptoms, but it doesn't affect the underlying destruction. The memantine mechanism is less intuitive. People with Alzheimer's lose NMDA (N-methyl-D-aspartate) receptors, yet memantine, an NMDA blocker, also seems to help with symptoms.[4964] Unfortunately, neither tends to improve symptoms enough to make much of a difference.

A meta-analysis of more than five dozen randomized clinical trials concluded that the symptomatic relief from either treatment was so small as to be "not clinically relevant."[4965] Cases of at least moderate improvement occurred uncommonly, but at no higher rate than those getting the placebo.[4966] So many trials have been done on so many patients that it is now "statistically conclusive that no pharmacological intervention achieves a clinically significant improvement of dementia symptoms and functioning in patients with AD [Alzheimer's disease]."[4967] But, that was before there was a new kid on the block: aducanumab (Aduhelm).

THE ADUCANUMAB FARCE

Aducanumab is the first new drug to be approved for Alzheimer's treatment in nearly twenty years.[4968] The FDA's approval of aducanumab proved to be

one of the most controversial in recent memory.[4969] Not only has the drug been considered to be clinically ineffective,[4970] a third of patients getting aducanumab suffered swelling or bleeding in the brain.[4971] Not a single member of the FDA expert advisory panel voted in favor of its approval,[4972] and three of the committee members resigned in protest,[4973] one calling it "probably the worst drug approval decision in recent US history."[4974] The response from the scientific community may best be summed up by a commentary written by the head of the American Geriatrics Society titled, "My Head Just Exploded.…"[4975]

Check out the whole fascinating saga in see.nf/aducanumab. A congressional investigation concluded the approval of aducanumab was "rife with irregularities," raising "serious concerns about FDA's lapses in protocol and [the drug company] Biogen's disregard of efficacy."[4976] That didn't stop the FDA from its 2023 accelerated approval of a similar antibody, lecanemab (Leqembi), of similar questionable efficacy and safety.[4977]

AMYLOID HYPOTHESIS QUESTIONED

The development of aducanumab was based on the proposal that Alzheimer's dementia is a result of the accumulation and aggregation of sticky, misfolded protein fragments called *amyloid beta*, which form plaques that lead to neuronal cell death and neurodegeneration.[4978] Compelling evidence for this "amyloid cascade hypothesis" comes from rare, inherited forms of Alzheimer's that are caused by gene mutations that specifically result in an elevation in amyloid beta.[4979] However, the vast majority of cases—more than 95 percent—of Alzheimer's disease are "sporadic," not known to be caused by a specific gene,[4980] so it's unclear if they share the same mechanism.[4981]

Skepticism of the amyloid cascade hypothesis centers around a series of disconnects. First, amyloid plaques can build up for decades before symptoms arise. Second, the amount of plaque correlates poorly with the severity of disease.[4982] As I mentioned before, as many as half the autopsies of individuals without dementia score as "probable" Alzheimer's disease and a third as bearing "definite" Alzheimer's pathology, based on plaque burden.[4983] And, third, the areas of the brain with the greatest neuron loss

are not in the same places where there is the most amyloid deposition.[4984] In fact, Dr. Alzheimer himself, five years after his groundbreaking discovery, wrote, "So we have to come to the conclusion that the plaques are not the cause of senile dementia.…"[4985]

A 2022 investigation into a seminal paper implicating amyloid alleged "shockingly blatant" data fraud, which has further tarnished the reputation of the theory.[4986] Perhaps amyloid buildup is just a manifestation of disease rather than the cause, just as skin lesions were a defining feature of smallpox but not the lethal pathology.[4987] Some posit that amyloid beta may even be protective, churned out by the brain as a defense mechanism. This could be consistent with the increased amyloid deposition found after head trauma.[4988] Regardless, the most damning failure of the amyloid cascade hypothesis is that amyloid-busting therapies like aducanumab don't work.[4989]

Dozens of different amyloid-targeted drugs have failed to slow cognitive decline.[4990] Those sticking to their guns, derided by skeptics as devout members of the "Church of the Holy Amyloid,"[4991] speculate that anti-amyloid drugs fail because they're given too late in the progression of the disease.[4992] After all, amyloid plaques can start forming as early as our late thirties.[4993] This finding has profound implications for the prevention of dementia.[4994]

CAUSAL THEORIES

Drug development for Alzheimer's disease has suffered a 99.6 percent failure rate, the worst of any therapeutic area,[4995] and the few we do have mostly just treat the symptoms.[4996] The good news, as a senior scientist at the Center for Alzheimer's Disease Research titled a review article, is that "Alzheimer's Disease Is Incurable but Preventable."[4997] Diet and lifestyle changes could potentially prevent millions of cases a year.[4998]

PRESERVING YOUR BRAIN'S BLOOD SUPPLY

There is an emerging consensus that "what is good for our hearts is also good for our heads"[4999] because clogging of the arteries inside the brain with atherosclerotic plaque is thought to play a pivotal role in the development of Alzheimer's disease.[5000] In my video see.nf/alzheimers, I trace this

connection, dating back to Dr. Alzheimer's first case.[5001] With no energy reserves of its own, the brain is very sensitive to nutrient deprivation.[5002] Interrupting that blood supply even for just a few minutes—for instance, by having a stroke—may double the risk of developing dementia and speed its onset by as much as a decade.[5003]

Autopsy studies have shown repeatedly that Alzheimer's patients tend to have significantly more atherosclerotic plaque buildup and narrowing of the arteries within the brain,[5004,5005,5006] particularly those leading directly to the memory centers.[5007] In light of such findings, some experts have even suggested that Alzheimer's be reclassified as a vascular disorder.[5008] Those with a total cholesterol of 225 mg/dL or higher have up to twenty-five times the odds of ending up with amyloid plaques in their brains ten to fifteen years later (compared to 224 mg/dL or less).[5009] Too much cholesterol in our blood is now universally recognized to be a risk factor for the development of Alzheimer's disease.[5010]

As I explore in see.nf/cholesteroldementia, cholesterol doesn't just help generate atherosclerotic plaques within our brain arteries; it may help seed the amyloid plaques that riddle the brain tissue of people with Alzheimer's.[5011] Under an electron microscope, we can see the clustering of amyloid fibers on and around tiny crystals of cholesterol.[5012] Drug companies have been hoping to capitalize on this connection to sell cholesterol-lowering statin drugs to prevent Alzheimer's, but statins themselves can sometimes cause cognitive impairment, including short- and long-term memory loss.[5013] For people unwilling to sufficiently change their diets, the benefits of statins outweigh the risks,[5014] but it's better if you can lower your cholesterol levels naturally by eating more healthfully to help preserve your heart, brain, and mind.

The number one recommendation of a 2022 consensus panel of experts for the prevention of cognitive decline centers around the concept that "brain health equals heart health."[5015] It is not surprising, then, that the dietary centerpiece of the "Dietary and Lifestyle Guidelines for the Prevention of Alzheimer's Disease" published in the journal *Neurobiology of Aging* was: "Vegetables, legumes (beans, peas, and lentils), fruits, and whole grains should replace meats and dairy products as primary staples of the diet."[5016]

Dietary Oxidized Cholesterol

Total brain cholesterol levels of Alzheimer's victims on autopsy are highly variable and not necessarily higher than in people who died from other causes.[5017] But, *oxidized* cholesterol levels are a different story.[5018] Levels have been shown to dramatically increase in the brains of people with Alzheimer's,[5019] as well as creep up in the spinal fluid of those with mild cognitive impairment.[5020] This adds to a constellation of evidence that oxidized cholesterol may be "the driving force behind the development of Alzheimer's disease."[5021] See the Oxidation chapter for how to reduce your exposure.

TAKING THE PRESSURE OFF

The first trial to showcase an effective strategy for the prevention of age-related cognitive impairment was published in 2019. Earlier, a study of three hundred Alzheimer's patients found that treating vascular risk factors, such as high cholesterol and blood pressure, may slow the progression of the disease but not stop it.[5022] That's why prevention is the key. The Systolic Blood Pressure Intervention Trial (SPRINT) randomized more than a whopping 9,000 older men and women with an average age of sixty-eight with high blood pressure to one of two treatment goals: drugs to push down the top blood pressure number (systolic) to under 140 or more drugs at higher doses to force systolic blood pressure below 120, which is closer to normal blood pressure. The study was planned to last for six years, but the more intensive drug regimen saved so many more lives, reducing overall mortality by 27 percent, that the trial was stopped halfway through.[5023] Were minds saved, as well?

The SPRINT MIND study followed the cognition of the SPRINT participants throughout the trial and for about two subsequent years. The 17 percent reduction in dementia in the intensive blood pressure–lowering group wasn't statistically significant, but the 19 percent drop in the risk of developing mild cognitive impairment was.[5024] Lowering blood pressures

therefore appears to prevent cognitive decline. The downsides were the side effects from the numbers and doses of drugs needed to attempt to normalize blood pressures. Yes, there were fewer cases of heart failure in the intensive treatment group, but there were more cases of kidney failure, fainting, and electrolyte abnormalities.[5025] A healthy diet and lifestyle would offer the best of both worlds: lower blood pressures plus a bounty of side benefits.

The arteries in the brain are designed to act not only as a conduit but also as a cushion.[5026] The elastic rebound of artery walls acts as a shock absorber for the pulsations of blood pumping up from our hearts. However, when the artery walls become stiffened with age, the pressure from the pulse can damage small vessels in our brain.[5027] This can cause "microbleeds" in the brain, which are found at about triple the frequency in people with high blood pressure, even if they have never been diagnosed with a stroke.[5028] High blood pressure is also associated with so-called lacunar infarcts,[5029] from the Latin word *lacuna*, meaning "hole." On CT scan, it looks as though your brain has been hole-punched.

These holes appear when little arteries in the brain get clogged and result in the death of a pea-sized region of the brain. Up to a quarter of the elderly have these little ministrokes, and most don't even know it.[5030] They are referred to as "silent infarcts" since they lack clinically overt stroke-like symptoms but are still associated with subtle deficits in physical and cognitive function and can double the risk of dementia.[5031] High blood pressure is also associated with brain shrinkage, specifically in the memory center of the brain.[5032] No wonder elevated blood pressure in midlife is associated with elevated risk of cognitive impairment and Alzheimer's dementia later on, even more so than having the so-called Alzheimer's gene.[5033]

Fourteen of fifteen cross-sectional studies correlated increased arterial stiffness with impaired cognitive performance, and six of the seven longitudinal studies found that arterial stiffness appeared predictive of cognitive decline.[5034] How can we reduce artery stiffness? Reduce our sodium intake. High sodium intake causes excessive arterial fibrosis, the accumulation of scar tissue in the walls of our arteries, resulting in stiffening.[5035] A meta-analysis of eleven randomized controlled trials found that cutting salt intake by less than a teaspoon a day can significantly reduce artery stiffness,[5036] in addition to lowering blood pressure.[5037]

The artery stiffness caused by excessive sodium intake is in fact one of the mechanisms by which too much salt raises blood pressure.[5038] However, excess salt intake is now recognized as a risk factor for dementia independent of blood pressure effects by impairing artery function as well.[5039] In mice, a high-salt diet directly leads to cognitive impairment[5040] and the development of hallmark Alzheimer's brain pathology.[5041]

DIET TRUMPS GENETICS

Few appear to be aware of the good news that much of Alzheimer's risk is modifiable.[5042] For example, one study found that only about a quarter of respondents were aware that high cholesterol and blood pressure increase the risk.[5043] A scoring system was developed for predicting the likelihood of a dementia diagnosis within the next twenty years based on a few factors within our control. Using the scoring system, a fifty-year-old man who didn't finish high school, is physically inactive and obese, and has high blood pressure and cholesterol can be more than *fifty* times more likely to develop dementia compared to a fifty-year-old man who is more educated and active, not obese, and has normal blood pressure and cholesterol, suggesting that we have an enormous influence on risk.[5044]

However, much of the popular press today treats Alzheimer's as a genetic disease, saying it's our genes, rather than our lifestyle choices, that determine whether or not we'll succumb. However, as I cover in depth in my Brain Diseases chapter in *How Not to Die*, when you examine the vastly varying distribution of Alzheimer's disease around the world, that argument begins to crumble.

The lowest validated rates of Alzheimer's disease are found in rural India,[5045] where people eat traditional, plant-based diets centered on grains and vegetables.[5046] A recent study in Taiwan found that vegetarians developed dementia at only two-thirds the rate of nonvegetarians.[5047] In the United States, one study found that those who don't eat meat (including eschewing poultry and fish) appear to cut their risk of developing dementia in half. And, the longer meat is avoided, the lower the dementia risk may fall. Compared to those eating meat more than four times a week, individuals who have eaten vegetarian diets for thirty years or more had three times lower risk of developing dementia.[5048]

See the box below for the good news about how much control we have over the "Alzheimer's gene" *APOE* ε4. Too often, doctors and patients have a fatalistic approach to chronic degenerative diseases, and Alzheimer's is no exception.[5049] "It's all in your genes," they say, "and what will happen will happen." Research shows that although you might have been dealt some poor genetic cards, you may be able to reshuffle the deck with diet.

The Single Most Important Gene for Longevity

Complex genetic mapping techniques, like genome-wide association analysis comparing the DNA of centenarians versus noncentenarians, for example, can identify genes associated with longevity. In my video see.nf/gwas, I describe how the whole process works and what researchers have found. A review of all such studies for lifespan only found one gene confirmed in multiple independent meta-analyses: *APOE*, the "Alzheimer's gene."[5050] Beyond just determining dementia risk, *APOE* is the single most important gene when it comes to having a long and healthy life (though, that's not necessarily saying much).[5051]

What does this gene do to have such a powerful impact on our health and longevity? It codes for the primary cholesterol carrier in the brain[5052] and plays a major role in packaging and transporting LDL ("bad") cholesterol throughout the body.[5053] The good news is that diet can trump genetics. In the video, I explain the so-called Nigerian paradox: how the population with the highest rate of the "Alzheimer's gene" has one of the lowest rates of Alzheimer's disease, thanks to their extremely low blood-cholesterol levels, due to a diet low in animal fat.[5054] Humans appear to have evolved to sustain an LDL level of around 25 mg/dL.[5055] The average in the Western world is approximately 120 mg/dL. Perhaps it's no wonder that heart disease is the leading cause of death in higher-income

countries, and dementia, according to the World Health Organization, is killer number two.[5056]

THE ROLE OF INFLAMMATION

More than a dozen theories have been published on the cause of Alzheimer's, and the "inflammation hypothesis" is one of them.[5057] I review the evidence favoring and opposing in see.nf/braininflammation. I conclude that inflammation may play a role, but you may have to catch it early.[5058]

Alzheimer's manifests as a disease of the elderly, but like heart disease and most cancers, it's a disease that may take decades to develop. Most Alzheimer's sufferers aren't diagnosed until they're in their seventies,[5059] but we now know that their brains began deteriorating long before that. Based on thousands of autopsies, pathologists seemed to detect the first silent stages of Alzheimer's disease—what appear to be tangles in the brain—in half of people by age fifty and even 10 percent of those in their twenties.[5060] The good news is that the clinical manifestation of Alzheimer's disease may be preventable.

THE ROLE OF OXIDATION

Is our brain just rusting? In see.nf/brainoxidation, I contrast the failed antioxidant supplement trials[5061] with the long-term population studies correlating the intake of brain-accessing antioxidants with lower rates of dementia. For example, in the most comprehensive and longest-running cohort to address the question, those averaging the anthocyanins in a single tablespoon of blueberries had a 76 percent lower risk of dementia compared to those getting the anthocyanins in less than a teaspoon or so of daily blueberries.[5062] (Sadly, the number one source of anthocyanins for those in the study was not blueberries but rather blueberry muffins.[5063])

Beyond their antioxidant activity, polyphenols like anthocyanins have been shown to protect nerve cells in vitro by inhibiting the formation of the plaques[5064] and tangles[5065] that characterize Alzheimer's brain pathology. In theory, they could also "pull out"[5066] metals that accumulate in certain brain areas that may play a role in the development of Alzheimer's and other neurodegenerative diseases.[5067]

The "aluminum hypothesis" for the cause of Alzheimer's dates back to 1965, when the inadvertent injection of aluminum into the brains of rabbits induced cognitive deficits along with what initially looked like Alzheimer's disease tangles. Then, in the 1970s, it was first reported that the aluminum content of Alzheimer's brains was higher than that of control brains on autopsy.[5068] Following that, there was a rash of fatal dementia cases linked to dialysis fluids contaminated with aluminum.[5069] This trio of findings led researchers to suggest that aluminum, the third most abundant element on Earth (after oxygen and silicon),[5070] may play a role in the development of Alzheimer's disease.[5071]

The aluminum hypothesis came under heavy fire in the scientific community. Only later did we learn that the most vocal critics were secretly paid hacks for the aluminum industry.[5072] In hindsight, that was probably unnecessary, as the tide of evidence eventually turned against the role of aluminum,[5073] as I review in see.nf/aluminum. What convinced me was a meta-analysis that failed to find a connection between Alzheimer's[5074] and regular antacid use—the most important source of aluminum exposure.[5075]

As I explore in see.nf/aluminumpots, just because aluminum doesn't cause Alzheimer's doesn't mean that aluminum intake is necessarily benign. Those who cook and store acidic foods like yogurt and tomato in aluminum cookware suffer significantly more DNA damage, leading some regulators to recommend that consumers avoid the use of aluminum pots or dishes for acidic or salted foodstuffs.[5076]

In see.nf/antiperspirants, I note how European safety authorities and the FDA also specifically advise against using aluminum antiperspirants on damaged or broken skin,[5077,5078] which may even include avoiding them after shaving.[5079] As a "metalloestrogen,"[5080] aluminum absorption may explain why breast cancer may occur as much as twenty years earlier in women using antiperspirant and shaving their armpits more than three times a week.[5081]

You can also avoid high dietary sources by choosing nonaluminum baking powder for baking and avoiding processed cheese. Aluminum salts can give cheese "desirable slicing properties,"[5082] but that means a single grilled cheese sandwich can end up exceeding the World Health

Organization's provisional tolerable daily intake of aluminum by more than 200 percent.[5083]

IRON IN THE FIRE

If aluminum doesn't cause Alzheimer's disease, why does the metal-removing drug deferoxamine seem to help? A remarkable study published more than thirty years ago of the metal-chelating (binding) drug deferoxamine is one of the few clinical trials ever to suggest a change in the course of Alzheimer's.[5084] Details in see.nf/deferoxamine, but basically, the researchers attributed the halving of the rate of cognitive decline in the deferoxamine group to the ability of the drug to bind aluminum, but deferoxamine was designed as an iron chelator.[5085] Deferoxamine's affinity for iron is six times greater than for aluminum, and iron is a thousand times more abundant in the brain.[5086] Might the dramatic effects be due to ridding the brain of excess iron?

I review the evidence in the video, but iron does seem to co-localize to Alzheimer's plaques;[5087] however, it only appears to accelerate plaques in people with preexisting amyloid buildup, so excess iron just seems to hasten the disease rather than initiate it.[5088] As I explore in see.nf/copper, copper also seems to co-locate with brain pathology,[5089] though it may only present a problem in those who consume too much saturated fat. In the Chicago Health and Aging Project, elderly Chicagoans who got the highest copper doses—largely from multivitamin and mineral supplements—were only at greater risk of cognitive decline when high copper intake was combined with a diet high in saturated fats. In that case, they lost cognition as if they had aged nineteen years during the six years of the study. The researchers proposed that the saturated fat led to the initiation of amyloid plaque buildup, and copper then enhanced disease progression.[5090] The practical implications could be to eat a lot of fruits and vegetables, given the natural metal-chelating effects of many polyphenols, and avoid copper-containing supplements, as well as excessive intake of iron and saturated fat.[5091]

Attention started to be paid to saturated fat and cholesterol in relation to Alzheimer's disease in the 1990s with the discovery of the role of the "Alzheimer's gene" protein apoE4, the principal cholesterol carrier in the brain.[5092] High saturated fat consumption (sourced predominantly from dairy, meat, and processed foods) is linked to poorer memory[5093] and accelerated cognitive decline. In the Harvard Women's Health Study, for example, higher saturated fat intake was associated with a significantly poorer trajectory of cognition and memory. Women with the highest intake of saturated fat had a 60 to 70 percent greater chance of cognitive deterioration over time, while women with the lowest saturated fat intake had the brain function of women six years younger.[5094]

Meta-analyses of all such studies have found that higher saturated fat consumption is associated with a 40 percent increased risk of cognitive impairment,[5095] a 46 percent increased risk of Alzheimer's disease, and more than twice the risk of developing dementia in general.[5096] A recent review concluded that the link between saturated fat intake and Alzheimer's appears to be "conclusive and detrimental."[5097] How can we cut down on saturated fat? By cutting down on the top sources in the American diet: cheese, cake, ice cream, and chicken, followed by pork, burgers, and then beef in general.[5098]

There are a number of indirect mechanisms by which saturated fat could contribute to dementia risk, including insulin resistance, high blood pressure, inflammation, or a clogging of cerebral blood vessels,[5099] but it may also make the brain vasculature leaky. Saturated fat may increase Alzheimer's disease risk by disrupting the blood-brain barrier.

The permeability of the blood-brain barrier can be quantified by injecting a dye into people's veins and seeing how much of it leaks into the brain on MRI scan.[5100] Those with Alzheimer's or vascular dementia tend to have leakier brain vessels than age-matched controls.[5101] These disease processes can cause a breakdown of the blood-brain barrier, but this leakiness appears to precede the dementia.[5102] Leakage rates have been found to be elevated in mild cognitive impairment and cerebral small vessel disease, the prodromal syndromes for Alzheimer's disease and vascular dementia.[5103]

Even in healthy individuals, blood-brain barrier leakiness tends to get worse with age,[5104] especially in regions of the brain particularly vulnerable to age-related deterioration, suggesting that the barrier disruption may play a role in run-of-the-mill cognitive decline.[5105] What can we do to maintain the integrity of our blood-brain barrier? Being overweight or obese in middle age correlated with degraded blood-brain barrier function twenty-four years later.[5106] In terms of dietary factors, saturated fat and cholesterol[5107] or just dietary cholesterol alone[5108] can worsen blood-brain barrier permeability. Saturated fat can cause a thirtyfold increase in blood-brain barrier dysfunction in mice and dietary cholesterol a sevenfold increase, both of which can be blocked by a cholesterol-lowering drug.[5109] This may represent a double whammy, since eating saturated fat can increase the production of the amyloid precursor protein from the intestine that's turned into amyloid beta in mice, as well as increase its secretion into the bloodstream.[5110] A single meal high in saturated (dairy) fat can cause a sevenfold increase in amyloid protein levels in the blood.[5111] Combined with blood-brain barrier leakiness, this could explain the proliferation of plaques in fat-fed animal models.[5112] In reference to the burgeoning science in this area, one recent biology journal primer was titled, "Amyloid Beta Emerges from Below the Neck to Disable the Brain."[5113]

WHAT A SINGLE FATTY MEAL CAN DO TO OUR BRAINS

In my Anti-Inflammatory chapter in *How Not to Diet*, I review a litany of studies showing how just a few days on a high-fat, ketogenic diet can blunt cognition,[5114] which may take weeks to recover from.[5115] Even a single high-saturated-fat meal has been shown to impair cognitive performance in people within five hours.[5116] This might be due to brain inflammation. Saturated fat fed to lab animals crosses their blood-brain barrier, accumulates in the center of the brain, and triggers inflammation. The original studies on animals used lard-based diets, but it appears butterfat causes similar results.[5117] The scenario can also be re-created in a petri dish. When the main saturated fat in a typical American diet (found mostly in dairy and meat)[5118] is dripped onto neurons in vitro, inflammation can be turned on like a light switch.[5119] Fortunately, it is possible to reverse this.

When the animal subjects were once again fed their regular low-fat food, the inflammation in their brain disappeared.[5120]

Granted, extrapolating data from animal studies is infamously fraught with difficult challenges.[5121] For starters, the diets are not comparable. High-fat, lard-based rodent food may be around 60 percent fat,[5122] for instance, but even bacon is only about 40 percent lard.[5123] So, we could eat a bacon-only diet and still not get the fat intake of the rodent diet. Saturated fat has been put to the test in people, though.

Researchers covertly increased the saturated fat intake of study participants in randomized crossover trials and found it reversibly induces negative changes in inflammation, mood, brain function, and resting metabolic rate, and even appears to undercut motivation to exercise.[5124,5125] Study subjects became 12 to 15 percent less physically active when they were on diets high in saturated fat compared to low–saturated fat ones.[5126] Note that the researchers used palm oil, which is a saturated *plant* fat that can be found in some vegan spreads, nondairy cheeses, and other processed foods. So, an anti-inflammatory diet is not only more plant-based in general; it is specifically centered around whole, unprocessed plant foods.

POLLUTING YOUR BRAIN

Besides saturated fat and oxidized cholesterol, what else might be in the meat supply to account for meat eaters having up to two to three times the risk of developing dementia compared to vegetarians?[5127] In the Glycation chapter, I discussed the role of advanced glycation end products in baked, broiled, grilled, fried, and roasted meat in age-related cognitive decline,[5128] brain shrinkage,[5129] mild cognitive impairment,[5130] and the development[5131] and progression of Alzheimer's disease.[5132] Persistent pollutants, like chlorinated pesticides, may be another factor.

Among U.S. elders, DDT and its breakdown product, DDE, are associated with increased risk of accelerated cognitive decline,[5133] as well as the diagnosis and severity of Alzheimer's disease.[5134] See see.nf/ddtdementia for details. The toxins are still in our body because they're still in our food supply. Samples were collected from supermarkets across the United States, and fish, other meats, eggs, and dairy had five to

ten times higher levels of dioxins and PCBs than the plant foods that were tested.[5135]

ENDOTOXINS

Recently, endotoxins have been proposed as an underlying mechanism for the link between saturated fat and cognitive impairment.[5136] I review the evidence in see.nf/endotoxins, but basically, there are two ways to cut down on endotoxin bursts after meals. One is to not eat so many in the first place. (See here.) But, if you do eat meat, the addition of fiber-rich foods can blunt the endotoxin surge. As I show in the video, eating a Sausage and Egg McMuffin with a high-fiber cereal significantly reduced bloodstream endotoxins compared to a McMuffin alone. The fiber also reduced the associated oxidative stress, clearly showing "profound effects on metabolic and inflammatory events after the meal."[5137]

LIFESTYLE

Advanced age is the strongest known risk factor for declining cognition,[5138] but 40 percent of dementia cases appear to be attributable to modifiable risk factors that we can control.[5139] In addition to cleaning up our diets, we can reduce dementia risk by preventing head injuries, not smoking (quitting or not starting to begin with), avoiding secondhand smoke and other sources of air pollution, limiting alcohol use, getting sufficient sleep, reducing obesity, and keeping physically active.

HEAD INJURIES, AIRBORNE POLLUTANTS, AND ALCOHOL

Up to 30 percent of all traumatic brain injuries are sports-related.[5140] That may be why former professional soccer players appear to be five times more likely to die from Alzheimer's disease than matched controls,[5141] especially among those playing field positions characterized by executing more "headers."[5142] A study of former National Football League players suggests American football also places athletes at risk.[5143] Boxers even have their own term—"dementia pugilistica"—to describe the punch-drunk syndrome of former prizefighters.[5144] Less than 1 percent of dementia cases globally are probably attributable to traumatic brain injury, but it's still

worth taking precautions.[5145] Bicycle helmets may reduce the risk of serious head injury by as much as 60 percent compared to unprotected cyclists.[5146] Protective headgear is also recommended for high-risk impact sports,[5147] as are policies eliminating body checking in youth ice hockey.[5148]

In contrast, as many as 14 percent of global Alzheimer's disease diagnoses are potentially attributable to smoking.[5149] Tobacco is a major risk factor for stroke, which itself increases dementia risk, as well as having a direct effect of increased brain amyloid burden and oxidative stress.[5150] The good news is that the risk of ex-smokers is similar to that of never-smokers.[5151] Interventional studies of smoking cessation to prove cause and effect are, like studies entailing major dietary change, hard to do because of the lack of long-term compliance. One can, however, show that the cognition of successful quitters is significantly better over time compared to those in cessation trials who failed to stop smoking.[5152] Even secondhand smoke exposure has been associated with increased risk of Alzheimer's and other forms of dementia.[5153]

Dementia and cognitive decline have also been consistently associated with exposure to ambient air pollution. Interest in the impact of air pollutants was sparked twenty years ago by the paper "Air Pollution and Brain Damage,"[5154] in which Alzheimer's-type pathology was found in the brains of dogs raised in cities with high pollution versus low pollution.[5155] In the human brain, the presence of magnetite nanoparticles suggests pollutants from traffic exhaust may be traveling directly to the brain through olfactory nerves from inside the nose,[5156] though pollutants could also indirectly lead to brain injury through systemic inflammatory effects.[5157]

Alcohol-related dementia has been referred to as a silent epidemic.[5158] Excess alcohol consumption may contribute to as many as 24 percent of cases of dementia. What about light drinking?[5159] Hopes that low-level alcohol consumption might even be beneficial for cognition[5160] were dashed by a Mendelian randomization study that found, if anything, alcohol consumption causes earlier onset of Alzheimer's disease.[5161] The good news is that those quitting even heavy drinking followed by prolonged abstinence can experience a recovery of lost brain volume and cognitive function.[5162]

Don’t Kiss Your Memories Goodbye

Another risk reduction strategy is being careful who you smooch. Amyloid beta is strongly conserved throughout evolution. The human variant dates back at least four hundred million years and today can be found in most vertebrate species.[5163] So it must have some sort of beneficial function. Historically, survival of the fittest has been less about the dynamics of predator against prey than about the starkest us-versus-them—the microbial threats that prey on us all. Amyloid beta may be part of our immune system, an antimicrobial peptide that protects us against brain infections. It has been shown to be antibacterial, antifungal, and antiviral against a range of common pathogens. For example, temporal lobe samples from Alzheimer’s brains are better at killing off *Candida* yeast, a cause of fungal meningitis, than samples from the same part of the brain from those who died of other causes.[5164]

Amyloid beta also binds to herpes simplex virus 1 (HSV-1), leading to protective viral entrapment.[5165] HSV-1 is the virus that normally causes cold sores (also known as fever blisters) but it can also infect the brain. Is it possible that infection with this common virus could trigger amyloid deposition in our body’s attempt to suppress it but thereby, inadvertently and eventually, lead to Alzheimer’s disease?

I was surprised to find about a hundred scientific publications linking HSV-1 infection to Alzheimer’s disease.[5166] In one study, for instance, researchers followed tens of thousands of individuals and found that those with either oral herpes (HSV-1) or genital herpes (HSV-2) were more than twice as likely to develop dementia during the sixteen-year follow-up period. Even more convincing (and offering a dose of good news) is that those with HSV who took antiviral medications (like acyclovir) appeared to be 90 percent less likely to develop dementia compared to those

with untreated HSV.[5167] Unfortunately, there are not yet licensed vaccines to prevent getting infected in the first place, but you can reduce your risk of HSV-1 by avoiding kissing or sharing utensils, cups, water bottles, towels, or lip balm with those who have an active oral infection (though asymptomatic viral shedding can also occur).

GETTING BRAINWASHED EVERY NIGHT

Sleep is a great mystery. A trait shared across animal species, sleep must be of vital importance to survive natural selection pressures to eliminate such a vulnerable state.[5168] Indeed, cringeworthy experiments have shown that keeping animals awake long enough can be fatal within eleven to thirty-two days.[5169] One function of sleep that has been elucidated in recent years is the clearance of toxic waste by-products[5170] through a newly discovered drainage system in the brain.[5171] This may explain why PET scans show that even a single all-nighter can cause a significant increase in accumulation of amyloid beta in critical brain areas.[5172] Find out more about this brain-wide fluid transport network termed the glymphatic system in my video see.nf/brainwash.

Unfortunately, this brain filtration system appears to decline with age.[5173] See see.nf/glymphatic for the role that sleeping position could potentially play. (Teaser: Sleeping on our right side could theoretically maximize brain drainage.[5174])

Might Melatonin Help?

What about using melatonin to improve sleep quality, in the hopes of clearing out extra debris?[5175] There was an interesting case report of identical twins. Both had Alzheimer's disease, but only one was treated with melatonin. The treated twin not only appeared to sleep better but also had milder memory impairment.[5176] Melatonin has been shown to improve the memory of aging-

accelerated rats considered to be laboratory models for Alzheimer's disease,[5177] but what about in people?

A total of seven randomized, double-blind, placebo-controlled trials of melatonin for Alzheimer's disease have been performed on hundreds of patients, lasting between ten days and twenty-four weeks. Those randomized to melatonin appeared to sleep better, but, sadly, melatonin had no effect on improving cognitive abilities.[5178]

EXPANDING WAIST, SHRINKING BRAIN

Overweight individuals have about one-third higher risk of developing dementia, and those who are obese in midlife seem to have about 90 percent greater risk.[5179] I explore this large body of data in my video see.nf/obesitydementia, including how excess body fat can impair cognition at any age,[5180] which correlates with structural brain differences.[5181] The brain appears to shrink as the waist expands,[5182] perhaps due to the inflammation and oxidative stress, both related to obesity.[5183] Based on a meta-analysis of twenty studies, mental performance across a variety of domains can be significantly improved with even modest weight loss, though no studies have yet been done to determine if this then translates into a normalization of Alzheimer's disease risk.[5184]

EXERCISE YOUR BRAIN

The improved cognition in weight-loss studies may also be confounded by exercise.[5185] I review all the key interventional studies in see.nf/exercisebrain. Added exercise tends to improve the cognition of adults with normal cognition[5186] or mild cognitive impairment.[5187] Based on a meta-analysis of nearly a hundred randomized controlled trials, more important than session duration, weekly frequency,[5188] program duration, or intensity[5189] may be total training time—a total of about fifty-two total hours of exercise to establish a cognitive benefit.[5190] Unfortunately, an exercise intervention failed to slow cognitive decline once dementia was diagnosed.[5191]

How does exercise work exactly? Neurotrophins are a family of growth factors that promote the development, function, and survival of neurons (the nerve cells in our brain).[5192] The most abundant neurotrophin is called *brain-derived neurotrophic factor*, or BDNF,[5193] the levels of which appear to correlate with integrity of the hippocampus, the memory center of the brain.[5194] On autopsy, most studies show decreased BDNF in the brains of people with Alzheimer's.[5195] Since it crosses the blood-brain barrier, BDNF levels in the brain can be estimated by measuring its levels in the blood.[5196] Compared to healthy controls, those with Alzheimer's have significantly lower BDNF blood levels.[5197]

Given the neuroprotective properties of BDNF, it would make sense that low levels might contribute to the disease,[5198] but how do we know that the Alzheimer's isn't just leading to a drop in BDNF instead of the other way around?[5199] The Framingham Heart Study, a longitudinal study that followed thousands of people over time, found that having higher BDNF blood levels appears to cut in half the risk of developing Alzheimer's over the next decade.[5200] And, once you have the disease, higher levels of BDNF seem to predict a slower cognitive decline.[5201] Bolstering the causal case, people born with genetic variations that naturally lead to lower BDNF secretion do appear to suffer impairments of cognitive function and brain health.[5202]

Thankfully, boosting BDNF is as easy as lacing up our walking shoes. Physical activity is the best studied factor for boosting BDNF.[5203] Based on twenty-nine trials involving more than a thousand subjects, single sessions of exercise, regular exercise, and especially acute exercise in the context of regular exercise have been shown to increase BDNF levels.[5204] Cycling at 70 percent maximal work rate for just ten minutes, for example, can significantly elevate levels.[5205] The greater the workout intensity, the greater the rise in BDNF,[5206] but even among elderly individuals with limited ambulation, a physical therapy intervention using progressive dynamic resistance training seemed able to boost BDNF blood levels.[5207]

So, is BDNF one of the reasons exercise boosts brain power? Yes, at least in rodents. Researchers have clearly shown that blocking BDNF blocks the memory-enhancing effects from exercise in rats and mice, effectively proving the role of BDNF in mediating the exercise benefit. In

people, the best we can do is try to see if the level of exercise-induced improvement in BDNF corresponds with the level of exercise-induced improvement in memory performance. This only seems to be the case in four of the ten studies on the matter, though, so the answer is less clear.[5208]

Boosting BDNF with Calorie Restriction

Fasting has been espoused as a way of rejuvenating the body as well as the mind,[5209] but after fasting for just eighteen hours, you can start to get really irritable.[5210] Remarkably, after a few days of fasting, you may experience a sometimes euphoric mood enhancement,[5211] for which BDNF may play a role. I explore this phenomenon in my video see.nf/fastingbdnf. Fasting, by definition, is unsustainable, though. What about more modest caloric restriction?

Cutting 25 percent of calories from our daily diet has been shown to cause a 70 percent rise in BDNF after only three months.[5212] Over that same time period, just a 10 percent or so reduction in calories can improve memory performance.[5213] Is there anything we can *add* to our diets to boost BNDF levels so we can get the benefits without the hunger?

Boosting BDNF with Food

Caloric restriction studies can sometimes be confounded by changes in dietary quality.[5214] For example, one study in which those on low-calorie diets had higher BDNF levels involved not just eating less but also eating more healthfully—less saturated fat and sugar, and more fruits and veggies.[5215] A single high-fat meal can suppress our BDNF levels within hours. We know it's the fat itself because researchers see the same response after injecting fat straight into people's veins.[5216] This may help explain why increased consumption of saturated fats in a high-fat diet may contribute to brain dysfunction, including neurodegenerative diseases, long-term memory loss, and cognitive impairment.[5217]

In my video see.nf/foodbdnf, I compare it to the Soviet fasting trials for schizophrenia. After the patients were fasted for up to a month, they were put on a diet that excluded meat and eggs. When the researchers reported remarkable effects even years later, that was for the patients who stuck with the diet. Those who broke the diet evidently relapsed, whereas the closer the diet was followed, the better the effect.[5218] Since we know from a

randomized controlled trial that removing meat and eggs can improve mental states within just two weeks,[5219] it's hard to know what role the initial fasting itself played in the reported improvements.

In the video, I go through all the foods that have been shown to boost BDNF. These include high-flavonoid fruits and vegetables,[5220] nuts,[5221] turmeric,[5222] and cocoa powder. For example, researchers randomized older men and women to a daily high-flavonoid chocolate drink (containing the flavonoid content of about two and a half tablespoons of natural cocoa powder) or a low-flavonoid chocolate drink (equivalent to around two tablespoons of Dutched cocoa).[5223,5224] Those randomized to weeks of more flavonoids experienced significant increases in BDNF levels and global cognitive function.[5225] One food is capable of boosting BDNF after just a single meal: rye groats.

Healthy young adults were randomized to a late-evening meal of either a whole-grain bread containing intact rye kernels or regular white bread. Before breakfast the next morning, more than ten hours after eating their evening meals, their blood was drawn. Those who had eaten the whole intact rye the night before had 33 percent higher BDNF levels. Given the timing, this is suspected to be a microbiome effect, bolstered by a corresponding 30 percent increase in butyrate levels in the blood. Remember, butyrate is a good bacteria by-product of the gut fermentation of fiber and other prebiotics,[5226] and it increases BDNF expression in mice.[5227] The administration of probiotics—the good bacteria themselves—did not seem to affect BDNF levels,[5228] so it may be better to pamper the good bugs we already have.

MIND YOUR MICROBIOME

BDNF is just one of the ways fiber-derived butyrate may contribute to brain health. Elderly individuals with higher levels of butyrate in their blood tend to have lower levels of amyloid in their brains on PET scan. In vitro, butyrate inhibits the neurotoxic clumping of amyloid beta.[5229] In rats, it acts as a cognitive enhancer in those with impaired memory function,[5230] and, in a mouse model of Alzheimer's, butyrate profoundly reduces amyloid levels in the brain and improves cognitive function[5231]—even at a late stage of the

disease.[5232] Butyrate may even prevent amyloid beta in the blood from even getting into the brain in the first place.[5233]

"Germ-free" mice raised Bubble Boy–style in a sterile environment have a leaky blood-brain barrier, which is normally meant to wall off the brain from any toxins circulating in the bloodstream.[5234] Butyrate maintains and repairs the barrier function of the gut,[5235] so perhaps the mice's lack of good gut bugs could explain the leaky brain. Indeed, researchers proved it was the butyrate by restoring the germ-free mice's blood-brain barrier function with butyrate or just by seeding their guts with fiber-eating bacteria.[5236]

The release of butyrate is not the only way our good gut bugs can interact with our brain. There is a big nerve—the vagus nerve—that goes directly from our gut straight up into the brain. There are certain *Bifidobacteria*[5237] and *Lactobacillus*[5238] probiotics that can be fed to mice that ameliorate anxiety- or depression-related behaviors, as well as reduce their stress hormone levels, but they only work in animals with an intact vagus nerve. When the nerve is cut, so is the line of communication between their gut bugs and their brains, and the effects are abolished. In humans, in what sounds like science fiction, stimulating the vagus nerve with an electric current was found to significantly enhance memory retention,[5239] but eating fiber-rich foods is probably more pleasant than surgical electrode implantation.

Our microbiome can also modulate inflammation in the body.[5240] Most of the variation in gut bugs between people is attributable to differing diets,[5241] and switching from a fiber-rich, plant-based diet to an animal-based one not only significantly reduces butyrate levels within days but it fosters the growth of pro-inflammatory bacteria.[5242] This is consistent with cross-sectional data that find that those eating more plant-rich diets typically have an anti-inflammatory microbiome, whereas those eating more animal-rich diets tend to have more pro-inflammatory species.[5243]

Researchers were able to prove the role of bad gut bugs by performing fecal transplant studies with mice. They replicated the same kind of brain inflammation and dysfunction seen in lard-fed mice by just transferring the gut bacteria fostered by lard-eating mice into other mice that had not eaten lard.[5244] The closest we've come in people is showing that feeding mice feces from obese humans impairs their memory (compared to being fed

fecal matter from normal-weight humans). If bad gut flora contribute to cognitive dysfunction, how about treating Alzheimer's patients with antibiotics in an attempt to wipe out the bacteria? A pilot study of an antibiotics cocktail suggested that there was enough potential benefit to run a more rigorous trial.[5245] Unfortunately, the follow-up study failed to show any significant effect.[5246]

There have been more than twenty randomized trials on probiotics and cognition in mostly healthy adults, with no overall benefit found across the board.[5247] (One study even found probiotics impaired memory, compared to placebo.[5248]) But, just looking at five studies done on those affected by mild cognitive impairment or Alzheimer's disease, a variety of *Lactobacillus* and/or *Bifidobacteria* species for twelve weeks did appear to move the needle and improve cognition compared to the control group.[5249]

BRAIN SUPPLEMENTS

Over the last twenty years, Big Pharma has invested more than half a trillion dollars into dementia treatment research, so far to little avail.[5250] In light of this, many have turned to supplements. An AARP-commissioned survey found that 36 percent of people seventy-four and older take a supplement for brain health,[5251] to the tune of billions of dollars a year.[5252] The most commonly marketed brain supplement is one I'd never heard of before (a consequence, I guess, of never having owned a television): Prevagen.[5253]

JELLYFISH STING

Prevagen contains a protein derived from a luminescent jellyfish that the company claims has been "clinically shown to improve memory,"[5254] but even its own study failed to show significant improvements in any of the nine measured cognitive tasks that were tested,[5255] leading the AARP to accuse the company of "deceiving millions of aging Americans."[5256] Prevagen may be more than just a waste of money, as the manufacturer was cited for failing to report more than a thousand adverse events relayed by consumers to the FDA.[5257] More on this shameful story in see.nf/prevagen.

A 2019 survey by the Pew Charitable Trusts found that more than half the respondents believed that the FDA requires supplements to be tested for

safety, but this isn't true.[5258] One study of dozens of supplements sold as cognitive performance boosters found that most (71 percent) claimed an ingredient on the label that wasn't actually in the supplement, and, even worse, 38 percent contained ingredients that are not even allowed to be in supplements, such as prohibited drugs.[5259] Another study of a dozen "brain health supplements" similarly found that eight out of twelve were misbranded (missing an ingredient promised on the label), and ten out of twelve were deemed adulterated (containing unlisted compounds—for example, caffeine in a product that explicitly highlighted "DECAFFEINATED" on its label). Only one out of twelve supplements was genuinely third-party certified and contained what its label said it did.[5260]

GINKGO

Ginkgo biloba is one of the most common "brain health" supplements,[5261] with as many as 2 percent of Americans taking it.[5262] Over the last few decades, an extract of gingko leaves has become one of the most widely used herbal treatments for dementia.[5263] Details in see.nf/ginkgo, but the bottom line is that a Cochrane review concluded that the "evidence that Ginkgo biloba has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable."[5264]

GINSENG, ROSEMARY, SAGE, AND LEMON BALM

Ginseng is another herbal remedy that's been tested in randomized controlled trials, and, sadly, most such studies flopped.[5265] What about culinary herbs you can actually eat?

In *Hamlet*, Ophelia notes that rosemary is for remembrance,[5266] an idea that goes back at least a few thousand years to the ancient Greeks, who claimed that the fragrant herb "comforts the brain … sharpens understanding, restores lost memory, awakens the mind.…"[5267] Even just sniffing rosemary may have an effect, as suggested by a study of cognition in a room infused with rosemary essential oil (compared to lavender essential oil or no odor at all).[5268] Furthermore, the boost in performance has been correlated with the amount of a rosemary compound that made it into their bloodstream, presumably through their lungs or nasal passages.[5269] What about just eating it?

Older adults with an average age of seventy-five were given two cups of tomato juice with either about a half teaspoon of powdered, dried rosemary (an amount one might use in a typical recipe), a full teaspoon, two teaspoons, more than a tablespoon, placebo pills, or nothing at all. Compared to placebo, memory speed improved after the lowest dose, but *worsened* after the highest dose, suggesting that more isn't necessarily better.[5270]

Sage and lemon balm are two other herbs in the same botanical family prized in folk medicine for their purported brain benefits.[5271] Cognitive benefits were also found within hours of consuming a teaspoon of dried sage or a tea bag's worth (1.6 g) of dried lemon balm.[5272] Note, however, that a trial using rosemary, sage, and lemon balm *extracts* showed no memory enhancement, suggesting consuming the herbs whole is preferable.[5273] Note also that these studies just tracked the acute effects of single doses in healthy individuals. Are there any herbs or spices that can be used to actually improve cognition over time?

Aromatherapy

The bump in cognitive performance from sniffing rosemary essential oils was demonstrated in young, healthy volunteers,[5274] but what about those who really need it? A group of Japanese researchers posed a pie-in-the-sky notion that certain smells could lead to "nerve rebirth" in people with Alzheimer's.[5275] Twenty-five years ago, simply raising such a possibility as a hypothetical was heretical. Everybody knew that dead neurons cannot be replaced.[5276] That's what we were all taught, until 1998.

Patients with terminal cancer volunteered to be injected with a special dye that gets incorporated into the DNA of new cells. On autopsy, researchers then went hunting for nerve cells that lit up and there they were: New nerve cells were found in the brain that did not exist months or even days before, demonstrating that "the human brain retains the potential for self-renewal throughout life."[5277] The

accompanying editorial was titled “Take Comfort in Human Neurogenesis.”[5278]

Of course, that doesn’t mean smells can cause such revitalization. An aromatherapy regimen of rosemary, lemon, lavender, and orange essential oils was attempted with Alzheimer’s patients for a month,[5279] and the trajectory of their steady decline in cognitive function appeared to reverse over that period. Weeklong before-and-after studies of both lavender oil and a combination of rosemary and lemon oils appeared to show similar effects.[5280] But, the studies all lacked a control group. Even with a control, though, how do you eliminate the placebo effect?

To test the power of expectancy effects, volunteers were given a memory test and then asked to repeat the test while exposed to sage essential oil. Some were randomly told that sage has a positive influence on memory, while others were told that sage impairs memory. You can probably guess what happened. Those expecting the sage to help did better, and those expecting the sage to hurt did worse.[5281] It would seem that our psychological expectations are able to trump any actual physiological effects. However, researchers have tried to come up with some creative solutions.

In one study of patients with dementia, researchers alternated months of applying a lavender-scented oil to the participants’ faces versus an unscented oil to their feet, or vice versa. So, everyone was getting the care and attention of the oil massage, but if there really was some benefit to breathing in lavender, then one would presume they would do better during the months they have the lavender on their face rather than on their feet. But they didn’t, which suggests lavender doesn’t help.[5282] Most aromatherapy trials for dementia similarly flopped,[5283] but there was one notable exception I detail in see.nf/lemonbalm.

Two studies have subsequently been published to try to replicate the remarkable results I review in that video. In the first, there was a 38 percent reduction in agitation and

aggression, a 50 percent reduction in depression and dysphoria (the opposite of euphoria), and a significant improvement in neuropsychiatry symptoms overall. But, pretty much the same was found in the unscented control group.[5284] In other words, just a minute or two of touch and social interaction can make a big difference, but there did not seem to be any specific benefit from the lemon balm. The second study did not clarify matters. Lemon balm appeared to reduce agitated behavior in participants without dementia but not in those with dementia, while lavender seemed to have the opposite effect, improving behavior in participants with dementia but not those without it.[5285] Obviously, more research needs to be done, especially given the safety and simplicity of aromatherapy interventions. But who's going to fund such studies—Big Balm?

TURMERIC

In see.nf/turmericdementia, I relay a remarkable case series in which the symptoms of three Alzheimer's patients dramatically improved after being treated with turmeric.[5286] The investigators concluded that this was the first demonstration of turmeric as an "effective and safe drug" for the treatment of Alzheimer's. Of course, it's not a drug at all. Turmeric is just a spice you can buy inexpensively at any grocery store. The researchers had given study participants around a quarter teaspoon a day, which would come out to less than five cents.

I review the available evidence in see.nf/curcumind, but ultimately, though there may be a small cognitive benefit for curcumin supplementation in older adults without dementia,[5287] the two randomized, double-blind, placebo-controlled trials of curcumin in patients with Alzheimer's both failed to show cognitive benefits.[5288,5289] Why didn't researchers see the same dramatic results with curcumin supplements that were reported in the case reports of those given turmeric? Perhaps those cases were total flukes. On the other hand, perhaps turmeric, the whole food, may be greater than the sum of its parts. Curcumin is just one of hundreds of phytochemicals found in turmeric.[5290] In response, some

researchers have suggested creating a blend of components that "represents turmeric in its medicinal value better than curcumin alone."[5291] But why concoct some artificial mixture when Mother Nature already packaged it all in turmeric? Because a common spice can't be patented, and if you can't patent it, how are you going to charge more than five cents?

SAFFRON

Although there were intriguing anecdotes of recovery using the spice turmeric,[5292] the best data we have on spice-based interventions for Alzheimer's are for saffron, with three double-blind trials (detailed in see.nf/saffron) showing promise. Saffron does not appear to improve cognition in individuals without dementia, however.[5293]

The three trials were funded by noncommercial public grants, not supplement or spice companies.[5294] However, they were all conducted in Iran, which controls about 90 percent of the world's saffron crop.[5295] So, promoting saffron consumption may be of national interest, which reminds me of the New Zealand government funding research on kiwifruit. But who else is going to fund studies on a simple spice?

Each saffron flower only produces a few threads, such that you need 50,000 flowers to make a single pound of spice. That's enough flowers to fill a football field. No wonder it's the most expensive spice in the world, retailing for about $200 an ounce. It doesn't take much, though. The cognition studies used as little as 0.125 g a day, which is only about four small pinches of fifteen threads each.[5296] Side effects may include an elevation of mood, as eleven randomized trials have found that, overall, saffron benefits mild to moderate depression significantly better than placebo[5297] at doses as little as a single pinch a day (30 mg).[5298] Daily doses are considered safe up to 1.5 g a day (fifty pinches).[5299] (Saffron is typically sold in containers holding 1 or 2 g.) Taking 5 or more grams a day can cause serious reactions, and overdoses involving 12 to 20 grams a day may be fatal.[5300]

VITAMIN D

As of 2019, vitamins such as vitamin D replaced *Ginkgo biloba* as the most common component of "brain health" supplements.[5301] Observational

studies have found that those with lower vitamin D levels have poorer cognition over time[5302] and are more likely to develop dementia.[5303] There are so many confounding factors when it comes to the sunshine vitamin, though. For example, those with lower levels are more likely to be less physically active, smokers, and obese,[5304] and each one of those may independently affect the brain. Randomized controlled trials have found that vitamin D can improve cognition in diseased rats[5305] and mice, but what about us?[5306]

An interventional trial finding no effects of vitamin D on young adults was published in 2011, but it wasn't until 2018 that a trial was conducted on elderly people with mild cognitive impairment. A randomized, double-blind, placebo-controlled trial showed that 400 IU of vitamin D a day for twelve months significantly improved cognitive function over placebo.[5307] The next year, a similar trial was published, but with 800 IU a day for those with full-blown Alzheimer's. That worked, too.[5308]

The best dosing is uncertain.[5309] An ambitious trial comparing 600 IU, 2,000 IU, and 4,000 IU a day for a year in overweight older women with low vitamin D blood levels found that those taking 2,000 IU a day performed better in learning and memory tests than those taking only 600 IU, whereas the 4,000 IU group did worse in one measure (reaction time). However, other trials of relatively healthy adults comparing 2,000 IU versus 800 IU[5310] or 4,000 IU versus 400 IU[5311] found no clear differences in overall cognitive performance.

ANTIOXIDANTS, MULTIVITAMINS/MINERALS, AND SOUVENAID

Oxidative stress is implicated in the development of Alzheimer's and further brain deterioration. Might antioxidants help? I review the interventional evidence in see.nf/brainvitamins. Supplementation with vitamin E, selenium, or both failed to prevent Alzheimer's, but the data on treating the disease are mixed, with two studies suggesting vitamin E supplementation made things better,[5312,5313] and one finding that it may make things worse.[5314]

Similarly disappointing outcomes have been reported for other antioxidants,[5315,5316] the multivitamin and mineral supplement Centrum

Silver,[5317] zinc,[5318,5319] calcium,[5320] or Souvenaid, a nutritional drink branded as Fortasyn Connect, as I document in my video see.nf/centrum.

B VITAMINS

For background on what homocysteine is, what it does, and all the preclinical and epidemiological evidence linking it to dementia, check out my video see.nf/homocysteine. In short, it's a toxic metabolite naturally formed in the body that can then be detoxified using three vitamins: folate, vitamin B_{12}, and vitamin B_6.[5321] A number of recent systematic reviews and meta-analyses of randomized controlled trials of B-vitamin supplements have found no effect on global cognitive function for healthy[5322] or impaired individuals,[5323] nor do they appear to slow cognitive decline.[5324] Normally, this would close the case, but a deeper dive suggests the situation may be more complicated.

The concern is that B-vitamin deficiencies give rise to homocysteine, which in turn causes brain dysfunction. If B-vitamin supplements are given to people who don't have B-vitamin deficiencies and don't have high levels of homocysteine, then negative results don't really help to answer the question at hand. In the VITACOG trial, for example, hundreds of men and women with mild cognitive impairment were randomized to placebo or the B vitamins that detoxify homocysteine—folic acid (the supplement form of folate), B_{12}, and B_6—for two years. No overall cognitive benefit was found. But, when the analysis was restricted to only those who needed the supplementation, that is, those who started out with higher-than-average homocysteine levels, then researchers saw a significant benefit in global cognition and some measures of memory.[5325] Even more remarkable was the reduction in brain shrinkage.

As we age, our brains slowly atrophy. The brains of those aged ninety and older weigh about 10 percent less than brains of those in their fifties. That comes out to a loss of about 5 oz of brain.[5326] Shrinkage is much accelerated in patients suffering from Alzheimer's disease, while an intermediate rate of shrinking is found in people with mild cognitive impairment. In the VITACOG study, the rate of brain atrophy in those with high homocysteine levels who were randomized to the B-vitamin supplements was cut in half.[5327] In regions especially vulnerable to the

Alzheimer's disease process, the B-vitamin supplements reduced shrinkage by as much as sevenfold.[5328] The researchers concluded, "We show that a simple and safe treatment that targets homocysteine can slow down the accelerated rate of brain atrophy found in mild cognitive impairment."[5329]

Sufficient B-vitamin status can only account for a fraction of failed trials, though; the vast majority of studies involved those with elevated homocysteine levels greater than 12 µmol/L.[5330] A wider-ranging issue is the lack of baseline measurements of cognitive function. They are missing from about three-quarters of participants in the trials.[5331] This is because most of the large B-vitamin supplementation trials were originally set up to investigate the effects of lowering homocysteine levels not on cognition but on cardiovascular disease, and researchers merely added in cognitive measurements at the end as a secondary outcome.[5332] Why do we care about baseline cognitive measurements? If the participants were randomly assigned to B vitamins or placebo and then, months or years later, ended up with the same brain scores, doesn't that effectively prove the B vitamins had no cognitive benefit? Not if there was no decline in either group. If there was no measurable cognitive decline in the placebo group, then there's nothing for the B vitamins to thwart. "In other words," a pair of reviewers wrote, "you cannot prevent something that is not occurring."[5333]

The Alzheimer's Disease Cooperative Study fulfilled both criteria necessary to properly put B-vitamin supplementation to the test—high homocysteine levels at baseline and a decline in mental functioning in the placebo group. Eighteen months later, there was no overall difference in cognition between the two groups.[5334] However, a planned subgroup analysis did find a significant slowing of cognitive decline in the B-vitamin group among those with mild dementia, just not for those further along. What about preventing the nutrient deficiencies in the first place?

HOW TO LOWER HOMOCYSTEINE

Most people get enough B_{12} and B_6, but the reason the elderly individuals may be stuck at a homocysteine level of 11 µmol/L[5335] is that they aren't getting enough folate.[5336] That should come as no surprise since folate is found concentrated in beans and greens, and 96 percent of Americans don't

even get the minimum recommended amount of beans or dark green leafy vegetables.

Since folate tends to be the limiting B vitamin for the general population, the FACIT trial randomized more than eight hundred older men and women to folic acid supplements or placebo for three years. Those in the folic acid group dropped their homocysteine from an average of 13 down to 10, yielding demonstrable cognitive benefits—and not just by a little. The researchers estimated the extra folic acid gave people the performance of someone 4.7 years younger for memory, 1.7 years younger for sensorimotor speed, 2.1 years younger for information processing speed, and 1.5 years younger for global cognitive function.[5337] All that for a cost as low as two cents a day.

So, should all older adults take folic acid supplements? Everyone needs to get enough folate, which is one of many reasons I recommend people eat dark green leafy vegetables and legumes every day, but, as I noted here, folic acid is not folate and may carry safety concerns. So, the best way to get folate may be from food.

Even just one week on a plant-based diet can drop elevated homocysteine levels by 20 percent, from around 11 µmol/L to 9 µmol/L,[5338] which is a normal level for those replete with B vitamins.[5339] This may be directly due to the folate-rich vegetables and beans or indirectly due to the fiber in the plants. Every 1 g of daily fiber consumption may increase folate levels in our blood by nearly 2 percent, perhaps by boosting folate production in the colon by all our friendly gut bacteria.[5340]

Another explanation for the rapid improvement could be from the decreased intake of methionine, an amino acid that comes mostly from animal protein. Homocysteine is a breakdown product of methionine. After eating bacon and eggs for breakfast and a steak for dinner, for example, homocysteine levels spike in the blood.[5341] Thus, decreased methionine intake on a plant-based diet may be another factor contributing to lower, safer homocysteine levels.

The irony is that those who eat plant-based diets long-term can develop terrible homocysteine levels. Meat eaters may average 11 µmol/L, but vegetarians can be at nearly 14 µmol/L and vegans at 16 µmol/L.[5342] Why? Vegetarians and vegans get a lot of fiber and folate, but not enough vitamin

B_{12}, which in modern times is only found dependably in animal products, fortified foods, or supplements. As I noted here, a regular, reliable source of vitamin B_{12} is critical for anyone eating a plant-based diet. (It's possible Leonardo da Vinci's stroke might have been from his non-B_{12}-fortified vegetarian diet elevating his homocysteine levels.[5343]) However, when vegans take B_{12}, their homocysteine levels drop below 5 µmol/L.[5344] Why not just down to 11 µmol/L like the rest of the population? The reason the general public may be stuck up at 11 µmol/L is presumably due to a lack of folate. Once vegans got enough B_{12}, they could finally fully exploit the benefits of their fiber- and folate-rich plant-based diets and achieve the lowest levels of all.

Cognitive Stimulation, Music Therapy, and Cryostimulation

There are a few common nondrug, non-supplement, non-lifestyle approaches to dementia treatment, such as "use-it-or-lose-it" mental stimulation,[5345] group social activities,[5346] music therapy,[5347,5348,5349] and cryotherapy,[5350] that I profile in see.nf/cog. All unfortunately offer little or no lasting cognitive improvement but may provide some peripheral benefits.

BRAIN FOODS

Given what we've learned about the beneficial effects of plant food constituents, like polyphenols and fiber, and the detrimental effects of animal and junk food components, like salt and saturated fat, it should come as no surprise that a systematic review and meta-analysis of diet quality and dementia found that healthier diets are associated with significantly lower risk of developing Alzheimer's disease and dementia in general. Healthier dietary patterns were typically defined as being higher in fruits, vegetables, legumes, and whole grains, and lower in meats.[5351] In a cohort study that followed more than 5,000 adults with an average age of fifty-one for sixteen

years, a healthier diet was also associated with the small minority (4 percent) who achieved "ideal aging," meaning they were free of chronic disease and had peak performance in physical, mental, and cognitive tests. (Some of the ideal aging criteria were easier to attain than others. The first on the list was "Being alive.")[5352]

The World Health Organization Guidelines for reducing the risk of cognitive decline and dementia encourage eating a diet centered around "[f]ruits, vegetables, legumes (e.g. lentils, beans), nuts and whole grains," while limiting added sugars, salt, saturated fat, and the trans fats found in processed foods and, naturally, in meat and dairy.[5353] Certain plant foods, however, may stand out.

Using the largest twin registry in the world, researchers concluded that "greater fruit and vegetable consumption may lower the risk of dementia and Alzheimer's disease."[5354] The reason it's so useful to study twins is that we can get special insight into environmental and dietary influences if one gets Alzheimer's and the other doesn't, since, genetically, twins are so similar. A meta-analysis of all such observational studies found that each additional serving (100 g) of fruits or vegetables a day was associated with a 13 percent reduction in the odds of cognitive impairment and dementia.[5355] Of the half dozen cohort studies that followed tens of thousands of people for up to thirty years, those in the highest category of fruit and vegetable consumption had a 43 percent lower risk of developing Alzheimer's disease compared to those who ate the least.

Any fruits and vegetables in particular? In a recent state-of-the-art review on preventing Alzheimer's disease specifically, the directors of Loma Loma Linda University's Alzheimer's Prevention Program laid out seven "key takeaways":[5356]

1. Reduce processed sugars.
2. Reduce fats, especially saturated fat.
3. Reduce animal products.
4. Reduce processed foods.
5. Consume more plants of all varieties, especially greens and beans.
6. Increase consumption of fruits, especially berries.
7. Reduce salt consumption.

Note that berries and greens were singled out, the brain foods of the fruit and vegetable kingdoms. Eating strawberries and spinach can mitigate age-related cognitive decline in rats.[5357] What about in people?

BLUEBERRIES

There are 8,000 different kinds of polyphenols found ubiquitously in foods of plant origin,[5358] but berries are packed with them.[5359] There is a subset of polyphenols called anthocyanins that are natural red, blue, and purple pigments capable of crossing the blood-brain barrier and localizing in brain regions involved in learning and memory.[5360] Given their powerful antioxidant and anti-inflammatory properties, aging researchers started feeding berries to rodents.

Older rats fed blueberries or strawberries experienced a reversal in age-related decrements of cognitive performance.[5361] The first experiments on older humans weren't published until 2010, starting with a small pilot study. Older men and women suffering from memory complaints were given either the juice equivalent of a whopping four to six cups of wild blueberries or a placebo drink each day for twelve weeks.[5362] The apparent cognitive improvements after the three months of the study were sufficient to inspire a more rigorous trial with a more modest daily serving size. Healthy men and women between the ages of sixty and seventy-five were randomized to the equivalent of one cup a day of regular (non-wild) blueberries (in freeze-dried powder form) or placebo (a blueberry-flavored and colored powder with the same calories, but no actual berries). Compared to placebo, the real berry group again experienced improvements in certain cognitive measures. The researchers concluded, "These findings show that the addition of easily achievable quantities of blueberry to the diets of older adults can improve some aspects of cognition."[5363]

The participants in the follow-up study were cognitively intact. Is it possible that one cup of regular blueberries is sufficient to boost cognition in healthy people, but five cups of wild blueberries are needed for the cognitively impaired? A study using a single cup of regular blueberries for mild cognitive impairment wasn't published until 2020. The randomized, double-blind, placebo-controlled trial found significant cognitive enhancement over placebo after a few months.[5364]

Even a single meal can do it. Multiple randomized controlled trials have shown that kids do significantly better on executive function and memory performance tests (but not reading) in the hours immediately following the consumption of the equivalent of about one and a half cups of wild blueberries compared to placebo.[5365,5366,5367,5368] Similar acute cognitive benefits within hours of consumption of a single dose of wild blueberries (one cup's worth) have also been demonstrated in adults, particularly in the context of more demanding tasks and cognitive fatigue.[5369]

Dairy Buries Berries

In the one trial that did not show clear beneficial effects of blueberry consumption, the berries were blended in milk.[5370] We've known for fifteen years that adding milk to black tea can completely blunt the positive effects of tea on artery function. The researchers blamed casein—a protein in milk that binds polyphenols and can prevent their absorption.[5371] The one plant-based milk that's been tested (soymilk) did not show the same irreversible binding.[5372] But eating milk chocolate or dark chocolate with a glass of milk blocks the absorption of about half of select cocoa polyphenols.[5373] Similarly, adding milk to coffee results in fewer than half of the chief polyphenols making it into your system,[5374] and the same happens with berries and cream.[5375]

Mixing strawberries with water causes a nice spike in strawberry anthocyanins in our blood over the next three hours, but that spike is cut by about half if the same strawberries are mixed with milk.[5376] It's the same with blueberries, as laid out in a study titled "Antioxidant Activity of Blueberry Fruit Is Impaired by Association with Milk." Researchers found that the total antioxidant capacity of our bloodstream shoots up within an hour of consuming a cup and a half of blueberries with water, and it remains elevated five hours later. With milk, one might expect less of a bump, but study participants ended up even worse than

when they started. After eating a whole bowl of blueberries, they had *less* antioxidant capacity in their body—because they ate them with milk.[5377] That could explain the lack of clear cognitive benefit in the berries and milk study, as well as the heterogeneity in blueberry blood pressure–lowering studies. The studies that used water showed a significant benefit, but the ones that incorporated milk or yogurt did not.[5378]

Aside from the milk study, fourteen out of fifteen randomized controlled trials of blueberries and mental performance found a significant improvement in at least one cognitive domain.[5379,5380] Four out of five interventional studies on improving artery function also found a blueberry benefit.[5381,5382] This may help explain some of the cognitive effects, as functional MRI scans have found blueberry consumption can improve blood flow to critical regions of the brain.[5383]

Most of the blueberry cognition studies were done on children or younger adults, but a few tried out berries on older populations. One found that taking fish oil alongside blueberries appears to eliminate any memory enhancement for some reason.[5384] Another suggested protection from postoperative cognitive dysfunction. General anesthesia can muck with the minds of the elderly. As many as one in four to one in three people over the age of sixty suffer a reduction in cognitive function after being put under on the operating table, and this can last for weeks or months.[5385] However, when older individuals were randomized to get a little more than a pint of blueberries' worth of blueberry juice a day for two weeks before getting elective major surgery, they suffered significantly less postoperative memory disturbance, compared to participants who got nothing.[5386] But, as we know, with a do-nothing control group, placebo effects cannot be ruled out. Some are of the opinion that it is too early to draw "definitive conclusions"[5387] and that blueberries are not ready to be "administered in routine clinical practice,"[5388] but what level of evidence do you need when we're talking about a food that's healthy anyway?

OTHER BERRIES

In rats, raspberries can ameliorate some of the learning and memory impairments induced by a high-fat diet,[5389] but cherries can also boost rat cognition,[5390] yet when put to the test in people, tart cherry juice failed to significantly improve outcomes compared to control beverages[5391] after taking into account the sheer number of variables tested.[5392] Cranberry juice also flopped.[5393] As I detail in see.nf/mindberries, a bunch of different berries were able to improve cognition in both the young[5394] and the old,[5395] though the longest interventional trial period has only been twenty-four weeks.[5396]

To see if short-term improvements in cognition translate into affecting the course of brain aging, we must look to observational trials that follow subjects for multitudes for years. For example, one study followed the cognition of hundreds of twins over a decade and found that the anthocyanins in less than a quarter cup of blueberries a day or around a daily cup of strawberries seemed to slow cognitive aging by four years.[5397] These results suggest that simply eating a handful of berries every day, an easy and delicious dietary tweak, may slow your brain's aging by years. That's one of the reasons I have them every day at breakfast.

VEGETABLE NITRATES

Of eighteen different food groups, consumption of vegetables was associated with the least brain volume loss over time.[5398] In cohort studies large enough to get even more granular, of all categories of vegetables, dark green leafies showed among the strongest protective association against cognitive decline.[5399,5400] Those eating green vegetables every day had 78 percent lower odds of suffering from cognitive impairment.[5401] The Rush Memory and Aging Project compared the cognitive decline over five years in men and women with an average age of eighty-one who ate green leafy vegetables every day versus those eating less than a serving a week and made an extraordinary discovery. Are you sitting down? Quoting from the study: "The rate of decline among those who consumed 1–2 servings per day was the equivalent of being 11 years younger compared with those who rarely or never consumed green leafy vegetables."[5402] So *now* are you sitting down … to a big salad?

In the Harvard Nurses' Health Study, the only category that appeared to beat out green leafies for cognitive function were cruciferous vegetables, like broccoli, cabbage, and cauliflower; veggies like kale and collards got double billing, straddling both groups.[5403] Broccoli sprout juice[5404] or straight sulforaphane,[5405] the compelling cruciferous component, shows a broad range of neuroprotective effects in vitro against everything from arsenic and carbon monoxide to pesticides and memory-erasing drugs. Sulforaphane has also been shown to be directly protective in various rat and mouse models of Alzheimer's disease,[5406] but it wasn't put to the test in people until recently.

The 2021 study involved randomizing older men and women to the amount of sulforaphane precursor found in three cups of broccoli[5407] each day for twelve weeks. It provided the first direct evidence that cruciferous vegetables may improve working memory and processing speed.[5408] However, given that population studies also single out non-cruciferous greens—spinach, for example, has even been referred to as an "anti-Alzheimer plant"[5409]—might other components in greens also play a role? For instance, what about nitrates?

As we age, our cerebral blood flow drops, which may influence cognitive decline and the development of neurodegenerative disease.[5410] This reduction in the amount of blood flowing through our brain may be due to an age-related decrease in the production of nitric oxide, that "open sesame" molecule that dilates our blood vessels, causing them to widen and thereby increasing blood flow. But production of nitric oxide can be boosted by the consumption of nitrate-rich vegetables, like leafy greens and beets, which is one of the reasons they can improve athletic performance. What about cognitive performance?

Check out see.nf/braingreens for all the studies, but basically, nitric oxide can not only improve brain function but maybe even structure—the development of connectivity networks more closely resembling those of younger adults. This was taken as evidence of the potential enhancement of neuroplasticity in older brains with nitrate-rich vegetables.[5411]

Dark green leafy vegetables are also one of the most concentrated sources of carotenoids[5412] and vitamin K.[5413] Higher levels of the plant-based vitamin K (*phylloquinone*, or vitamin K_1) are associated with higher cognitive function in centenarians, but that is not the case with higher levels of an animal-based form of vitamin K (*menaquinone-4*, a type of vitamin K_2). So, the higher levels of K seen in more cognitively intact centenarians may have just been a proxy for greens consumption. For example, blood levels of plant-based vitamin K were highly correlated with the levels of lutein,[5414] a carotenoid in greens that concentrates in the human brain.[5415]

Our brain is especially vulnerable to free radical attacks, due to its high fat content and cauldron of high metabolic activity.[5416] We certainly don't want our brain to go rancid. In my video see.nf/brainlutein, I review the importance of lutein for brain health, based in part on autopsy studies. If only there were a way we could physically look into the living brain with our own two eyes. There is—with our own two eyes!

The retina, the back of our eyeball, is actually an extension of our central nervous system. It's an outpouching of the brain during development, and, right in the middle, there's a yellowish spot. This is what doctors see when we look into your eye with that bright light. That spot, called the macula, is our HD camera, where we get the highest-resolution vision, and it's packed with lutein (from the Latin *luteus* for "yellow").[5417] Since levels in the retina can correspond to brain levels, our eyes can be a window into our brain, and indeed the amount of "macular pigment," which consists of lutein and other carotenoids in greens, like zeaxanthin, correlates with cognitive test scores[5418] and improvements of brain function[5419] and structure.[5420]

Where is lutein found? The avocado and egg industries like to boast about how much of these macular pigments is in their products, but the real superstars are dark green leafy vegetables. A half cup of cooked kale has fifty times more lutein than a hard-boiled egg; a spinach salad would offer more lutein than a fifty-egg omelet.[5421] Even Avocado Board–funded studies couldn't show guac-related benefits,[5422,5423] but adding as little as 60 g of spinach, which is like one-fifth of a 10-oz package of frozen spinach, can significantly boost macular pigment in most people within a month.[5424]

As you can see in see.nf/luteintrials, lutein/zeaxanthin supplements can improve vision[5425] and cognition,[5426] but while they can help both prevent and treat a leading cause of age-related vision loss[5427] (see the Preserving Your Vision chapter), supplements do not appear to improve the cognition of those already stricken with Alzheimer's disease.[5428]

Lion's Mane Mushroom

Small studies on about 1 to 3 g a day of powdered lion's mane mushroom (known, less palatably, as bearded tooth fungus) found some cognitive benefits for those with normal cognition[5429] and mild cognitive impairment,[5430] but not early Alzheimer's, though there was an improvement in the ability to perform activities of daily living, a measure of independence. Details on these studies and more in see.nf/mane.

COFFEE AND TEA

In the Adventist Health Study-2, the largest prospective study of plant-based eaters to date, I was surprised to see the average dietary polyphenol intake of nonvegetarians was *higher* than the vegetarians and vegans. Why would this be? Mainly because the nonvegetarians drank more coffee,[5431] which is the leading source of polyphenols in the United States.[5432] Is coffee consumption good for the brain? It's complicated, as I detail in see.nf/coffeetea, but basically, an apparent lack of overall association between coffee drinking and dementia may be obscured by deleterious effects of high coffee consumption[5433] potentially balancing out protective effects of low coffee consumption.[5434]

Data on green tea, however, appear to have a linear dose-response, meaning that any green tea consumption is better than none when it comes to risk of cognitive deficits, and the more, the better.[5435] Interventional studies have found that *black* tea can acutely improve attention and alertness,[5436] but population studies did not find it related to the risk of dementia or cognitive decline.[5437]

BRAIN-BOOSTING SPICES

Garlic compounds[5438] and extracts[5439] have been shown to ameliorate age-related cognitive dysfunction and reduce Alzheimer's neuropathology in rodents. To test garlic in people, young healthy volunteers were randomized to five weeks of twice-a-day capsules containing just an eighth of a teaspoon of straight garlic powder, like you would find at any grocery store. Compared to placebo capsules matched for color, texture, size, shape, and even smell, those getting the pinches of garlic powder experienced significantly improved memory and attention.[5440] As I detail in see.nf/brainspice, ginger may help in middle age,[5441] and as little as a quarter teaspoon of ground black cumin seeds can have positive cognitive impacts in both the young[5442] and the old.[5443]

KEEN AS A BEAN

The association between legume consumption and improved cognitive performance[5444] has been used to try to explain why dementia prevalence is lower in East Asia, where people eat ten to forty times more soybean products compared to those in the West.[5445] I review the conflicting population data in see.nf/brainsoy, but in terms of interventional evidence, there have been sixteen randomized controlled trials involving more than a thousand participants, and, overall, soy or soy compound interventions have been found to improve overall cognitive function and memory.[5446] For example, disguising soybeans in chili to randomize people to higher soy diets resulted in significant improvements in short- and long-term memory within ten weeks.[5447]

Some Are More Equol Than Others

There has been one randomized, double-blind, placebo-controlled trial of soy isoflavones in Alzheimer's patients. After six months, no cognitive benefits over placebo were found for a few daily servings of soy foods' worth;[5448] however, there was preliminary evidence of benefit among those who were equol producers.[5449] Among elderly

Japanese, equol producers also had less than half of the white matter brain lesions on MRI, compared to nonproducers.[5450] Check out see.nf/equol for details, but basically, some people benefit from soy even more than others since they have gut bacteria that can soup up an isoflavone in soy into an even more beneficial compound called equol.[5451]

About half of Japanese and Korean people can produce equol, but only about one in seven Americans can.[5452] Excessive use of antibiotics can wipe out our good bugs and turn an equol producer into a nonproducer, but how can we acquire the right bugs in the first place?[5453] There is a group of Westerners with high equol production rates: vegetarians, perhaps because they eat more fiber,[5454] or less dietary fat[5455] or cholesterol.[5456] Whatever it is about those eating plant-based diets, they may soon be the only remaining majority equol producers, as Asian populations continue to westernize their diets.[5457]

WHOLE GRAINS FOR WHOLE BRAINS?

Based on cross-sectional studies of thousands of men and women older than the age of fifty, high whole-grain intake is positively associated with the Successful Aging Index, a measure representing not only the avoidance of disease and disability but also the maintenance of cognitive function and engagement in physical, social, and productive activities.[5458] This was determined after attempts to control for various other dietary and lifestyle factors, but it's impossible to control for everything. When mice were randomized to barley instead of white rice, they lived significantly longer, suffered less hair loss, achieved a glossier coat, were better able to balance on a rod and hang upside down for longer, and retained better long-term spatial memory.[5459] In contrast, as I document in see.nf/braingrain, the human interventional evidence to date is underwhelming.

BRAIN HEALTH NUTS

Frequent nut eaters tend to live longer[5460] and think better,[5461] but that doesn't mean the nuts necessarily have anything to do with either. In see.nf/nutbrains, I address some of the factors confounding population studies on nut consumption. The bottom line is that evidence from interventional studies on nuts for cognition has been underwhelming, though a substudy of PREDIMED suggested that if you're eating half a handful of nuts a day, it may be worthwhile to go up to a full palmful, and if you're using regular olive oil, it may be worth the switch to extra-virgin.[5462]

FISH OIL FAIL

What about fish oil for brain health? A review of dementia risk reduction strategies compiled a list of common attributes of purportedly brain-healthy diets. People are encouraged to limit their intake of meat, including poultry, and fatty, sugary, and salty processed foods, as well as eat a predominantly plant-based diet rich in fruits and vegetables (especially berries and greens), legumes, and whole grains. But, there is also a tendency to encourage people to eat fatty fish.[5463]

Recommendations for fish consumption are based on observational data finding, for example, a significantly lower risk of Alzheimer's (but not dementia more broadly) in fish eaters,[5464] a significantly lower risk of dementia (but not Alzheimer's disease specifically) in fish oil supplement takers,[5465] and greater hippocampal volume associated with higher levels of omega-3s in the blood.[5466] Fish eaters also tend to eat more greens and berries, smoke less, exercise more,[5467] and have higher education levels than non-fish-eaters.[5468] Fish oil supplement takers also appear to eat more fruits and vegetables, smoke less, and exercise more than those who don't take those supplements, and they also tend to have higher socioeconomic status.[5469] To see if the apparent benefits of aquatic omega-3s from population studies are real and not just due to associated confounding factors, researchers have performed dozens of randomized, controlled, interventional trials.

There have been three randomized, placebo-controlled trials of omega-3s for Alzheimer's disease over periods of six, twelve, and eighteen months, and, unfortunately, they failed to show a cognitive benefit.[5470] Maybe the

study participants' disease had progressed so much by the start of the study that it was too late by then?[5471] The World Health Organization funded the latest and largest comprehensive review of long-chain omega-3s (from algae or fish) for cognitive outcomes, and researchers found no significant protection from cognitive impairment or dementia and only "clinically unimportant" effects on global cognition. The reviewers conclude: "People concerned about their cognitive health should be advised that taking long-chain omega-3 supplements is not helpful for cognition.…"[5472]

IS THERE A THRESHOLD EFFECT?

The concept of vitamins was first described by none other than Dr. Funk.[5473] In his landmark paper in 1912, he discussed the notion that there were complex compounds our body couldn't make from scratch, so we had to get them from our diet.[5474] By the mid-twentieth century, all the vitamins had been discovered and isolated,[5475] but it wasn't until the 1960s that we realized that certain fats were essential, too,[5476] including omega-3 fats concentrated in foods like flaxseeds and walnuts that our body can elongate into the long-chain omega-3s DHA and EPA, which we can also get preformed from algae or fish sources.[5477]

The fact that it took so long and under such extreme circumstances to demonstrate the essential nature of omega-3s (see.nf/essentialfats) illustrates how hard it is to develop overt omega-3 deficiency. Of course, the amount required to avoid deficiency is not necessarily the optimal amount for health. (See my scurvy example here.) There doesn't appear to be any cognitive benefit of long-chain omega-3 supplementation for the general public, but what about for those who don't eat fish?

Consider the famous Multidomain Alzheimer Preventive Trial, in which more than a thousand elderly individuals with memory complaints were randomized to DHA and EPA (in fish oil) or placebo for three years. Overall, the DHA and EPA had no significant effect on the rate on cognitive decline.[5478] However, most of the subjects were eating fish and thereby already getting preformed DHA and EPA in their diets. So, perhaps there is a threshold for protection and they all started out above it. Finding no benefit in general population studies like this cannot fully inform us about the role of long-chain omega-3s in brain health. That would be akin to

giving half of these people oranges, finding no difference in scurvy rates (zero in both groups), and concluding that vitamin C plays no role in scurvy.

What if you sifted back through the Multidomain Alzheimer Preventive Trial data and just looked at what happened to those who had low levels of fish consumption (as estimated by low blood levels of long-chain omega-3s)? That's exactly what the researchers did, and they found that for at least one measure of executive function, there was significantly less decline in the fish oil group compared to placebo.[5479] One always has to be careful with post hoc analyses, so the results are considered exploratory rather than conclusive. Nonetheless, this could potentially explain why clinical trials of long-chain omega-3s have so often failed. Perhaps it's because the studies were not focused on those who could benefit most—that is, those who start out with low levels in the first place.

OMEGA-3 SUPPLEMENTS

So, should people who don't eat fish consider taking DHA and EPA for optimal brain health? That's the question I address in see.nf/dhabrain. Jumping straight to the interventional evidence, a randomized, double-blind, placebo-controlled trial of cognitively intact elderly found both a significant improvement in executive function and significantly less brain shrinkage after about six months of long-chain omega-3 supplementation compared to placebo.[5480] A similar twelve-month trial of algae-based DHA in cognitively impaired elderly showed significantly improved cognitive function (including full-scale IQ) and volume of the hippocampus—that seat of memory in the brain—compared to placebo.[5481] So, having sufficient EPA and DHA long-chain omega-3s may be important for preserving brain function and structure, but what's "sufficient" and how do we get there?

As I describe in the video, those who don't eat fish tend to fall below a tentative omega-3 threshold that can be reached by taking 250 mg of a mix of pollutant-free (algae-derived) EPA/DHA. Technically, the only omega-3 that is truly essential is ALA, the plant-based, short-chain omega-3, because we can make DHA and EPA from it.[5482] However, the efficiency of this conversion varies and may decline with age.[5483] So, while most DHA supplementation trials in the general population fail to abate cognitive

decline,[5484] until we know more, non-fish-eaters should consider supplementing[5485] with 100 to 300 mg of DHA a day.[5486]

WHY NOT JUST EAT FISH?

The comprehensive World Health Organization review that failed to find appreciable cognitive benefits to long-chain omega-3 supplementation suggested that perhaps any upsides are counterbalanced by the potential neurotoxic contamination of fish and fish oil products with heavy metals, organochlorines, polychlorinated biphenyls, and polycyclic aromatic hydrocarbons.[5487] This may help explain studies that have found higher fish consumption predicting *worse* cognitive function.[5488] Most such findings have emerged from studies of children, but higher omega-3 levels have also been associated with higher levels of cognitive impairment and dementia in older adults.[5489]

Watch see.nf/fishbrain for details on the actual studies, but here's an illustrative case report: A ninety-one-year-old man with years of progressive memory loss was diagnosed with Alzheimer's disease. Cognitive testing showed he had dementia, and his friends and family assumed he was nearing the end of his life. However, a detailed history revealed that he had consumed swordfish once or twice a week for several years, and he was subsequently found to have severely elevated mercury levels. But, within ten months after high-mercury fish was removed from his diet, his mercury levels dropped to normal, his memory bounced back, and cognitive testing showed he no longer had dementia.[5490] So, it seemed he didn't have Alzheimer's disease after all but rather mercury poisoning from a handful of monthly meals of contaminated fish.

A systematic review and meta-analysis of toxic metals and Alzheimer's disease found that blood levels of mercury and another heavy metal, cadmium, were significantly elevated in Alzheimer's patients compared to controls.[5491] Switching to a plant-based diet can cut cadmium (and lead) levels in half within just three months, and lower mercury levels by 20 percent, as measured in hair samples, but the heavy metal levels bounce back when an omnivorous diet is resumed.[5492] Whether this helps account for the data showing two to three times lower dementia rates in vegetarians[5493] is unclear. Although blood levels of mercury are correlated

with Alzheimer's risk, brain mercury levels, assessed on autopsy, do not correlate with brain pathology.[5494]

Perhaps mercury blood levels are just markers for fish consumption and the real culprit is one of the other pollutants, like PCBs, that can get stuck in our body for decades.[5495] In that case, what about purified fish oil? The methods fish oil supplement manufacturers use, like distillation, leave considerable amounts of PCBs and other pollutants in the products, so much so that when taken as directed, salmon, herring, and tuna oils would exceed the tolerable daily intake for toxicity.[5496] Thankfully, one can get the benefits without the risks by getting DHA from algae instead,[5497] which is where the fish get it for themselves.[5498] So, we can cut out the middle-fish and get DHA at the bottom of the food chain, directly from the source.

BMAA in Seafood

Famed neurologist Oliver Sachs and colleagues solved a convoluted puzzle of a mysterious cluster on some exotic tropical isle of what seemed like three neurodegenerative diseases wrapped into one: ALS parkinsonism dementia complex.[5499] Affected natives were eating flying fox fruit bats who ate the seeds of the fruit of a tree that concentrated a neurotoxin called BMAA from blue-green algae that grow in its roots.[5500] As I document in see.nf/alsfish, BMAA gained global concern when it was then found in the brains of Floridians who died from Alzheimer's disease[5501] and in Florida seafood at levels comparable to the contaminated fruit bats.[5502]

In my follow-up video see.nf/alsdiet, I note that some researchers consider BMAA to be a strong contender as a major contributor to Alzheimer's disease,[5503] especially after monkeys fed BMAA-spiked food developed Alzheimer's-type pathology in their brains.[5504] The greatest strike against the theory, however, is that some of the autopsy studies—including the most comprehensive one—found no trace of BMAA in Alzheimer's brains at all,[5505] part of an ongoing

debate about the sensitivity of different testing methods.[5506] Until the matter is settled, some consider it prudent to try to limit exposure.[5507]

In addition to fish and crustaceans,[5508] BMAA is found concentrated in shark products and certain algae supplements. Shark fins (used for soup)[5509] have among the highest BMAA levels recorded,[5510] and fifteen out of sixteen shark cartilage dietary supplements were found to be contaminated.[5511] Of eighteen blue-green algae (*A. flos-aquae*) and spirulina supplements, eight contained toxins at levels exceeding the tolerable daily intake values, but only two contained BMAA.[5512] However, of five protein powder supplements containing spirulina that were tested, four turned up contaminated.[5513]

EAT FOR YOUR BRAIN'S HEALTH

Knowing what components or specific foods we should—or shouldn't—include to help protect our brain function is critical, but what is the best overall diet for preserving our mind?

GIVEN THE FINGER

Given the apparent efficacy of various individual lifestyle interventions, what if we combined some of them? The first large, randomized, controlled trial of a multidomain, lifestyle-based intervention for at-risk older adults was the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (or FINGER, for *FINnish GERiatric*), published in 2015.[5514] More than a thousand men and women in their sixties and seventies were randomized to either a combination of nutritional guidance, exercise, cognitive training, and vascular risk factor management or a control group receiving only regular general health advice. After two years, the improvement in cognition was significantly better in the lifestyle intervention group, though the effect size was small (0.13).[5515] (Effect size can be quantified as a "standardized mean difference" [SMD]. An SMD of 0.2 is considered small, 0.5 moderate, and 0.8 large.) On a population scale,

even small effects can have important public health implications, but why wasn't there a greater impact?

The rather modest results of interventional trials like FINGER have been used to argue against a major role for lifestyle behaviors in the prevention of dementia, but it may actually be because they didn't go far enough. For example, the recommended "brain-healthy diet"[5516] in the FINGER trial was no more than advice to eat four servings of fruits and vegetables a day, for example, and to choose lower-fat meat and dairy. It's true that the more participants stuck to the diet recommendations, the better they did, but small changes may only beget small results.[5517]

MEDITERRANEAN DIET

What about broader sweeping changes, like a Mediterranean-style diet? There have been dozens of observational studies following a total of nearly 100,000 people for three years up to twelve years that found those scoring higher on a Mediterranean diet index tended to have less of a decline in global cognitive function. However, the effect size was again relatively small,[5518] and there was no discernible reduction in the rates of incident dementia or mild cognitive impairment.[5519] About a dozen randomized controlled trials of Mediterranean-style diets have reported on seventy-two cognitive test outcomes, but only a small percentage—eight out of seventy-two—showed a statistically significant advantage.[5520,5521]

To see how the Mediterranean diet could be improved, researchers tried to tease out its protective components. Fish consumption showed no benefit, and neither did moderate alcohol consumption. The two critical pieces appeared to be vegetable consumption and the higher ratio between unsaturated fats and saturated fats, essentially the balance between plant fats and animal fats.[5522] Of all the dietary features of Mediterranean diet scoring, the one most linked to better cognitive performance and greater total brain volumes is reduced meat consumption.[5523]

MIND DIET

To devise a diet tailored to protect the brain, researchers at Rush University Medical Center chose components that reflected the most compelling evidence to create their Mediterranean–DASH Intervention for

Neurodegenerative Delay (MIND) diet. The DASH diet, which stands for Dietary Approaches to Stop Hypertension, was originally designed for cardiovascular defense. From it, they took its emphasis on reducing saturated fat, sweets, and meats (including fish). From the Mediterranean diet, they took dairy restriction and the emphasis on beans and nuts, but, instead of potatoes, the MIND diet took as its centerpiece the consumption of green leafy vegetables at least six times a week. And, instead of fruit in general, it specifically emphasized berry consumption. The MIND diet also gave people points for reducing their intake of fast food or fried foods to less than once a week.[5524] "Combining the two diets," the Academy of Nutrition and Dietetics summarized, "the MIND diet emphasizes natural, plant-based foods, specifically promoting an increase in the consumption of berries and green leafy vegetables, with limited intakes of animal-based and high saturated fat foods."[5525]

Watch see.nf/mind to see what it can do. In short, there have been about a dozen studies on the MIND diet, and they all found that greater adherence to it was associated with benefit to at least some aspect of cognition, with seven of the nine trials that measured global cognitive function finding benefits across the board,[5526] including up to a 53 percent lower risk of developing Alzheimer's disease.[5527] And, the side effects may include a longer life. Compared to the bottom third of MIND diet scores, those of an average age of seventy achieving the upper third had a 37 percent lower risk of dying in the subsequent twelve years.[5528] However, as of yet, there has only been one randomized controlled trial to properly test the diet. So far, so good, with the three-month pilot trial finding that those randomized to advice to follow the MIND diet had significant improvements in six out of eight cognitive measures.[5529]

The Harvard Nurses' Health Study was large enough to try to tease through the MIND diet's components to see what was predominantly driving the apparent benefit, and the researchers concluded it was the reduction in saturated and trans fats.[5530] If the key factor in the Mediterranean diet is meat reduction and the crux of the MIND diet seems to be cutting down on the saturated fat and trans fats in butter and junk, then what about trying whole food, plant-based nutrition?[5531]

In my video see.nf/antiaging, I explore the possible reasons why longtime vegetarians are as much as three times less likely to develop dementia.[5532] It could be because they're exposed to less saturated fat,[5533] cholesterol,[5534] animal protein,[5535] or AGE gerontotoxins.[5536] However, though just moving away from animal foods without regard to the healthfulness of plant-based replacements appears to protect from cognitive impairment,[5537] MIND diet scoring more closely aligns with cognitive performance than just scoring for reduction of animal products, suggesting that there may be benefits to the emphasis on healthy plant foods, like greens and berries.[5538]

So maybe it's also because plant-based diets protect against oxidative stress and inflammation.[5539] Dietary factors may also influence the effect of stress on cognitive decline. Diets characterized by high intake of animal proteins, saturated fats, and added sugars, along with low intake of plant-based foods, can increase the release of corticosteroid stress hormones like cortisol from the adrenal glands, which may promote the development of dementia.[5540]

The key takeaways for preventing Alzheimer's with diet are: Reduce added sugars, added salt, saturated fat, animal products, and processed foods in general, and eat more plants (especially greens and beans) and fruits (especially berries).[5541]

THERE ARE NO RANDOMIZED CONTROLLED TRIALS OF PARACHUTES

After reading this chapter, you might be surprised to see conclusions from systematic reviews on what we can do to prevent cognitive decline like this one: "The current literature does not provide adequate evidence to make recommendations for interventions."[5542] Researchers cite the lack of sufficient randomized controlled trials as a basis for these kinds of conclusions.[5543] Randomized controlled trials are undeniably the gold standard for testing new medications. The highest level of evidence is necessary because drugs kill an estimated 100,000 Americans every year. I'm not talking about overdoses, medication errors, or illicit drugs. Regular, FDA-approved prescription drugs are the sixth leading cause of death in the

United States.[5544] So, you'd better make absolutely certain the benefits of new drugs outweigh their potentially life-threatening risks.

However, if you're talking about healthy lifestyle behaviors, the side effects are all essentially good, so we arguably don't need the same level of evidence to prescribe them. In my video see.nf/rctdementia, I profile a "modest proposal" published in the *Journal of Alzheimer's Disease* for a series of randomized controlled trials for dementia prevention. I mean, how can we *really* know that traumatic brain injury raises dementia risk unless we randomize folks to get beaten in the head with baseball bats? Until we have randomized control data, how can we physicians recommend patients not get hit in the head? While we were at it, we could chain thousands to treadmills versus couches for a few decades or hook thousands on cigarettes.[5545] The editorial concluded: "It is time to realize that the ultimate study … in regard to lifestyle and cognitive health in aging *cannot be done*. Yet the absence of definitive evidence should not restrict physicians from making reasonable recommendations based on the evidence that is available."[5546]

Having said that, as I'm writing this in 2023, a randomized controlled trial to see if a whole food, plant-based diet and lifestyle program can slow down, stop, or even reverse the course of Alzheimer's disease is currently wrapping up. Dr. Dean Ornish and colleagues have randomized fifty-one patients with early Alzheimer's to essentially the same diet and lifestyle program he used to reverse the progression of heart disease, type 2 diabetes, hypertension, high cholesterol, and early-stage prostate cancer.[5547] With the recognition that this book would probably be published after their initial results were released, Dean gave me an exciting sneak peek at their preliminary findings—and what do you know: It looks like plant-based lifestyle changes are going to end up beating the new $50,000 biotech infusions for efficacy without causing your brain to swell and bleed.[5548]

PRESERVING YOUR MUSCLES

A loss in muscle mass is a characteristic of aging found in every species studied so far.[5549] In people, muscle mass tends to start to decline after age

thirty,[5550] accelerating after age fifty to a loss of 1 to 2 percent every year.[5551] By eighty, approximately 50 percent of the fibers in the muscles of our limbs are lost.[5552] The annual loss of muscle strength can be even more dramatic, suggesting a loss of muscle *quality* as well as quantity.[5553] This is not just because people tend to become less active with age.[5554] Even among master athletes like marathon runners and weight lifters who remain fit throughout their lives, performance tends to decline after about forty, dropping in half by age eighty.[5555]

A POUND OF FLESH

Excessive age-related loss of skeletal muscle mass, strength, and function is termed *sarcopenia*, from the Greek *sarx* for "flesh" and *penia* for "loss." Approximately 25 percent of us suffer from sarcopenia by our late sixties and 40 percent by the time we're eighty,[5556] with rates running as high as nearly 70 percent in those seventy and older living in nursing homes.[5557]

Sarcopenia is associated with not only an increased risk of falls but an overall shorter lifespan.[5558] The loss of muscle strength may be even more important, though, as it is tied to mortality regardless of muscle mass.[5559] This applies to both upper and lower body strength,[5560] though hand grip strength is commonly used as a proxy for total body strength.[5561] Every kilogram of force decline in annual grip strength is correlated with a 33 percent increased risk of mortality. Even grip strength in middle age is highly predictive of late life disability twenty-five years later.[5562]

Frailty is a closely related concept. Though recognized for centuries, its definition wasn't standardized until 2001.[5563] Frailty is defined as having at least three of the following five criteria: weakness (as measured by grip strength), unintentional weight loss (of ten pounds or 5 percent of body weight in the past year), exhaustion (self-reported), slow walking speed (based on the time to walk fifteen feet), and low physical activity.[5564] Individuals meeting one or two of the criteria are classified as "pre-frail."[5565] About one in forty are frail by age sixty-five, one in four after age seventy-five,[5566] and one in three of those older than eighty-five.[5567]

The heritability of muscle mass and strength may be as high as 50 to 60 percent.[5568] What can we do for the rest over which we may have some control?

USE IT OR LOSE IT

A study following sedentary Americans over the age of sixty-five for twelve years found that they lose about 1 percent of their muscle mass every year.[5569] In contrast, a similar study in Japan found age-related decreases in muscle mass "were trivial."[5570] Why the difference? In the Japanese study, the participants were informed of their results, so they often tried to improve through strength training before their next check-in. This was especially true among the middle-aged men, who got so competitive that their muscle mass may have actually *increased* with age, which shows that the steady loss of muscle mass with age is not inevitable. You just have to put in some effort.

Although we have yet to work out the best "dose"—timing, frequency, and repetitions[5571]—resistance exercise is considered the most effective strategy to prevent age-related muscle weakness,[5572] treat muscle loss,[5573] and improve physical function.[5574] For example, older men and women with an average age of seventy on a generic twenty-four-week strength training program with three sessions a week experienced about a 10 percent increase in leg muscle mass, a 40 percent increase in lower and upper body strength, and about a 20 percent decrease in sit-to-stand time,[5575] which is a measure of physical function that can predict fall risk.[5576] Exercise interventions are considered the key to maintaining the independence of frail and pre-frail individuals,[5577] but they can also reverse their frailty designation. Frail men and women with an average age of eighty were randomized to a program that combined endurance, strength, coordination, balance, and flexibility exercises for an hour a day, five days a week. All forty-nine of the individuals in the control group started out frail, and they remained frail. But sixteen of the fifty-one individuals in the exercise group (31 percent) reversed their frailty status within six months.[5578]

On the other hand, inactivity—or even a drop in activity levels—can actively make matters worse. Anyone would lose muscle mass after lying in bed for days at a time, but older adults on bed rest appear to lose muscle mass six times faster than younger people. Within just ten days of being on bed rest, older study subjects (average age sixty-seven) lost two pounds of lean leg mass,[5579] which is more than younger subjects (average age thirty-eight) lost in an entire month of bed rest.[5580] Immobilizing one leg in a knee

brace for four days caused a similar drop (about 10 percent) in muscle strength in young and old individuals, but, a week later, the strength of the subjects in their twenties was fully recovered, whereas the strength of those in their sixties still remained relatively impaired.[5581] This helps explain why 30 to 60 percent of elderly patients may lose some independence in basic activities of daily living in the course of a single hospital stay.[5582]

Even a milder form of disuse can lead to muscle atrophy. Elderly men and women were asked to reduce their activity by dropping their daily step counts from their moderately active 6,000 steps a day down to around 1,400 daily steps. Within just two weeks, they lost about 4 percent of the lean mass in their legs, about 1.3 pounds. The investigators concluded, "This superficially 'benign' intervention of simply reducing daily steps demonstrates just how deleterious a period of inactivity … can be for older persons."[5583] This is especially worrisome given that older adults have such difficulty even with heavy strength training to recover muscle losses due to disuse and neglect. Use it or lose it—sometimes for good.

DEFUELING THE FLAMES

In the step-reduction study, the decline in activity was accompanied by an increase in markers of inflammation. For example, researchers found a 25 percent rise in the subjects' C-reactive protein levels within two weeks of reducing their step counts.[5584] The muscle wasting in cancer is mediated by inflammation; what about the muscle wasting of aging?[5585] Those suffering from sarcopenia,[5586] pre-frailty, and frailty[5587] do indeed tend to have higher levels of systemic inflammatory markers, such as C-reactive protein, which are independently associated with lower muscle mass and diminished upper and lower body strength.[5588] This has led to suggestions that anti-inflammatory diets may help.[5589]

Meta-analyses of observational studies, including a representative sample of the U.S. population,[5590] have found up to twice the odds of sarcopenia[5591] and frailty[5592] for those eating more pro-inflammatory diets. Eating high on the Dietary Inflammatory Index has also been associated with low grip strength, low walking speed,[5593] and impairment in the activities of daily living. This has all led to the proposal that chronic

inflammation is a "key underlying mechanism" of frailty, but observational studies can't prove cause and effect.[5594]

An inflammatory trigger would help explain why saturated fat—the single most pro-inflammatory component of the Dietary Inflammatory Index[5595]—is associated with greater risk of sarcopenia.[5596] Compared to those getting about 8 percent of their calories from saturated fat—which meets the U.S. federal recommendation of less than 10 percent[5597] but exceeds the American Heart Association's advice to stay below 6 percent[5598]—those getting twice as much (16 percent) lost the amount of lean mass that you generally see with ten years of aging.[5599] This may help explain why the leg muscles of CrossFit trainees eating a ketogenic diet may shrink by as much as 8 percent.[5600] However, a more likely explanation is that without enough of the preferred fuel (carbohydrate), their bodies started burning more of their own protein.[5601] What about all the protein they were eating, though?

HUMAN PROTEIN REQUIREMENTS

In my video see.nf/proteinhistory, I trace the saga of enthusiasm for protein in the nutrition world,[5602] peaking with what was called the Great Protein Fiasco,[5603] followed by a massive downward recalculation of human protein requirements by the 1970s.[5604] To this day, however, some still obsess about protein.[5605] For example, those promoting Paleolithic diets try to make the case for protein from an evolutionary perspective.[5606]

One food, however, has been fine-tuned over millions of years to contain the perfect amount of protein just for us:[5607] human breast milk, which may actually have the lowest protein concentration compared to any other animal in the world, at less than 1 percent protein by weight.[5608] This is one of the reasons why dairy milk can be so dangerous for babies.[5609] Although the protein content in breast milk has been described as "extremely low," it's exactly where it needs to be—at the natural, normal level for our species.

The "low" protein level in human breast milk (about 6 percent of calories) doesn't mean that's all that adults need. At that level, elderly individuals would not be able to maintain their muscle mass.[5610] Adults can weigh ten times more than infants, but we only eat about four or five times

more than babies do, so our food needs to be more concentrated in protein. Nevertheless, people tend to get about twice as much as they need.[5611] The recommended dietary allowance (RDA) is 0.8 g of protein per kg of body weight per day for all adults regardless of age, which is about your ideal weight in pounds multiplied by four and then divided by ten. So, someone whose ideal weight is 100 pounds may require up to 40 g of protein a day. On average, they probably only need about 30 daily g of protein, which is 0.66 g per kg, but we round it up to 0.8 g because everyone's different and we want to capture most of the bell curve.[5612] As I'll detail in the Protein Restriction chapter, people may be more likely to suffer from protein excess than protein deficiency.[5613]

Some advocate for protein intake for older individuals in excess of the official recommendations. Among them, not surprisingly, are consultants for the National Cattlemen's Beef Association and members of the Whey Protein Advisory Panel for the National Dairy Council.[5614] They argue that age-related muscle loss may be a consequence of "anabolic resistance" among the elderly, a diminished muscle-building response to weight training or protein intake, but most studies have failed to detect such a phenomenon.[5615] Indeed, the most comprehensive[5616] study on the protein needs of healthy adults found no difference in protein requirements with age,[5617] and authorities in the United States,[5618] the EU,[5619] and globally[5620] agree. However, just because the elderly don't *require* more protein doesn't necessarily mean they wouldn't benefit from more. And what about *unhealthy* adults already suffering from frailty or sarcopenia?

DOES EXTRA PROTEIN INCREASE MUSCLE MASS OR STRENGTH?

I do a deep dive in see.nf/muscleprotein, but basically, when all the studies on protein or amino acid supplementation for older men and women were put together, overall, there was no significant improvement in lean body mass or upper or lower body muscle strength.[5621] Even the term "lean body mass" can be misleading.[5622] Because high protein intake alone can cause liver and kidney swelling,[5623] an increase in total body lean mass may just be a reflection of "increased visceral organ size"[5624] or water retention.[5625]

In nonfrail older adults, extra protein or essential amino acid supplementation appears to have little[5626] or no[5627] effect on muscle mass,

strength, or performance when taken alone or added to an exercise regimen. What about in those who really need it—sarcopenic, pre-frail, or frail individuals? One of the first things doled out by doctors is a "nutrition shake" like Ensure, typically an ultraprocessed sugary mess of corn syrup, oil, and protein concentrates, often laced with artificial colors, flavors, and sweeteners. Though Big Pharma giants like Abbott Laboratories (makers of Ensure) spend millions of dollars a year in lobbying and campaign contributions to help make these products medicine's go-to choice,[5628] a systematic review and meta-analysis of randomized clinical trials on such drinks for the management of frailty published in 2021 found no discernible benefit for any measured outcomes—muscle mass, muscle strength, muscle function, frailty status, cognitive function, or mortality.[5629]

Researchers have been trying to find effective ways to treat sarcopenia for decades, and, so far, only resistance exercise has consistently yielded benefits.[5630] One of the largest and most rigorous studies to treat pre-frail and frail adults was published in 2021. Hundreds were enrolled to test the effects of leucine, whey protein, soy protein, creatine, and a combination of creatine and whey versus a placebo control (cornstarch) in the context of a sixteen-week resistance training program. The strength training itself worked, increasing muscle mass and function, but everything else flopped. No added benefit to frail or pre-frail individuals taking any of those supplements compared to taking the cornstarch placebo.[5631]

IN HARM'S WHEY

I was surprised that neither milk[5632] nor milk protein[5633] was able to bulk up people more. After all, milk is naturally designed to put a few hundred pounds on a baby calf within just a few months. Of all proteins, the milk protein whey stimulates the greatest response in terms of short-term muscle protein synthesis, likely due to its high concentration of leucine, the amino acid that triggers mTOR. (If you remember from the mTOR chapter, that's the enzyme that accelerates growth but may also accelerate aging.) Straight leucine supplements also fail to add muscle.[5634] If leucine stimulates muscle protein synthesis, why doesn't this translate into greater muscle mass?

Muscle tissue is in constant flux.[5635] Every day, our entire musculature undergoes about a 2 percent turnover rate. Giving people a bolus of

specially tagged protein, researchers were able to follow it through the body. About 10 percent of it gets socked away in our muscles within hours after consumption.[5636] In other words, we are what we just ate. Surprisingly, though, there is no correlation between these acute changes in muscle protein creation and long-term changes in muscle mass,[5637] as verified by MRI scans.[5638]

We used to think protein timing was important and that there was a narrow window of opportunity right after exercising to boost muscle growth, but again, the short-term measures don't predict long-term results. Instead, strength training appears to increase overall muscle protein-making capacity for whenever the protein is available.[5639] This realization led to the busting of another protein myth—the thought that it was better to spread protein intake throughout the day since muscle protein synthesis maxes out at a certain dose.[5640] If anything, when actually put to the test, the opposite result was found.[5641,5642,5643,5644]

This also explains why plant proteins can accrue muscle on par with animal proteins.[5645] For example, even though the acute muscle protein synthesis to whey protein is greater than soy protein in the immediate hours after consumption,[5646] the accretion of muscle mass and strength is the same. Even beef studies funded by the National Cattlemen's Beef Association weren't able to show a difference,[5647,5648] just as American Egg Board–funded studies failed to find muscle benefits from adding eggs.[5649,5650] However, JUST Egg, a plant-based egg patty made out of mung beans, did seem able to improve muscle strength, at least in what appeared to be a post hoc analysis of an eight-week randomized controlled trial.[5651]

So, in the end, whey protein may just leave one to suffer added mTOR activation side effects.[5652] Superficially, this includes the acne endured by whey-supplementing athletes[5653] and bodybuilders.[5654] More important, dermatologists editorialized that restricting dairy could help "prevent more serious mTOR … -driven diseases of civilization like obesity, diabetes and cancer."[5655] In a bid to slow muscle wasting in cancer, for example, researchers tried giving leucine to cancer-ridden mice but only ended up doubling the growth of their tumors.[5656] The isoflavone phytoestrogens in soy may do the opposite—suppressing mTOR, at least in mice[5657]—while alone boosting human lean mass independent of the protein in a randomized, double-blind, placebo-controlled trial.[5658] Just the isoflavones

alone boosted fat-free limb mass at a daily dose equivalent of about three-quarters of a cup of tempeh, two-thirds of a cup of boiled soybeans, or a half cup of soy nuts.[5659]

PLANT PROTEIN PREFERRED

The association between plant-based dietary patterns and muscle mass, strength, and function is inconsistent,[5660] but some studies have shown that plant protein in particular is linked to a lower risk of sarcopenia,[5661] pre-frailty, and frailty,[5662] improved physical performance,[5663] and more successful aging, as measured in scales that take into account functional impairments, self-reported vitality, mental health, chronic diseases, participation in social activities with friends and family, and the number of yearly excursions.[5664] Researchers suggest it might be due to differences in the protein itself, such as the lower methionine content benefit in plant proteins I'll cover in the Protein Restriction chapter, but it could also be from the nutritional baggage that accompanies protein from animal sources.[5665]

Food is a package deal. If you go to the Harvard School of Public Health's web page on protein, you'll see that it emphasizes the source rather than the amount of protein as being most consequential for health. This is because foods present a "protein package," which can contain saturated fat and sodium on one hand, or antioxidants and fiber on the other. This is why its number one tip for making the best protein choices is "Get your protein from plants when possible."[5666]

Aren't Plant Proteins Inferior and Incomplete?

All nutrients come from the sun or the soil. Vitamin D, the "sunshine vitamin," is created when skin is exposed to sunlight, and everything else comes from the ground. Minerals originate from the earth, and vitamins from the plants and microorganisms that grow from it. The calcium in a cow's milk (and in her two-hundred-pound skeleton) came from all the plants she ate, which drew it up from the

soil. We can cut out the middle-moo, though, and get calcium directly from the plants.

Where does protein come from? Protein is made up of an alphabet of amino acids, most of which we can make from scratch, but some are "essential," meaning our body can't make them so they're essential to get from our diet. But other animals don't make them either. All essential amino acids originate from plants and microbes, and all plant proteins have all the essential amino acids.[5667] The only truly "incomplete" protein in the food supply is gelatin, which is missing the amino acid tryptophan, so the only protein source you couldn't live on is Jell-O.[5668]

Those eating strictly plant-based diets average about 20 percent more protein than the recommended daily allowance.[5669] Those who don't know where to get protein on a plant-based diet *don't know beans*. (Legumes like beans, split peas, chickpeas, and lentils are the protein superstars of the plant kingdom, but protein is found in all whole plant foods to varying degrees.) That's protein quantity, though. What about protein *quality*?

The concept that plant protein was inferior to animal protein arose from studies performed on rodents more than a century ago. Scientists found that infant rats don't grow as well on plants.[5670] However, infant rats don't grow as well on human breast milk either. Does that mean we shouldn't breastfeed our babies? Of course not! Rat milk has ten times more protein than human milk[5671] because baby rats grow about ten times faster than baby humans.[5672]

It is true that some plant proteins are relatively low in certain essential amino acids. So, almost fifty years ago, the myth of "protein combining" came into vogue—literally, in the February 1975 issue of *Vogue* magazine. As I detail in see.nf/combining, this fallacy was refuted decades ago.[5673] Outdated concerns about plant protein digestibility have also been effectively debunked based on updated human data.[5674] We know from muscle biopsies, DXA scans,

ultrasound imaging, and strength testing that both vegans and omnivores have comparable muscle gains in response to resistance exercise.[5675]

ANTIOXIDANTS FOR AGE-RELATED MUSCLE LOSS?

Antioxidants could be one muscle-preserving component of the plant protein package. Oxidative stress is suggested to play a central role in the onset of sarcopenia.[5676] For example, mice missing a major antioxidant enzyme suffer a dramatic acceleration of age-related muscle loss,[5677] and some epidemiological studies have tied higher antioxidant intake with increased grip strength and faster walking speed.[5678] Human muscles are certainly highly responsive to vitamin C intake. Even half a kiwifruit can triple muscle concentrations. That's where an estimated two-thirds of our body's vitamin C is pooled.[5679]

Vitamin C is necessary as an enzyme cofactor for the synthesis of both collagen and carnitine, and thereby plays a key role in muscle structure and function.[5680] However, the observational data relating vitamin C intake and/or blood levels with muscle outcomes are mixed. Three of the five studies on vitamin C and muscle mass measures, including the largest one, found a protective association,[5681,5682,5683] while the other two studies found no association either way.[5684,5685] The hand grip data are similarly split,[5686,5687,5688,5689] though all three of the frailty studies found a protective association,[5690,5691,5692] but so did only one[5693] of the four studies on vitamin C and the prevalence of sarcopenia.[5694,5695,5696] I couldn't find any interventional trials on treating frailty or sarcopenia with antioxidants, but there have been randomized controlled trials using vitamin C and/or vitamin E supplements to boost resistance training gains in lean mass, muscle strength, or performance over placebo, but they all universally failed.[5697] The more consequential component of the plant protein package may be fiber.

FIBER FOR FRAILTY

There seems to be a microbiome "signature" of frailty. Fecal samples from frail individuals show a striking lack of bacterial diversity[5698] and, in

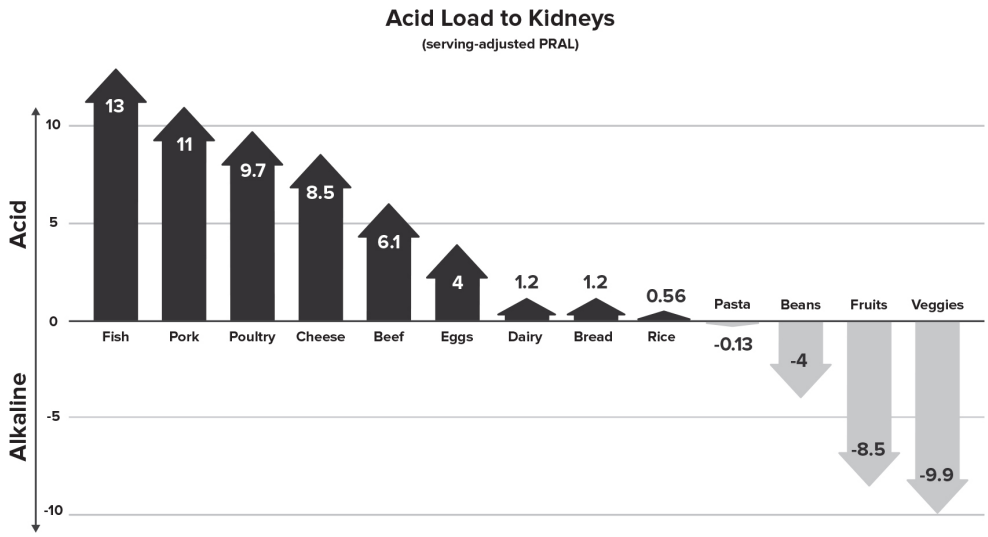
particular, a deficit of fiber-eating "good bacteria"[5699] such as *Lactobacillus*.[5700] Fecal transplant studies I feature in see.nf/musclefiber peg it as a cause, just not a consequence, of the condition, and interventional studies show that randomizing people to fiber-rich foods,[5701,5702] prebiotics,[5703] or certain probiotics can improve performance.[5704] I conclude it's probably preferable to foster the growth of our own fiber feeders by feeding them fiber, which has the dual benefit of also cutting down[5705] on protein putrefaction toxins like indoxyl sulfate[5706] thought to play a role in muscle wasting.[5707]

CAUGHT OFF BASE

As we age, the ability of our kidneys to excrete acid declines.[5708] To buffer the acid, our kidneys produce the base ammonia from the amino acid glutamine, which it can effectively pull from our muscles.[5709] As acid levels rise, our adrenal glands release stress hormones like cortisol, which degrade our muscle proteins,[5710] releasing glutamine and other amino acids our liver can turn into glutamine, which then allows our kidneys to generate ammonia to neutralize the acid.[5711] So, part of the muscle breakdown as we age may be our body's attempt to maintain its pH (acid/base) balance.[5712] Potassium bicarbonate supplements have been shown to improve muscle performance,[5713] but as I detail in see.nf/muscleph, the best way to keep our kidneys from dipping into the protein stores from our musculature may be to eat an acid-neutralizing (alkaline, or base-forming) diet.[5714]

HOW TO REDUCE YOUR DIETARY ACID LOAD

Note in the below figure that not all plant foods are alkalinizing and not all animal foods are equally acidifying. Fish, including tuna, is the single most acid-producing food, followed by pork, poultry, cheese, then beef. (Actually, eggs are more acid-producing than beef on a gram-for-gram basis, but people tend to eat less of them at one sitting.) Some grains can be a little acid-forming, such as bread and rice, but, interestingly, not pasta. Beans are significantly acid-*reducing*, but not as much as fruits are, even tart ones like citrus. Vegetables are crowned as the most alkaline-forming foods.[5715] However, beans and other legumes are the only major sources of protein that are alkaline-forming instead of acid-forming.



A strictly plant-based diet can flip our diet from acid-forming to net alkaline and significantly raise urine pH, whereas eating plant-based just a few days a week has been found to reduce the acid load but not eliminate it.[5716] Vegans have to actually eat their vegetables, though.

Salt intake also appears to increase stress hormone production through an acid/base mechanism,[5717] potentially explaining why high-salt diets are associated with reduced muscle function.[5718] So, we should also aim to cut down on processed foods, which are the source of about 75 percent of sodium intake in the United States.[5719]

Drop Acid

Our dietary acid/base imbalance doesn't only affect muscle health. For millions of years before we learned how to hunt or mine salt, our ancestors ate a net neutral or alkaline-generating diet.[5720] The shift to an acid-generating diet has been implicated in a wide range of disorders, including osteoporosis, type 2 diabetes, high blood pressure, kidney stones, depression, anxiety,[5721] gout,[5722] and renal failure.[5723] When mice were given alkaline water to drink, their telomeres elongated[5724] and their survival increased compared to controls,[5725] leading to editorials like "Is $NaHCO_3$ [baking soda] an Antiaging Elixir?"[5726] In

see.nf/bakingsoda, I explain why it's preferable to alkalinize from the produce aisle.

MUSCLE FOODS

Higher fruit and/or vegetable intake is also linked to half the odds of sarcopenia,[5727,5728] nearly half the odds of developing slow walking speed,[5729] and about a third reduced odds of weak grip strength and poor physical performance,[5730] but the only three fruits and vegetables for which I could find interventional studies on this topic are blueberries,[5731] garlic,[5732] and spinach.[5733] As I detail in see.nf/musclefoods, all three improved muscle quality, performance, mass, and/or strength.

JOE SIX-PACK

Coffee also prevents muscle loss in aging rodents. I discussed the role of coffee boosting autophagy in the Autophagy chapter. Muscle tissues have one of the highest autophagy rates, which is considered essential for muscle integrity.[5734] Mice deficient in autophagy develop a severe loss of muscle mass and strength,[5735] so the "autophagic failure" of aging may play a role in our age-related decline in muscle mass.[5736] This led researchers to try putting diluted coffee in the water bottles of aged mice. Compared to the mice randomized to drink plain water, those that stopped and smelled (and drank) the coffee ended up with 13 percent greater muscle mass in their hind limbs and 18 percent greater grip strength after a single month. I know what you're thinking: The caffeinated mice must have been buzzing on the exercise wheel. But, no. The muscle gains occurred without changes to their activity levels.[5737]

Epidemiological studies have tied greater coffee drinking with higher physical performance[5738] and a greater muscle mass index,[5739] less functional disability at two or more cups a day,[5740] and less sarcopenia at three or more daily cups.[5741] But reverse causality often cannot be excluded in observational studies. Maybe those with reduced mobility are less likely to buy or prepare coffee, or perhaps they have fewer opportunities to drink it socially.[5742] That's where interventional studies come in.

An analysis of more than twenty meta-analyses on caffeine and exercise performance found caffeine to be ergogenic (performance-enhancing) for aerobic activity and muscle strength, power, and endurance,[5743] based on studies going back more than a century.[5744] However, most of the studies have been performed on young men after a single acute dose, typically the amount of caffeine found in two cups of coffee taken around an hour before the activity.[5745] Caffeine does seem to improve functional fitness,[5746] balance, and endurance[5747] in older men and women, as well, but this again was following an acute dose. When young people drank three cups of coffee a day for a month, though, their fat-free mass went up by about a pound while their fat mass dropped one to two pounds.[5748] Coffee can bulk up mice,[5749] but no word yet on older humans.

A POWDER KEG

Cocoa beans may help, too. Three tablespoons of cocoa powder a day significantly improves walking performance.[5750] Unfortunately, as I explore in see.nf/cocoamuscles, the tastiest cocoa doesn't work. Researchers randomized older adults to either natural cocoa, highly Dutched (alkalinized) cocoa, or placebo, and the Dutched cocoa didn't help any better than placebo. Some of the bitter compounds that are removed in the Dutching process are the flavonoid phytonutrients thought responsible for the beneficial effects. But older men and women given a tablespoon of natural, unprocessed cocoa a day for twelve weeks experienced a significant improvement in muscle mass index, grip strength, and all four physical function tests.[5751] And, refreshingly, the study was *not* funded by Hershey, as were many of the others.

CREATINE

I address the shortcomings of HMB (ß-hydroxy ß-methylbutyrate), magnesium, omega-3s, and vitamin D supplements for age-related muscle loss in my video see.nf/hmb, but there is a supplement that may help: creatine.

Creatine is a compound formed naturally in the human body that is primarily involved with energy production in our muscles and brain.[5752] It's

also naturally formed in the bodies of many other animals, including those we may consume, so when we eat their muscles, we can take in some extra creatine through our diet. (The compound was named after *kreas*, the Greek word for "meat," in which it was first isolated.[5753]) We need about 2 g a day, so those who eat meat may get around 1 g from their diet and their body makes the rest from scratch. There are rare birth defects where you're born without the ability to make creatine, in which case you have to get it from diet,[5754] but, otherwise, our body can make as much as we need to maintain normal concentrations in our muscles.[5755]

When people cut out meat, the amount of creatine floating around in their bloodstream goes down,[5756] but the amount in their brain remains the same, because our brain just makes all the creatine it needs.[5757] The level in vegetarians' muscles is lower,[5758] but that doesn't seem to affect performance, as both vegetarians and meat eaters respond to creatine supplementation with similar increases in muscle power output. If the creatine in vegetarians' muscles was insufficient, then presumably it would have had an even bigger boost.[5759] So, basically, when you eat meat, your body just doesn't have to make as much.[5760]

If creatine muscle content dropped as we grew older, that might help explain age-related muscle loss, but that doesn't seem to be the case. Biopsies taken from the muscles of younger and older adults show no difference in creatine content.[5761] Still, if it improves performance, maybe more would help. According to the International Society of Sports Nutrition, creatine monohydrate is the single most effective ergogenic supplement available to athletes for increasing exercise capacity and lean body mass during training.[5762] It's no wonder surveys show that 70 percent or more of athletes have used creatine supplements.[5763,5764] What can it do for older adults?

Without exercise? Nothing. Most studies on creatine supplementation alone show no benefits for muscle mass, strength, or performance.[5765] This makes sense, given the mechanism. Creatine supplementation delays muscle fatigue, which enables people to work out longer and harder. It's that additional volume and intensity that lead to the muscle benefits. So, creatine alone doesn't help, and creatine taken in the context of the same training that's carefully controlled and deliberately equalized doesn't help either.[5766] But, when older people are allowed to exercise as much as they

can, most studies on the prevention and treatment of sarcopenia with creatine supplementation show augmented lean mass,[5767] as it does in young adults.[5768]

Adding 3 to 5 g of creatine a day and two to three days of resistance training a week led to an additional three pounds of lean mass over an average duration of about four months.[5769] Some of this lean mass may be water weight, though, not muscle. Creatine causes water retention that can show up as lean mass,[5770] but, compared to placebo, creatine combined with resistance exercise increases muscle strength, as well.[5771] And, the additional gains in mass and strength can persist at least twelve weeks after stopping the creatine in older adults, as long as the resistance training is maintained.[5772]

A reason I never advocated for creatine supplementation in older adults for muscle preservation was that systematic reviews up through 2017 concluded that adding creatine to training increased muscle mass and strength, but this did not appear to translate to improved functioning.[5773] However, in 2019, an updated meta-analysis found a significant improvement over placebo in sit-to-stand test performance,[5774] which is a decent predictor of reduced falls risk.[5775] Again, this was only when accompanied by strength training. There have still been no consistent benefits discovered for supplementing with creatine alone. So, creatine should always be prescribed with a progressive strength-training regimen.[5776]

The Society on Sarcopenia, Cachexia and Wasting Disease convened an expert panel who, despite the lack of long-term trials, suggest creatine be used for the management of sarcopenia.[5777] The recommended dose to achieve muscle saturation is 3 g a day.[5778] Within a month at that slow and steady rate, you achieve the same muscle levels as loading with 120 g over a period of a week.[5779] Note, though, that for older adults, it takes at least twelve weeks of creatine-supplement resistance training to see a significant additive effect.[5780] Recent evidence suggests that taking creatine after exercise might be slightly preferable to taking it before, but this has yet to be verified.[5781]

Are there any side effects? Well, if one can extrapolate from mice, one side effect may be longevity. The average healthy lifespan of creatine-fed mice was found to be 9 percent longer than control mice, and those on

creatine performed better on neurobehavioral tests, especially improved memory skills.[5782] But, is taking creatine safe? That's the question I explore in detail in see.nf/creatinerisk.

In short, the only serious side effects appear to be among those with preexisting kidney impairments or those taking whopping doses of 20 g or more a day for four weeks or longer,[5783] though as many as half of creatine supplements exceeded the maximum level recommended by food safety authorities for at least one contaminant.[5784] One third-party supplement testing outfit that checked for impurities chose as its top pick the BulkSupplements brand, which also happened to be the cheapest at about ten cents per daily 3-g serving, which is about a level teaspoonful.[5785]

Essential Tremor

In *How Not to Die*, I extensively address Parkinson's, since it's one of our leading killers, but the most common movement disorder is what's called *essential tremor*—affecting one in twenty-five adults over the age of forty and up to one in five of those in their nineties.[5786] In addition to the potentially debilitating hand tremor, there can be other neurological manifestations, including cognitive impairment, depression, and sleeping problems.[5787] As I explore in see.nf/tremor, most of the attention has focused on a class of tremor-producing chemicals called *beta-carboline alkaloids*,[5788] a type of heterocyclic amine, the class of carcinogens that are formed in a high-temperature chemical reaction between some of the components of muscle tissue.[5789]

For those reluctant to reduce their meat consumption, different marinades have been tested to reduce the formation of these compounds. Hibiscus extracts failed to alter levels[5790] and red wine made things nearly ten times worse,[5791] but a Caribbean marinade[5792] and a variety of berry extracts helped. For example, marinating camel meat in strawberry juice for twenty-four hours before frying can

reduce the formation of one beta-carboline alkaloid as much as 40 percent.[5793]

Are there any dietary treatments once you already have the disease? Vanillin—the primary fragrant compound in vanilla extract—was found to be beneficial against tremors induced by these chemicals in rats, but there have yet to be any clinical studies.[5794]

PRESERVING YOUR SEX LIFE

There is a stereotype of older adults as asexual, but this is ageist and inaccurate.[5795] Sex is a valued part of our full adult lives, as evidenced by the fact that the vast majority (85 percent) of surveyed nursing homes report residents engaging in sex acts.[5796] However, sexual activity does tend to decline with age. Though some blue zone nonagenarians continue to be able to "honestly vouch" for their active sex lives,[5797] a national U.S. survey of thousands of older adults found a progressive decline in sexual activity with age, from 73 percent of people between the ages of fifty-seven and sixty-four down to just 26 percent of those aged seventy-five to eighty-five.[5798] Of that 26 percent, most (54 percent) had intercourse two to three times a month, but 23 percent had sex at least once a week. The drop in sexual activity may have less to do with age per se and more to do with declining health.[5799]

The number one reason given for lack of sexual activity among older adults was their or their partners' physical health problems or limitations. This implies that general body upkeep can help keep people actively engaged in all life has to offer, but approximately half of older men and women report specific issues, most often low sexual desire in women and erectile difficulties in men.[5800] Although only a minority appear distressed by these sexual problems,[5801] sexual dysfunction can be a canary in the coal mine for broader health issues.[5802]

In a study in which more than 2,000 men and women were followed for about six years, those with a higher frequency of sexual activity had a significantly lower risk of dying. Those having sex fifty-two or more times

a year (approximately weekly) seemed to have only half the mortality rate compared to those having sex once or less a year, even after controlling for physical activity and health conditions, such as obesity, high blood pressure, diabetes, or heart disease. Even though sexual activity may just be an indicator of general health, it might also have protective physical and mental health benefits.[5803] For example, endorphins—feel-good chemicals released during sex—have been shown to improve natural killer cell function.[5804]

Researchers suggest that the reduction in premature death risk may be because sex is a form of exercise, but people may overestimate their exertions in bed.[5805] One of the "Seven Myths About Obesity" identified in *The New England Journal of Medicine* is that a bout of sexual activity burns a few hundred calories.[5806] So, you may think, *Hey, I could get a side of fries with that!* If you hook people up (literally *and* figuratively) and actually measure their oxygen consumption during the act (assuming they don't get too tangled up in all the wires and hoses), having sex only turns out to be the metabolic equivalent of bowling. The average bout of sexual activity may only last about six minutes, and a young man might expend approximately twenty-one calories during intercourse. Because of baseline metabolic needs, he would have spent roughly one-third of that just lounging around watching TV, so the incremental benefit is plausibly on the order of fourteen calories.[5807] So, maybe he can have one fry with that.

Whether a cause or consequence of ill health, sexual difficulties can be improved with lifestyle changes. Smoking cessation, exercise, and a healthier diet—for example, higher fruit and vegetable intake—have been associated with lower risk of both male and female sexual dysfunction.[5808] An interventional trial randomizing diabetic men and women to a more Mediterranean-type diet confirmed that dietary changes can slow the deterioration of sexual function in both sexes[5809] and cut the emergence of new sexual dysfunction in half.[5810]

Passing the Sniff Test

Love may be at first sight and beauty in the eye of the beholder, but vision is not the only sense associated with

physical attractiveness and romantic partner preference. Body odor signals a variety of information on matters such as eating habits, hygiene, health, and more.[5811] In a survey of heterosexual college students, men rated visual information as being most important for selecting a lover, while women considered smell to be the single most important physical feature. In other words, women ranked body odor as more important for attraction than "looks."[5812]

Men may be more discriminating in this department than they think. For example, heterosexual men can unconsciously discriminate between body odor samples from pregnant women versus ovulating women. Functional MRI scans show the two different samples light up different areas of men's brains.[5813] How do postmenopausal women smell? What about older men?

As we age, men and women both begin developing a distinctive body odor. The Japanese even have a name for it: *kareishu*.[5814] It appears to be due to a chemical we start producing as early as age forty called *2-nonenal*, which has an unpleasant grassy and greasy odor, caused by the oxidation of omega-7 fats that are increasingly exuded from our skin.[5815]

What can we do to make ourselves smell better? Eat mushrooms. Researchers in Japan carried out a randomized, double-blind, placebo-controlled trial of three different doses of a champignon mushroom extract on the breath odor, pillow odor, pajama odor, and fecal odor of older men and women. Testers sniffed for bad breath one handsbreadth away from the study subjects' mouths as they talked for a minute or two, smelled their used pillowcases and pajamas, and evaluated their fecal odor; the "cooperating person evaluated the smell after the subject used the toilet."

Every dose of the mushroom extract beat out placebo for every test. Within two to four weeks, the mushrooms improved the smell of the participants' breath, bedding, clothing, and poop.[5816] I had never heard of champignon

mushrooms. Would they have to be ordered from some rare and exotic mushroom shop? I was pleasantly surprised to learn that champignon is just another name for regular white button mushrooms, the cheapest, easiest-to-find mushrooms you can get just about anywhere. To pit it against a placebo, the researchers had to use an extract they could stuff into a capsule. They didn't describe the extraction process, but if it were just dried mushroom powder, the biggest dose they used would only translate into about a single small mushroom a day.[5817]

What else can we try? In my video see.nf/bodyodor, I show how eating chlorophyll can help, reducing underarm odor at doses on the order of 100 mg a day,[5818] the amount of chlorophyll you could get in about a dozen leaves of spinach.[5819] So, before slathering aluminum onto your armpits, I recommend first trying to deodorize from the inside out by eating a big salad every day, which may improve your body odor two ways: by hitting the chlorophyll threshold and improving your health.[5820]

As I explore in the video, the induction of inflammation with injections of endotoxin (see here) gives people an aversive body odor compared to those getting placebo injections.[5821] So, does eating meat make people smelly? The *kareishu* elderly person smell is thought to arise in part from "high animal fat–containing modern diets," but there's only one way to find out. Czech researchers decided to put it to the test, publishing their results in "The Effect of Meat Consumption on Body Odor Attractiveness."[5822] Not just body odor, mind you, but body odor *attractiveness*.

For two weeks, male "odor donors" were placed on a diet that either included or excluded meat and, during the final twenty-four hours, had pads taped into their armpits to collect their body odor. Then, thirty women assessed "fresh odor samples"—hot off the pits—for their pleasantness, attractiveness, masculinity, and intensity.

A month later, the study was repeated with the same men, but this time they followed the opposite diet. The same women were used as judges. The men, incidentally, were paid 2,000 in Czech currency for their time and "potential inconvenience caused by the prescribed diet." And the women who had to sniff all of those armpit pads? They were not paid, though they did receive a chocolate bar for their participation.[5823]

So, whose body odor was the most pleasant, the most attractive? The results showed that the "odor of donors when on the nonmeat diet was judged as significantly more attractive, more pleasant, and less intense." No differences were noted for masculinity.[5824] The researchers concluded that meat may have a "negative impact on perceived body odor hedonicity."[5825] In other words, those eating more plant-based evidently smell perceptively more pleasurable.

FEMALE SEXUAL FUNCTION

The most frequently reported sexual symptom among older women is low libido, followed by poor lubrication and pain during intercourse.[5826] Though there are safe, natural solutions, Big Pharma has money-grabbed women's privates.

MEDICALIZING WOMEN'S LIBIDO

In a textbook case of disease mongering, the pharmaceutical industry has promoted female sexual dysfunction as a mental disorder,[5827] harkening back to the first edition of the *Diagnostic and Statistical Manual of Mental Disorders*—psychiatry's diagnosis manual—which listed frigidity as a mental disorder, along with homosexuality.[5828] The latest manifestation is "hypoactive sexual desire disorder," a disease invented by drug companies. There are certainly women troubled by low libido, but that doesn't make it a medical condition. In fact, even women with a normal libido can get diagnosed with hypoactive sexual desire disorder: "A woman who is highly interested in sex, just not with her current partner, can still qualify for a

diagnosis"—and the drug. Even a "woman who is happy with her sex life may still qualify for a diagnosis of hypoactive sexual desire disorder if her partner is dissatisfied.…"[5829]

I review the shameful saga of the approval of flibanserin (sold as Addyi) in my video see.nf/hsdd. Clinical benefits are marginal, and the side effects significant.[5830] Combining it with alcohol, for example, can cause dangerously low blood pressure and fainting, problems so serious that the FDA put a black box warning—its most serious safety alert—on the drug insert hardly anyone reads.[5831] Even without alcohol, it can cause severe drops in blood pressure and "sudden prolonged unconsciousness."[5832] As pharmacology professor Adriane Fugh-Berman put it, these types of serious side effects "might be acceptable in a cancer drug, but they are entirely unacceptable in a drug given to healthy women for an invented condition."

GET YOUR JUICES FLOWING

Eating more healthfully can extend not only your life but also your love life. Generally speaking, heart-healthy lifestyle changes are sex-healthy lifestyle changes because of the critical role blood flow plays in the sexual responses of both men and women.[5833] For example, researchers can use MRI techniques to measure clitoral engorgement within minutes of exposure to an erotic video.[5834] This helps explain why sexual function in women is significantly affected by the presence of vascular diseases caused by the atherosclerotic narrowing of blood flow[5835] and arterial dysfunction.[5836] Rabbits made to be atherosclerotic by being fed dietary cholesterol suffer a decrease in induced clitoral erections.[5837] (Yes, all female mammals have clitorises, as do some birds and reptiles.[5838])

Cholesterol doesn't just build up inside the arteries that feed our heart muscle, but inside all our blood vessels. In the heart, atherosclerosis can cause a heart attack, and in the brain, it can cause a stroke. In our legs, it can cause peripheral vascular disease and result in debilitating cramping, and in our vertebral arteries, it may cause disc degeneration and lower back pain. And clogs in our pelvic arteries can lead to sexual dysfunction, including decreased vaginal engorgement and "clitoral erectile insufficiency syndrome," defined as "failure to achieve clitoral tumescence," or

engorgement. This is thought to be an important factor in female sexual dysfunction.[5839]

Women with higher cholesterol levels report significantly lower arousal, orgasm, lubrication, and sexual satisfaction. The same appears to hold true for women with high blood pressure.[5840] The Framingham Risk Score incorporates both cholesterol and blood pressure, and women with a score indicating even a 2 percent ten-year risk of developing heart disease have nearly twice the risk of sexual dysfunction.[5841] No wonder women randomized to a plant-rich diet experienced a significant improvement in overall sexual function.[5842]

Lubrication is all about blood flow, too. The hydrostatic pressure from all the additional pelvic blood flow in a sexually aroused vagina forces fluid to leak onto the surface wall of the birth canal as vaginal lubrication.[5843] How can we improve blood flow? If you remember from the Preserving Your Mind chapter, the flavonoid phytonutrients in cocoa can help open up arteries, peaking at about ninety minutes after consumption.[5844] So, might that Valentine's Day chocolate make a difference? Women who eat chocolate were found to have higher female sexual function index scores, but the effect disappeared once age was taken into account.[5845] So, chocolate appeared to flop as an aphrodisiac, perhaps because its fat and sugar counteract the benefits of the flavonoids in straight cocoa powder.

What are some whole-food sources of flavonoids? Onions are a major source. "Fresh onion juice" was found to enhance copulatory behavior … in rodents. For those of us less interested in how to "increase the percentage of ejaculating rats"[5846] and looking for something other than onion juice for our hot date, apples are the next largest source of flavonoid intake in the United States.

A study out of Italy found that women who ate apples on a daily basis scored significantly higher on an index of overall female sexual function than women consuming less than an apple a day.[5847] Note that the researchers only counted women who ate unpeeled apples, because the phytonutrients are concentrated in the peel, so we don't know if there's a link with peeled apples. Either way, as an observational study, all that could be demonstrated is a correlation between apple eating and improved sexual function. If proven to be cause and effect, the research suggests this could

lead to "identifying new compounds and food supplements to use in female sexuality recovery." Or, you can just try eating an apple.

SHOT DOWN IN FLAMES

Women randomized to an increased intake of fruits, vegetables, nuts, and beans with a shift from animal to plant sources of fat experienced a significant increase in sexual function.[5848] The same was found for men and erectile function.[5849] The largest study on diet and erectile dysfunction (ED) found that each additional daily serving of fruits or vegetables may reduce the risk of ED by 10 percent.[5850] This could be due to increased circulation, as well as decreased inflammation.

A review on inflammation and sexual dysfunction concluded that men and women should switch to a diet high in fruits, vegetables, whole grains, nuts, and seeds, and low in sodium and saturated fat.[5851] As I reviewed in the Inflammation chapter, fiber is the most anti-inflammatory dietary component and saturated fat the most pro-inflammatory one. A two-year interventional study that found a significant improvement in the sexual function of men and women randomized to a healthier diet also noted a significant reduction in levels of C-reactive protein, a marker of systemic inflammation. Even the same diet in smaller portions can help. Overweight diabetic women with sexual dysfunction randomized to around a fifteen-pound weight loss through portion control over a year,[5852] which is enough to drop C-reactive protein levels by about 40 percent,[5853] were more than twice as likely to regain normal sexual function.[5854]

You don't have a wait a whole year, though. Changes in inflammation in the blood can occur hour to hour, based on what we just ate. Researchers fed subjects sausage-egg-butter-oil sandwiches versus cheeseless pizza with whole-wheat crust.[5855] There is a pro-inflammatory signaling molecule in our body called *interleukin 18*, which is thought to play a role in destabilizing atherosclerotic plaque. As such, the level of interleukin 18 in the blood is a strong predictor of cardiovascular death.[5856] Within hours of eating the sausage sandwich, interleukin 18 levels rose about 20 percent. In contrast, those eating the whole food, plant-based pizza had about a 20 percent *drop* in interleukin 18 levels within hours of consumption,

reinforcing dietary recommendations to eat a diet high in fiber and low in saturated fat.

But the billions in profits are in pills,[5857] not plants, which is why the pharmacology of the female orgasm has been studied ever since 1960, when a researcher at Tulane University implanted tubes deep within the brain of a woman "of borderline defective intelligence" so he could inject drugs directly into her brain to induce repetitive orgasms. A man who had electrodes placed into similar parts of his brain was given a device for a few hours that allowed him to press the button himself to stimulate the electrode. He pressed the button 1,500 times.[5858]

Toying with Phthalates

Phthalates are hormone-disrupting chemicals found in PVC plastics linked to a number of adverse health effects, such as disturbing infant and child genital and behavioral development.[5859] Data have shown, for example, "incomplete virilization in infant boys"[5860] and reduced "masculine play" as they grow up,[5861] and, for girls, an earlier onset of puberty.[5862] In adults, phthalates can affect our sex lives, as I explore in see.nf/phthalates.

In addition to increasing breast cancer risk,[5863] they may impair testosterone production in men[5864] and decrease libido in women.[5865] Most phthalates come from food, based on fasting studies,[5866] but we can get similar drops from simply eating a plant-based diet for a few days.[5867]

The highest levels are found in meats, fats, and dairy.[5868] Poultry consistently comes out as being the most contaminated across the board with some of the highest levels ever reported.[5869] Diets high in meat and dairy may exceed the allowable daily intake set by the U.S. Consumer Product Safety Commission.[5870]

Even during total fasting, a few cases of phthalate urine spikes were noted after showers, suggesting contamination in personal care products.[5871] This may be avoided by

choosing unscented products, since phthalates are used as a fragrance carrier.[5872] Certain phthalate levels are now banned from children's toys,[5873] but not from toys for adults. "Jelly"-based sex toys are often made from a plasticized vinyl material loaded with phthalates. Although opting for water-based lubricants may reduce phthalate transfer a hundredfold, such sex toys may still have opposite the intended effect.[5874]

TESTOSTERONE "REPLACEMENT" FOR WOMEN

Testosterone is linked with sexual desire in both men and women.[5875] Women normally produce testosterone throughout the life cycle. Although postmenopausal ovaries continue to produce testosterone,[5876] levels naturally decline with age—falling by approximately 50 percent by age fifty.[5877] This is thought to play a role in the decline in libido (using masturbation frequency as a partner-independent proxy).[5878]

A syndrome of "female androgen deficiency" symptoms has been popularized, but there is no evidence that testosterone "replacement" helps with mood, well-being, or hot flashes, nor bone, cardiovascular, or metabolic health.[5879] The only evidence-based reason to try testosterone in postmenopausal women is for the treatment of low sexual desire that's causing distress,[5880] though as I detail in see.nf/t4women, efficacy is insufficient to warrant FDA approval, especially given the uncertainty about long-term side effects.[5881] DHEA, which can convert into testosterone within the body, fails to significantly improve desire and sexual function,[5882] but natural ways to raise testosterone levels in women are listening to music[5883] and avoiding mint tea.[5884]

Smell to High Heaven

What else can older women do to improve their sexual desire if they so choose? There are two aromatherapy regimens that may help. Women randomized to smell the aroma of lavender for twenty minutes twice a day for twelve

weeks experienced a significant improvement in menopausal symptoms, including sexual desire, compared to sniffing the control, which was diluted milk.[5885] Neroli oil, also known as bitter orange, appeared to work even faster. Just five minutes twice a day for five days led to a significant increase in sexual desire at even just a 0.1 percent concentration of the essential oil, compared to instead sniffing the carrier (almond) oil alone.[5886] It's hard to rule out placebo effects, since the controls were not matched for intensity. A better research design might have incorporated synthetic fragrances, but they still may be worth a try.

THE ROOTS OF THE MATTER: GINSENG, MACA, AND ASHWAGANDHA

What about other dietary supplements, such as three roots, ginseng, maca, and ashwagandha? For details, see see.nf/roots, but essentially, ginseng flopped for female sexual dysfunction,[5887] though one small trial of about three-quarters of a teaspoon of maca powder suggested benefit.[5888] Ashwagandha (from *ashwa*, meaning "horse," and *gandha*, meaning "smell,"[5889] because the roots evidently possess the "distinctive smell of a wet horse"[5890]) may also help[5891] but cannot be recommended due to rare cases of liver toxicity. (What else should we expect from a plant with the nickname *poison gooseberry*?[5892])

VAGINAL MOISTURIZERS

Typically starting about four to five years after their last period, about half of postmenopausal women suffer from what they used to call *vulvovaginal atrophy*,[5893] but now referred to by the name *genitourinary syndrome of menopause* (GSM). The Vulvovaginal Atrophy Terminology Consensus Conference Panel of the North American Menopause Society decided that the term GSM was more "publicly acceptable." Not that the original descriptor wasn't accurate, but the panel felt the word "atrophy" had "negative connotations" and the word "vagina" was "not a generally

accepted term for public discourse or for the media." The panel likened it to the parallel shift from "pejorative" impotence to "erectile dysfunction."[5894]

Whatever it's called, it involves changes to the vulva (external genitalia), vagina (birth canal), and bladder, caused by menopausal changes in hormone levels. Symptoms include vaginal dryness, burning, itchiness, and irritation, pain during penetrative sex, and postcoital bleeding from the thinning of the vaginal lining.[5895] Urinary symptoms can include recurrent bladder infections and incontinence.[5896] Some women with mild GSM remain asymptomatic. For others, symptom severity can preclude intercourse and result in discomfort even with just sitting or wiping. In a survey of thousands of women with GSM, 59 percent said their symptoms "considerably decreased their enjoyment of sexual activity," and 23 percent reported that it had an adverse effect on "general enjoyment of life."[5897]

While other menopausal symptoms tend to improve over time, like hot flashes, GSM symptoms tend to get progressively worse. Women rarely seek medical help, which is unfortunate, since there are safe and simple treatments available. The first-line treatments for mild to moderate vaginal dryness are lubricants and moisturizers.[5898]

Lubricants are designed to reduce friction during sexual activity, whereas vaginal moisturizers are used on a regular basis either daily or every two to three days as needed, to provide comfort by mimicking normal vaginal secretions, regardless of sexual activity. Water-based lubricants have the advantage of being nonstaining[5899] and are associated with fewer genital symptoms, such as discomfort or burning, compared to silicone-based lubricants.[5900]

What's the best vaginal moisturizer? A head-to-head study pitted Replens, an expensive vaginal moisturizer claiming special "bioadhesive" ingredients, versus a placebo gel of hydroxyethylcellulose, which is found in products ten times cheaper, like K-Y Jelly. After twelve weeks, the researchers found no difference between the two.[5901] This "striking" finding led to an accompanying commentary in the American Medical Association journal to conclude that, until there is evidence to suggest otherwise, "postmenopausal women experiencing vulvovaginal symptoms should choose the cheapest moisturizer or lubricant available over the counter.…"[5902]

There is another factor to take into account, though. The World Health Organization recommends, based on the SMI test, personal lubricants and vaginal moisturizers not exceed an osmolality of 380 mOsm/kg.[5903] That's a measure of how concentrated the dissolved components are. How did they come up with that number? By lubing up slugs. SMI stands for slug mucosal irritation. They cover slugs with lubricant over a five-day period and measure how much mucosal irritation and tissue damage the slug experiences. No adverse effects were found below the cutoff, but a product like K-Y Jelly at 2,463 mOsm/kg induced mild to moderate irritation, and something off the charts, like Astroglide at 5,848 mOsm/kg, caused severe irritation and tissue damage.[5904,5905]

Dozens of commonly used lubricants and moisturizers available worldwide have been put to the test, and the only two vaginal moisturizers that met the WHO criteria were the Ah! Yes VM brand aloe vera gel–based moisturizer and the Balance Activ brand's hyaluronic acid–based one. The only lubricants that made the cut were made by the brands Yes, Good Clean Love, and System JO, as well as one product by Durex, Sensilube gel, but not its Play Feel lubricant.[5906]

VAGINAL HORMONES

If over-the-counter lubricants and moisturizers are insufficient to control GSM symptoms, the American College of Obstetricians and Gynecologists and other professional societies recommend low-dose, local (vaginal) estrogen, unless there is a history of hormone-dependent cancers, like endometrial or breast cancer.[5907] It's considered safer and more effective than systemic hormone therapy.[5908] A meta-analysis of fifty-eight studies comparing vaginal to oral estrogens found that vaginal estrogen therapy offered better GSM symptom relief.[5909] Many women who are on systemic menopausal hormone therapy have to add on supplemental vaginal estrogens to control symptoms.[5910]

Vaginal estrogens are available as a variety of creams, suppositories, and rings. Thirty comparative trials have been performed, and there appears to be no difference in efficacy among the various preparations.[5911] However, they may take weeks before a noticeable alleviation of symptoms is detected and two to three months before the full effect is achieved.

Although a yearlong study could clearly demonstrate vaginal estrogen's benefit,[5912] studies as long as twelve weeks have failed to manifest superiority to placebo.[5913]

Estrogens applied to the vulva or vagina are systemically absorbed and convey the same black box FDA notice that oral estrogens carry,[5914] an all-caps warning of increased risk of "ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA."[5915] Vaginal estrogen is considered safer, though, since it can be used locally at much lower doses—as low as one-hundredth the oral dose needed to relieve hot flashes, for instance.[5916] The Harvard Nurses' Health Study didn't find any increased risks associated with vaginal estrogen use over eighteen years of follow-up.[5917] Randomized controlled trials lasting up to a year appear to confirm its safety,[5918] but there have been observational studies linking vaginal use to about a doubling of risk for endometrial cancer. However, one was done back in the 1970s, when higher estrogen doses were used,[5919] and the more recent study, out of Denmark,[5920] may have been confounded by concurrent oral estrogen exposure.[5921] Out of an abundance of caution, women who have survived hormone-dependent cancer should avoid even low-dose localized estrogen.[5922]

Those women may want to consider vaginal DHEA instead.[5923] Although oral DHEA doesn't appear to offer any benefit,[5924] in 2016, the FDA approved vaginal DHEA suppositories for pain during intercourse due to GSM.[5925] It is converted locally into estrogen and does not significantly affect systemic hormone levels.[5926] The downside is that it has to be administered nightly, whereas estrogen preparations are typically used twice a week and vaginal rings only every few months.[5927] For those who would rather have an oral treatment, there's ospemifene, a tamoxifen-type drug that has pro-estrogenic effects on the vaginal lining. However, it actually increases the rate of hot flashes and urinary tract infections in the short term, and insufficient data are available on long-term safety.[5928]

SOY JOY

Japanese-American women have the lowest rates of hot flashes in the United States, as well as the lowest rates of vaginal dryness.[5929] Might it be due in part to their greater soy consumption? There have been a few studies

on topical application of soy isoflavone vaginal gels[5930] showing a significant improvement in dryness and pain with intercourse over placebo gels,[5931] roughly on par with estrogen cream in a head-to-head test,[5932] but it's unlikely that these women are applying soy products topically. (A whole new meaning to the term "extra-firm" tofu?) What about just eating soy foods? Feeding isoflavones to older mice increases vaginal blood flow.[5933] What about in people?

Most oral soy supplements flopped,[5934] but as I explore in see.nf/soygsm, the three studies on soymilk and GSM symptoms show promise.[5935,5936,5937] A case report out of New York suggests that it may be possible to overdo it, though. A forty-four-year-old woman presented to her gynecologist with an "increase in desire that required her to self-stimulate to orgasm approximately 15 times daily." A month before, she had started an almost exclusively soy-based diet, eating in excess of four pounds of soy foods a day. Within three months of cutting back, her desire cooled to the point that she "engaged in satisfying sexual activity only twice daily."[5938]

FENNEL AND FENUGREEK

Fennel seeds, which are actually whole little fruits, have been shown to have hormonal effects, for example, offering significant relief from painful periods[5939] comparably to ibuprofen-type drugs.[5940] After menopause, fennel oil extract supplements didn't show any benefit for GSM symptoms,[5941] but whole fennel seeds, powdered into capsules to pit them against placebo in a double-blind, controlled trial, significantly improved menopausal symptoms at a dose of just a teaspoon a day.[5942]

Topical fennel creams are even more impressive. Within eight weeks, about 90 percent of those randomized to a vaginal fennel cream went from experiencing severe pain during intercourse to none, whereas pain didn't go away in any of those on the placebo cream. Vaginal dryness, itching, and pallor also completely disappeared in the fennel group.[5943] These extraordinary results were recently replicated successfully.[5944] Other studies have also found significant benefits to fennel vaginal creams for desire, arousal, lubrication, orgasm, and sexual satisfaction.[5945]

Fenugreek seeds are also hormonally active, as I document in see.nf/fenugreek. Men randomized to capsules containing fenugreek got

significant gains in body composition and upper (bench press) and lower (leg press) strength compared to placebo,[5946] along with a significant boost in total blood testosterone[5947] and a doubling of the frequency of morning erections.[5948] And the only side effect? It can make your sweat and pee smell like maple syrup.[5949] (Sounds like a bonus!)

What about sexual function in women? While the estrogen hormone estradiol stimulates vaginal lubrication and blood flow, facilitating a woman's capacity for sexual arousal and orgasm, it's the testosterone that's linked with sexual desire in both men and women. Fenugreek raises the levels of both estradiol and testosterone, resulting in an increase in sexual desire and function, translating into about a doubling of sexual activity compared to placebo.[5950] That was in premenopausal women, but the same dose was subsequently shown to improve sexual symptoms in postmenopausal women as well.[5951] However, it was not found to be as effective as estrogen cream in a head-to-head comparison.[5952]

MALE SEXUAL FUNCTION

"Sex is important to health," reported the *Harvard Health Letter*, noting "[f]requent sexual intercourse is associated with reduced heart attack risk."[5953] However, for men, this seems to be the perfect case for reverse causation. But low frequency of sexual activity appears to predict cardiovascular disease in men even independently of erectile dysfunction.[5954]

"SEX IS KICKING DEATH IN THE ASS WHILE SINGING." —CHARLES BUKOWSKI

Do men who have more sex actually live longer? I review the evidence in my video see.nf/sexlife, but in a nutshell, the researchers found that men with "high orgasmic frequency" appeared to cut their risk of premature death in half and, apparently, the more, the better: There was a 36 percent drop in mortality odds for every additional one hundred orgasms a year[5955] —but, apparently, not if you cheat. Extramarital sex in men was associated with higher cardiovascular risk for reasons laid out in the video.[5956]

When done right, though, love may protect your lover's life.[5957] Given the purported benefits of sexual activity, the authors of the orgasm study suggested a public health initiative should be launched, similar to the *at*

least five a day fruit and vegetable campaign aimed at increasing consumption of produce, though, they acceded, "the numerical imperative may have to be adjusted."[5958]

ED = EARLY DEATH

Up to thirty million men in the United States and approximately one hundred million men worldwide experience erectile dysfunction (ED), the recurrent or persistent inability to attain or maintain an erection for satisfactory sexual performance.[5959] Hold on. The United States has less than 5 percent of the global population yet up to 30 percent of world's impotence? We're number one!

ED is considered to be an important cause of decreased male quality of life[5960]—so much so that one early theory suggested that it may explain the link between impotence and heart attacks. Depression is a risk factor for coronary heart disease, and the thought was that men who couldn't get erections became *so* depressed that they die of a broken heart.[5961]

The real reason the United States is the world leader in ED may be our artery-clogging standard American diet. One in five ED cases may be psychological in origin, but most are "vasculogenic," meaning due to impaired penile blood flow.[5962] Every part of the body needs sufficient blood to function properly. Cholesterol can clog arteries in our inner and outer organs, causing aneurisms, heart attacks, strokes, kidney failure, spinal degeneration, and sexual dysfunction.[5963] Up to three-quarters of men with cholesterol-narrowed coronary arteries have some degree of erectile dysfunction.[5964] But Americans have red, white, and blue pills like Viagra. The problem is that those pills are just a stopgap measure to cover up the symptoms of vascular disease; they do nothing for the underlying pathology—the artery-clogging atherosclerosis that threatens one's life, along with one's love life.

Read my erectile dysfunction section in *How Not to Die* for further details, but basically, men in their forties with erection difficulties have up to a fiftyfold greater risk of having a cardiac event like sudden death.[5965] We used to think of ED in men under forty as being "psychogenic," all in their heads, but we are now realizing that the condition is more likely an early indicator of vascular disease. Over the age of seventy, only a minority of

men surveyed describe being bothered by their ED,[5966] but they may not realize the broader implications for the health of their arteries. Some experts contend that a man with ED—even if he does not have any cardiac symptoms—"should be considered a cardiac … patient until proved otherwise."[5967]

SURVIVAL OF THE FIRMEST

Given the underlying cause of physiological erectile difficulty, it's no surprise that an artery-healthy diet may be the cornerstone to prevent it. In a 2022 *Urology* paper titled "Consumption of a Healthy Plant-Based Diet Is Associated with a Decreased Risk of Erectile Dysfunction," researchers noted that the 500 percent increase in the number of Americans consuming a plant-based diet in recent years may be accompanied by an improvement in male sexual function. Note that this was apparent only with the consumption of *healthy* plant foods.[5968] Just cutting down on animal products but continuing to down soda with your french fries would not be expected to improve matters in the bedroom. Whole plants for swole pants.

This is consistent with findings from the Harvard Health Professionals Follow-Up Study that followed more than 20,000 men for a little over a decade, from the average age of sixty-two until seventy-three. The study found that those following healthier diets were significantly less likely to develop ED.[5969] A study of Canadian men with diabetes found that each additional daily serving of fruits or vegetables correlated with a 10 percent reduction in ED risk.[5970] This connection appears to extend to younger men, with fruit and vegetable consumption associated with lower ED risk even in men under forty.[5971]

Erectile function may be such a sensitive indicator of cardiovascular health that it may explain why men lost the bone in their penis.[5972] I produced a video on the subject, see.nf/baculum. Without a bone, only genuinely healthy males could "present a really stiff erection," evolutionary biologist Richard Dawkins wrote, "and the females could make an unobstructed diagnosis."[5973]

Bottling Up Your Feelings

A recent study found that men eating organic foods tended to be less likely to have ED.[5974] Interest in the role of pesticides in sexual function dates back more than fifty years[5975] to a report titled "Impotence in Farm Workers Using Toxic Chemicals," published in the *British Medical Journal*.[5976] Agricultural workers frequently exposed to pesticides have up to eight times the odds of a "flat erectile pattern" (lack of nocturnal erections), but it's not clear if there is any effect caused by the traces of pesticides left on conventional produce.[5977] The lower risk among organic consumers may be due to the fact that those eating organic also tend to eat less processed foods and more fresh foods.[5978]

The plastics chemical BPA is associated with declining male sexual function—decreased sexual desire, more difficulty having an erection, lower ejaculation strength, and lower level of overall satisfaction with sex life.[5979] Though we inhale some from dust and absorb some through our skin when touching BPA-laden receipts, 90 percent of our exposure to BPA is from our diet.[5980] In see.nf/bpa, I describe ways to limit our exposure: Reduce our use of polycarbonate plastics, which are usually labeled with recycle codes three or seven, and opt for fresh and frozen foods over canned goods, especially when it comes to tuna and condensed soups. If you do use plastics, don't microwave them, put them in the dishwasher, leave them in the sun or a hot car, or use them once they're scratched.[5981] Using glass, ceramic, or stainless steel containers may be even better,[5982] though, as it's not clear if BPA-free plastics like Tritan are any better.

SOFT PEDALING IT

There are other lifestyle behaviors that impact male sexual function. Smoking may almost double the risk of developing ED, and even secondhand smoke has been implicated.[5983] Experimentally, five of six dogs

exposed to just ten or so minutes of cigarette smoke could not achieve erections.[5984] It's hard to rigorously study smoking cessation because of frequent noncompliance, but successful quitters do show significantly improved erectile function. For example, in one six-month study, 54 percent of men who quit smoking regained erectile function compared to 28 percent of persistent smokers.[5985] Cannabis use is also associated with ED. A meta-analysis capturing data from thousands of men found that the prevalence of ED in cannabis users (69.1 percent) was about twice as high as in nonusers (34.7 percent).[5986]

Obesity can cause profound sexual dysfunction,[5987] which can be reversed with sufficient diet-[5988] or surgery-induced[5989] weight loss. Physical inactivity may also cause sexual inactivity,[5990] while regular aerobic exercise can improve erectile function[5991] almost as much as the latest generation of Viagra-type drugs.[5992] At least forty minutes of moderate to vigorous intensity aerobic exercise four times per week for at least six months is recommended for ED recovery.[5993] However, caution must be exercised when it comes to prolonged cycling.

In reference to the Scythians, a group of horse-riding people, Hippocrates wrote that "the great majority among them become impotent."[5994] What about Pelotons and other modern steeds? There are fifty million cyclists in the United States alone,[5995] and there is concern about the repeated compression of the pudendal nerves, which branch off the spine, loop down between the legs, then up into the genitals. At first glance, cyclists appear to have the same rates of ED as non-cyclists, but since cyclists tend to be younger, one has to adjust for age. Once you do that, effectively comparing same-age cyclists to non-cyclists, a systematic review and meta-analysis involving more than 3,000 cyclists found them to be at significantly higher risk.[5996]

What about bicycle seats with a cutout in the middle to relieve perineal pressure? They may actually make things worse! The pudendal nerve and artery don't travel along the midline but rather in Alcock's canals, along either side, and the decreased sitting surface area of cutout saddles can aggravate rather than relieve the pressure.[5997] Cyclists using cutout saddles have up to six times the risk of ED, but this seems limited to those who experience concurrent perineal numbness.[5998] What can you do? The greatest pressure in the critical region comes from leaning forward. Cycling

upright was found to result in 40 percent better penile oxygenation than cycling at a sixty-degree angle leaning forward.[5999] You can also regularly switch to standing up on the pedals during prolonged rides.[6000]

VIAGRA: A HARD SELL

Though cholesterol-lowering statin drugs have been shown to help with ED,[6001] the first-line treatment for medical management is the Viagra-type class of drugs known as phosphodiesterase type 5 inhibitors.[6002] They relax the muscle fibers in the penis that normally stanch the influx of blood. Until the "lecture that changed sexual medicine,"[6003] erections were thought to arise from the constriction of blood outflow rather than the expansion of blood inflow.[6004] The lecture, given by Professor Giles Brindley at the annual meeting of the American Urological Association in 1983, involved a visual aid. Before taking the podium, he injected his own penis with a muscle relaxer. Halfway through the lecture, to drive home his point, he proceeded not only to whip it out but then to waddle and waggle down to the front row, pants around his knees, to offer further inspection.[6005] The organizers were "not happy … as there were a fair number of wives in the audience."[6006]

Viagra works through a similar mechanism in oral form, originally starting out as a failed chest-pain drug with a serendipitous billion-dollar side effect.[6007] However, rates of discontinuation after about one or two years of use range from 32 to 69 percent in the United States.[6008] So, about half of men decide that the cons outweigh the pros,[6009] due to ineffectiveness,[6010] cost, or side effects,[6011] the most serious of which is non-arteritic ischemic optic neuropathy (NAION). As I detail in see.nf/naion, NAION typically manifests as waking up blind with usually temporary, but sometimes permanent, loss of vision in one or, rarely, both eyes.

For men who don't like drugs, there's always surgery—the implantation of penile prosthetics.[6012] Unbelievably, penile implant usage evidently dates back to the sixteenth century. Early experiments involved transplanting patients' rib cartilage or even their actual rib into their penis.[6013] The rib cage implants left men in a "permanently erect state," but the "Flexirod" technology in the 1960s, which allowed men to keep their ribs intact, had a hinge in the middle so the device could be bent down in half "for improved

concealment." Of course, proper sizing is important: If the implants are too small, there can be drooping at the tip, leading to a "supersonic transport (SST) deformity"[6014] (because of its "resemblance to the nose of Concorde" jet). Overlong implants can also be a problem, with the semirigid rods eroding through the glans (tip) of the penis.[6015] Ouch.

Now, there are inflatable devices, and perhaps one day there will be "expandable foams that respond to external magnetic fields" or metal-mesh technology "that could expand and retract in a cage-like fashion."[6016] (Try getting *that* through airport security.)

Getting Under Your Skin

Of the half dozen Viagra-type drugs presently on the market, sildenafil (Viagra) itself may have the greatest efficacy, but it also may have the highest rate of side effects.[6017] Acutely, it's remarkably safe. For instance, one man swallowed sixty-five tablets in a failed suicide attempt.[6018] However, now that Viagra has been around for more than two decades, some *chronic* effects may be cropping up. This includes glaucoma, one of the leading causes of blindness. It involves the degeneration of the optic nerve,[6019] and those using Viagra in the long term have up to nearly ten times the odds of developing it. But it's cancer that has the medical community rethinking the safety of this class of drugs.[6020]

I review the evidence in my video see.nf/viagra, but basically, one of the ways melanoma becomes invasive is through a gene mutation[6021] that downregulates the enzyme phosphodiesterase-5,[6022] which is what Viagra-type drugs do, perhaps helping to explain why those taking drugs like Viagra, Cialis, or Levitra do seem to be at significantly higher risk for this potentially deadly form of skin cancer.[6023]

An analysis of internet-ordered Viagra found that only 18 percent were authentic. Some of the pills contained a variety of contaminants, such as commercial-grade paint and other drugs, including amphetamines.[6024] On the flip side, "natural" sexual enhancement supplements are among the dietary supplements most tainted with pharmaceuticals.[6025] More than a dozen deaths have been attributed to taking sexual performance supplements laced with diabetes drugs that crashed dozens into hypoglycemic comas.[6026] Hold on. What about supplement manufacturers who say they have independent, third-party certification of purity? There is a practice called *dry labbing*, a dirty little secret of the supplements industry, where quality assurance laboratories just rubber-stamp fake documents.[6027] For a litany of other supplement industry malfeasance, see see.nf/supplements.

The story of BMPEA is a particularly egregious example, as documented by STAT,[6028] one of my favorite sources of medical journalism. A researcher at Harvard published a paper replicating prior research from the FDA detecting a designer amphetamine–like stimulant in various supplements sold in the United States.[6029] In response, one of the offenders, Hi-Tech Pharmaceuticals, the manufacturer of supplements with names like Black Widow and Yellow Scorpion,[6030] sued the Harvard researcher for libel, slander, and product disparagement,[6031] originally to the tune of $200 million in damages.[6032]

The head of Hi-Tech openly admitted that he was "hoping that we were able to silence this guy."[6033] While ultimately unsuccessful in court, Hi-Tech's lawsuit effectively sent a warning to other researchers. Hi-Tech's CEO is attributed as saying that he "hope[s] that the long and costly legal battle will scare away other academics from investigating the supplement industry."[6034]

A BONE TO PICK WITH ED SUPPLEMENTS

Are there any supplements that have been shown to work? I review the available evidence in see.nf/edpills. Vitamins A,[6035] B_3,[6036] C,[6037] and E[6038] flopped, and studies on vitamins B_6[6039] and D[6040] for ED had no control

group to rule out the placebo effect or even to document that they were superior to doing nothing.

One of the most popular ingredients in sexual enhancement supplements[6041]—and one of the most extensively studied[6042]—is ginseng. A meta-analysis of a half dozen randomized controlled trials found that four to twelve weeks of 1,800 to 3,000 mg a day of Korean red ginseng significantly improved erectile function compared with placebo.[6043] Of course, this is assuming there's actually ginseng in your "ginseng." Testing the authenticity of more than five hundred commercial ginseng products across a dozen countries in six continents, 24 percent were found to be adulterated.[6044]

Some natural "aphrodisiacs" are considered too risky. These include yohimbine, Spanish fly, mad honey, and Bufo toad, the latter of which has been banned by the FDA for its potential lethality.[6045] Death has also been attributed to yohimbine, though since it was purchased online, it may have been adulterated with other substances.[6046]

GYM MEMBER

Currently, recommended treatments for ED do nothing to treat and reverse the underlying cause of the problem, whether oral drugs, surgical penile implants, vacuum erection devices, intraurethral (pee hole) suppositories, or intracavernosal (into the shaft) injections.[6047] While the American Urological Association at least encourages physicians to inform patients about the importance of lifestyle change,[6048] the European Association of Urology guidelines go a step further, mandating that lifestyle changes "must precede or accompany ED treatment."[6049] And for good reason. In see.nf/edlifestyle, I detail interventional studies showing how effective exercise[6050] and healthy dietary changes can be in improving erectile function.[6051]

The Atkins Diet: Trouble Keeping It Up

Erectile dysfunction and heart disease can be two different manifestations of the exact same root problem: diseased

arteries—inflamed, oxidized, cholesterol-clogged blood vessels.[6052] Thankfully, atherosclerosis in both organs can be reversed with lifestyle changes that include anti-inflammatory, antioxidant, cholesterol-lowering foods.[6053,6054] I profile an illustrative case report in my video see.nf/atkins. The fellow started out pretty healthy, a fifty-one-year-old man with decent cholesterol, no measurable coronary artery plaque, and a working penis. He went on the Atkins Diet and lost a few pounds—and the ability to have an erection. Then he nearly died with a 99 percent blockage to his heart, before a return to a healthier diet was able to reopen blood flow throughout his body.[6055]

I wrote a book about the diet nearly twenty years ago. The Atkins Corporation threatened to sue me, but I kind of won by default, because it declared bankruptcy six months later. You can read the whole book, as well as my rather amusing back-and-forth with Atkins's lawyers, at atkinsfacts.org.

NUT UP

Consumption of at least one serving of vegetables a day and more than two servings of nuts a week was associated with a more than 50 percent decrease in the probability of ED in a snapshot-in-time cross-sectional study.[6056] The first interventional nut study on ED was published in 2011. As I detail in see.nf/pistachios, men eating three to four handfuls of pistachios a day for just three weeks experienced a significant improvement in blood flow through the penis, accompanied by significantly firmer erections.[6057]

But a fourteen-week, randomized, controlled trial of mixed nuts improved sperm counts[6058] and marginally increased orgasmic function and sexual desire but had no effect on erectile function.[6059] As I note in see.nf/mixednuts, the discrepancy is likely due to differences in study populations. The men in the pistachio study were in their forties and fifties, already plagued with chronic ED,[6060] whereas the average age in the mixed nut study was twenty-four years, so the younger men may have started out

with near-maximum circulation, leaving them without much nut wiggle room.[6061]

JUST BEET IT

What about vegetables? As discussed, the nitric oxide that allows blood vessels to relax can also be made directly from the nitrates concentrated in vegetables, such as greens and beets. Attempts were made to try to apply nitrates topically on the penis (in the form of a nitroglycerine gel normally used for chest pain), but it caused headaches in both the user and, unless used only under a condom, their partners.[6062] The benefits of vegetable nitrates may explain why eating greens is associated with not only reduced rates of heart disease[6063] but also a longer lifespan,[6064] not to mention the potential for a "veggie Viagra" effect. (See a list of the top ten sources here.) That could explain the link between vegetable consumption and improved sexual function[6065] and improved blood flow to the most important organ of the body, the brain.[6066] The only side effect of beeting out your brain may be adding a little extra color to your life—in the form of red stools and urine that is pretty in pee-nk.

Fruit-wise, pomegranate juice flopped (see.nf/pomegranate), but watermelon stood firm (see.nf/watermelon). Watermelon contains a compound called *citrulline*, which turns into arginine inside the body. Straight arginine can improve erectile function,[6067] but it can also cause gastrointestinal distress.[6068] Five daily servings of red watermelon's worth or that found in a single daily wedge of yellow watermelon (one-sixteenth of a modest-sized melon)[6069] can improve erection hardness.[6070] If this is news to you, it may be because the advertising budgets of drug companies like Pfizer, which rakes in billions of dollars annually from the sale of ED drugs, are about a thousand times[6071] that of the entire budget of the National Watermelon Promotion Board.[6072]

POSH SPICE

A half dozen studies have found that the spice saffron beat out placebo or rivaled medications like Prozac in the treatment of depression.[6073] It may be the red pigment, crocin, since that alone (in a dose equivalent to about a half teaspoon of saffron a day) beat out placebo as an adjunct treatment,

significantly decreasing symptoms of depression, symptoms of anxiety, and general psychological distress.[6074]

If the spice works as well as the drugs, one could argue that the spice wins,[6075] since it doesn't cause sexual dysfunction in the majority of men and women like most prescribed antidepressants do.[6076] Popular SSRI drugs like Prozac, Paxil, and Zoloft cause adverse sexual side effects in about 70 percent of people taking them,[6077] which can persist even after stopping the drugs.[6078] (Now that's depressing!) Not only is this not a problem with saffron; the spice may even be able to treat antidepressant-induced sexual dysfunction in both men[6079] and women,[6080] as I document in see.nf/crocin.

What about saffron for just regular ED? It was actually a saffron trial that inspired me to suggest the RigiScan engorgement-measuring machine for use in the documentary *The Game Changers*. Suggestive benefit for both oral[6081] and topical[6082] (rubbed on the penis) saffron was found, with caveats summarized in my video see.nf/saffroned.

Costs vs. Benefits

A review on diet and sexual health expounded on the pros and cons of various eating patterns. The benefits of continuing to eat the standard American diet were "[r]elatively affordable and easy to obtain," and downsides were "[i]ncreases risk of total mortality, cardiovascular disease, obesity, metabolic syndrome, stroke, chronic kidney disease, and breast, colon, and prostate cancer."[6083] Thankfully, eating more healthfully is becoming more and more convenient and may be among the cheapest ways to eat.[6084] A meat-free diet, for example, could save individuals an estimated $750 a year.[6085]

PRESERVING YOUR SKIN

The skin is the fastest-growing[6086] and largest organ in our body—about twenty square feet, accounting for about 10 percent of our body weight.[6087] It acts as the most conspicuous mirror of the aging process. As our skin becomes thinner, it is more easily damaged, loses volume and elasticity, and can sag and wrinkle.[6088]

The three main constituents that make up the bulk of our skin are collagen, hyaluronic acid, and elastin. Collagen,[6089] which makes up about 75 percent,[6090] contributes strength and firmness, hyaluronic acid maintains moisture in the skin by trapping water,[6091] and stretchy elastic fibers containing elastin make up about 1 to 2 percent of our skin and help it bounce back into shape.[6092]

As we age, the synthesis of collagen and elastin decreases by about 1 percent a year,[6093] as does overall skin thickness.[6094] The turnover rate of our skin can slow considerably, from every twenty-eight days in the young to forty to sixty days in the elderly.[6095] Our skin's microbiome also changes, in fact, so predictably that people's age can be guessed within about a four-year range just from a swab of the bacteria on their skin.[6096] We don't yet know enough about these bugs to assess their role in the skin aging process, though, which seems to revolve around oxidative stress. That's what causes age spots, also known as liver spots, clumps of oxidized fat and proteins known as age pigment or lipofuscin[6097] (from the Latin *lipo-* and *fuscus*, meaning "dark fat").

NOTHING NEW UNDER THE SUN

As little as 3 percent of skin aging is due to genetic factors, so-called intrinsic aging, and the rest—extrinsic aging—is from our lifestyle, that is, from what we do to our skin.[6098] You can get a sense of the difference by comparing the aging of skin from typically protected areas to skin that's been exposed to the sun—the skin on your tush or the inside of your upper arm, for instance, compared to the skin on your face or hands.[6099] Intrinsic aged skin does lose elasticity and develops fine wrinkles, but it is generally otherwise smooth and unblemished, with pigment diminishing toward

pallor. Extrinsic aged skin, on the other hand, can become leathery, bumpy, blotchy, and mottled, with coarse wrinkles and furrows.[6100]

Between 80[6101] and 90[6102] percent of facial aging among people with lighter skin tones is due to sun exposure. Those with darker skin are also affected, though they're relatively protected due to their built-in melanin sunscreen.[6103] That's why dermatologists now agree that there is nothing more important to slow the signs of aging than to protect your skin from the sun.[6104] To illustrate, a dramatic photo of a trucker who spent decades getting more sun on the left side of his face through his driver's side window was published in *The New England Journal of Medicine*,[6105] making him look a bit like a Batman villain. You can check it out at see.nf/trucker. Factors like sun exposure and smoking can make people look eleven years older. Cosmetic surgery, on the other hand, can make people look up to eight years younger.[6106] A healthy lifestyle may work even better at maintaining a youthful appearance.

Protecting our skin from the sun should be a lifetime endeavor. This can involve sunscreen, wearing sun-protective clothing, hats, and sunglasses, and avoiding direct sunlight during the peak hours of 10:00 a.m. to 4:00 p.m., instead seeking shady, covered areas.[6107] Sunbathing is frowned upon, even with sunscreens like zinc oxide or titanium dioxide, which offer broad-spectrum protection against both UV-A and UV-B rays.[6108] We now know that other wavelengths not covered by sunscreens, such as near infrared, also contribute to skin aging.[6109] Men and women who use tanning beds appear significantly older than those who don't, and those who sunbathe appear years older than they actually are, comparable to what is seen with smoking.[6110]

SOMETHING IN THE AIR

Beyond the oxidizing effects of rays of the sun are the oxidizing effects of oxygen in the air, as well as cigarette smoke, automobile exhaust, and other environmental pollutants.[6111] Cigarette smokers develop a distinctive pattern of prominent wrinkles known as "smoker's face."[6112] The effects are so significant that illustrating these aging effects can help smoking teenagers quit. Compared to only one out of eighty teens quitting in a control group, eleven out of eighty teens who had been shown digital aging software

presenting their future faces with and without smoking were successfully able to quit.[6113] A similar study presenting the deleterious effects of UV rays of facial images appeared to affect sustained behavioral change in regard to sun-tanning practices.[6114]

Even ambient air pollution has been correlated with signs of skin aging.[6115] Poor air quality index is significantly linked with age spots, increased wrinkling, and skin sagging.[6116] This is blamed on polycyclic aromatic hydrocarbons (PAHs).[6117] These combustion by-products coat diesel exhaust particles and are also formed when coal is burned, tobacco is smoked, and meat is grilled.[6118]

Tobacco smokers get about half their exposure to PAHs from cigarettes and the other half or so from food. For nonsmokers, though, 99 percent of their PAH exposure may come from their diet. The highest levels of these chemicals are found in meat, with pork apparently worse than beef,[6119] but even dark green leafy vegetables can get contaminated by pollutants in the air. So don't forage your dandelion greens next to the highway and make sure to rinse your greens under running water.[6120]

Since PAHs are fat-soluble, absorption of these chemicals may be diminished by eating foods that are lower in fat.[6121] However, they do not appear to build up in our body. Unlike persistent pollutants like PCBs, which may take fifty to seventy-five years to clear from the body after regularly eating farmed Atlantic salmon, for example,[6122] PAHs can pass through us in a single day. After eating a meal of barbecued chicken, a big spike in these chemicals can be seen in the diners' systems—up to a hundredfold increase. However, the body can detoxify most of the PAHs away within about twenty hours.[6123] Instead of detoxing, wouldn't it be better not to "tox" in the first place? A recent dermatology review article ended with this summary: "In conclusion, when patients inquire about a diet that might contribute to younger-looking skin, evidence supports the recommendation to follow a WFPB [whole food, plant-based] diet."[6124]

MEDICAL SKIN TREATMENTS

Anti-aging medicine is one of the fastest-growing medical specialties[6125] and often targeted at women, who are urged to restore their youthful appearance by "any and all available means."[6126] Ninety-two percent of

cosmetic procedures are performed on women, most commonly Botox, fillers, and laser or chemical peel skin resurfacing. Each year, millions in the United States undergo cosmetic surgery, including hundreds of thousands of face-lifts, known technically as *rhytidectomies*.[6127]

LOSING FACE

In see.nf/faceliftsbotox, I detail what we know about face-lifts. Basically, none of the techniques has been shown to be definitively better than others,[6128] and they're considered to be relatively safe when performed by a board-certified plastic surgeon.[6129] In the video, I discuss all the complication rates[6130] and the importance of tempering expectations.[6131]

HITTING THE HEADLINES

In the same video, I also cover Botox injections, the most common nonsurgical cosmetic procedure.[6132] In sum, adverse effects are transient and self-limited,[6133] but the increase in injections administered by nonmedical personnel[6134] raises concerns about a potential rise in extremely rare cases of respiratory failure and death occurring hours or even weeks after injection.[6135]

FILLING YOUR FACE

In see.nf/fillers, I cover the second most common cosmetic procedure, volumizing injections of soft tissue fillers.[6136] Adverse outcomes occur in about one in forty procedures, most commonly bruising,[6137] discoloration, swelling, or unsightly lumps and bumps.[6138] The most devastating filler complication is permanent blindness due to an accidental injection into an artery.[6139] More about that in the video, along with similar concerns about the increasing administration of fillers in spa-type (rather than medical) settings[6140] that may use illegal (non–FDA approved) fillers. There have been reports of injections with everything from rubber cement to Fix-a-Flat tire repair sealant, resulting in disfigurement and even death.[6141]

PEEL OUT

Another common cosmetic procedure is the chemical peel. About a million are performed every year, along with another million laser skin

"resurfacings"[6142] to provide a "controlled injury to the face."[6143] The reasoning is that the regeneration, repair, and remodeling of the damage caused to the skin can result in a more tightened appearance,[6144] but peels and laser resurfacings may or may not actually help with wrinkles.[6145] The inflammation caused by these types of facials causes edema (fluid retention) in the face, which, because of the swelling, can cause a transient improvement in the appearance of fine wrinkles but, in the end, may do more harm than good.[6146] Short-term side effects include bruising, swelling, itching, crusting, redness, infection, acne, and milia (little white cysts).[6147] Long-lasting side effects can include persistent redness, pigmentation changes, and scarring.[6148]

DIETARY SKIN TREATMENTS

Some animals use diet to increase their sexual attractiveness. Great tits, distinctive olive-and-black songbirds ubiquitous throughout Europe and Asia, tend to prefer carotenoid-rich caterpillars, which make their breast plumage brighter yellow to become more appealing to potential mates.[6149] Might there be a similar phenomenon in humans?

TANNING BED OF GREENS

When researchers showed study participants digital photographs of Asian, African, and Caucasian women and men and asked them to turn a dial to manipulate the skin tone of their faces until they felt the healthiest-looking color was reached,[6150] both female and male subjects preferred the yellow "golden glow" that can be achieved through "dietary carotenoid deposition in the skin."[6151] As I review in see.nf/glow, the healthier you eat, the healthier you may look, but the increase in facial attractiveness from eating more fruits and vegetables[6152] may drop within weeks once you stop,[6153] so you have to keep it up.

There's an entire tanning industry predicated on the belief that darker Caucasian skin appears to be healthier and more attractive, but research suggests that the perceived improvement in appearance from tanning is due to the associated increase in skin yellowness. When you separate out the shade from the hue, study participants actually preferred lighter—but yellower—skin.[6154] When high "kale" models were pitted against high tan

models, the golden glow from consuming carotenoid phytonutrients won out.[6155] So, may I suggest the produce aisle to get a good, healthy tan … gerine?

SAVE YOUR SKIN

I am not above appealing to vanity, especially for younger individuals for whom surveys suggest eating to improve appearance trumps eating for better health.[6156] So, I'm always excited when I see articles embrace studies with headlines like "Greens to Be Gorgeous."[6157] Fruits and vegetables don't just change our hue, though. As I document in see.nf/internalsunscreen, skin biopsies from women effectively randomized to a daily spinach salad showed a significant increase in collagen production, accompanied by an increase in skin elasticity and a decrease of facial wrinkles.[6158] This may have been due in part to an "inside-out" sunscreen effect, as less DNA damage was noted after the same degree of UV radiation. Kale,[6159] apple,[6160] and a combination of rosemary and grapefruit extracts[6161] had similar effects. Even just ten weeks before swimsuit season (but not four), eating a lot of an antioxidant-rich food, such as tomato paste, can reduce the redness of a sunburn by 40 percent.[6162]

Topical sunscreens and dietary photoprotection with foods like greens[6163] and sweet potatoes[6164] naturally complement each other for safeguarding our skin. Sunscreens have the advantage of working almost immediately and offering much stronger shielding, while *produce* protection builds up slowly over weeks and only achieves an SPF of 4, compared to 10 to 40 or even higher with typical sunscreens. On the other hand, sunscreens have to be deliberately applied, in sufficient amounts, with sufficient coverage—including all the hard-to-reach places—and then can still rub off, wash off, or be sweated off, whereas the protection from plants is ever-present and built-in all over.

ANTIOXIDANT DYNAMICS

Antioxidant levels in our skin are ever-changing hour to hour. Remember that argon laser study from here? Similar technology has been used to show a tight correlation between low antioxidant levels in the skin and the presence of facial furrows and wrinkles.[6165] This is consistent with data

showing significantly less skin aging over a fifteen-year period among those eating high-antioxidant versus low-antioxidant foods.[6166] This constantly fluctuating balance between the antioxidants we deposit in our skin from our diet and the onslaught of daily oxidant stresses sapping our reserves can provide insight into some other lifestyle behaviors that can affect skin health.

For instance, don't forget your beauty sleep. Compared to individuals getting eight hours of sleep, participants who were kept up for thirty-one consecutive hours and allowed only five hours of sleep were rated as having redder eyes, more swollen eyes, darker circles, hanging eyelids, paler skin, more fine lines and wrinkles, and droopier corners of their mouths.[6167] Those who are sleep-deprived are also perceived as being more tired (duh), less healthy, and less attractive than the well-rested.[6168] Over time, the oxidative stress associated with sleep deprivation could potentially translate into long-term differences in skin aging parameters.[6169]

Psychological stress may also affect skin aging.[6170] Higher stress hormone levels are associated with increased perceived age.[6171] Think how U.S. presidents look before and after one or two terms in office.[6172] In an aging study out of Boston, hundreds of participants had photographs taken over a ten-year time span. Those under financial stress, even after controlling for income (and health and attractiveness), were rated as looking significantly older than they were at baseline and aging significantly worse over time.[6173]

Antioxidant dynamics may also explain why alcohol consumption is linked not just to digestive tract malignancies but to skin cancer, too.[6174] As I note in see.nf/sunalcohol, after drinking about three shots of vodka, the level of carotenoid antioxidants in the skin drops dramatically within *eight minutes*,[6175] which translates into sunburn susceptibility that can be mediated by drinking it with orange juice.[6176] But berries are even better, so a strawberry daiquiri may lessen burn risk even more than a screwdriver.

Alcohol consumption does not appear to affect skin aging, though. One study found a significant correlation between skin wrinkles and alcohol consumption,[6177] but ten others found no significant associations in either direction.[6178] What about other beverages?

Perhaps not surprisingly, whole-body dehydration is associated with dry eye syndrome,[6179] a condition that disproportionally affects the elderly.[6180] What about hydration and dry skin? A systematic review found that studies show drinking an extra one or two liters (quarts) of water a day for four to seven weeks may improve skin hydration and decrease symptoms of skin dryness and roughness.[6181]

What about tea or coffee? Skin biopsies taken before and after drinking tea show that green tea compounds are deposited in human skin, but to what effect?[6182] The drinking of coffee[6183] or both tea and coffee[6184] is associated with fewer pigmented spots on the faces of Japanese women, but interventional studies are either absent (in the case of coffee) or disappointing (in the case of tea).

Skin biopsies show that a combination of oral and topical green tea increases the elastic tissue content of skin compared to placebos within eight weeks, but not enough to be noticeable to the naked eye.[6185] EGCG, one of the active components of green tea, can reduce UV-induced skin damage in rats,[6186] but when put to the test over three months in people, green tea supplements with the EGCG equivalent of eleven cups of tea a day showed significant photoprotection,[6187] though the equivalent of five daily cups of tea did not.[6188] Maybe the study period just wasn't long enough? A two-year, double-blind, randomized, placebo-controlled trial found a significant improvement in overall solar damage, redness, and telangiectasias (spider veins) on the sun-exposed arm skin of women randomized to consume the equivalent of about two and a half cups of green tea a day, but the same was also found in those randomized to the placebo group. In other words, just being part of the clinical trial may have led the women to change their sun exposure activities and benefit regardless.[6189]

In see.nf/topicaltea, I cover an extraordinary case report that suggested the topical application of green tea could prevent skin cancers,[6190] presumably due to decreased UV-induced DNA damage,[6191] but for those not at particularly high risk of skin cancer, topical green tea is considered to be too irritating to be used routinely.[6192] Once you already have a basal cell

carcinoma, applying a 10 percent green tea ointment doesn't seem to help.[6193]

An herbal tea that may help is a soothing South African infusion called honeybush (*Cyclopia*). After it was found to protect the skin of "nude" (hairless) mice from UV damage,[6194] water extracts of honeybush were tested in a randomized, double-blind, placebo-controlled trial. Rather than coming up with a placebo tea that looked and tasted the same, the honeybush tea was dried and powdered into capsules to pit against indistinguishable placebo pills. So, it's not clear how much tea was actually being tested, but after twelve weeks, it decreased eye wrinkle volume by about 28 percent more than placebo.[6195]

The other anti-wrinkling beverage may surprise you: hot cocoa. After drinking a beverage with about two and a half teaspoons of natural cocoa powder, subjects had a significant increase in blood flow within the skin within two hours.[6196] Drink it every day for six weeks, and the redness to the same UV dose is down by 15 percent and, after twelve weeks, by 25 percent. Skin thickness, density, and hydration also improved compared to the placebo, a cocoa from which most of the flavanols had been removed. No change was found in wrinkle severity after twelve weeks,[6197] but a twenty-four-week study found a significant improvement in skin elasticity and a decrease in wrinkle depth[6198]—just from adding less than a tablespoon of cocoa powder to their daily diet.

"Wrinkles Should Merely Indicate Where the Smiles Have Been." —Mark Twain

Wrinkles occur where fault lines develop in aging skin,[6199] a process comparable to breaking in leather gloves.[6200] Over time, the skin folding caused by everyday facial expressions etches the temporary grooves into permanent wrinkles.[6201] In see.nf/wrinkleformation, I cover the roles of Botox, "antiwrinkle" pillows and adhesive strips, genetics, and even the light emitted by smartphone screens. Of course, kids can scrunch up their faces all they want because the architecture of their skin has yet to be irreparably damaged,

so the key to preventing wrinkles is preventing the underlying structural damage that makes your skin susceptible to them via choices such as tobacco avoidance and regular sun protection.[6202]

AN ANTI-WRINKLE DIET

If you already have some wrinkles, is there any diet that might reduce them? While a predominantly meat-and-junk eating pattern was associated with more wrinkles,[6203] both a fruit-dominant diet and one with more fruits, vegetables, and nuts were associated with significantly less wrinkling.[6204] I run through all the specific foods associated with more or less wrinkling in see.nf/antiwrinkle, as well as the interventional data on almonds, flax, soy, and mangos—yay,[6205] yay,[6206] yay,[6207,6208] and nay,[6209] respectively.

The paucity of interventional trials limits the confidence one can put into recommendations, but the best approximations were summed up in a 2020 dermatology review titled "An Anti-Wrinkle Diet." Dietary defense strategies included antioxidant-rich foods (see the Oxidation chapter), anti-inflammatory foods (see the Inflammation chapter), anti-glycation foods (see the Glycation chapter), fiber-rich foods for our microbiome, foods like broccoli that boost DNA repair, and foods shown to be able to block collagen- and elastin-munching enzymes (at least in vitro), such as garlic, turmeric, and ginger. In other words, the best approximation for an anti-wrinkle diet is one that's centered around whole plant foods.[6210]

VEGAN VULNERABILITIES

One would expect that plant-based diets might be ideal for preventing and reversing skin aging,[6211] but there are a series of studies that expose some potential vulnerabilities. For example, the skin of vegan patients was found to be more vulnerable to inflammation in a study of phototherapy for psoriasis. Phototherapy typically involves the combination of light-sensitizing drugs with a UV lamp or laser light. After eight weeks of treatments, significantly more vegans (42 percent) ended up suffering severe redness as a side effect when compared to vegetarians (17 percent) or omnivores (10 percent). Why might that be? Because the vegans came

preloaded with *furocoumarins*, photosensitizing compounds found naturally in certain fruits and vegetables, such as parsley, parsnips, celery, and citrus. The vegans in the study were reportedly eating 1.3 pounds (600 g) of parsley a week. (That's six cups of parsley in seven days!) They also ate ten pounds of citrus, including two pounds of lemons, and pounds of parsnips and celery each week. It's great that they were getting such healthy produce, but these furocoumarin-rich foods could certainly make your skin more sensitive to getting sunburned.[6212]

Another phototherapy study, this time to destroy precancerous skin lesions, also found more severe skin inflammation in the vegan participants, as well as prolonged healing times. In the omnivores, the average healing time to wound closure was about ten days, which is considered normal. Complete skin healing in the vegans, however, took more than twice as long, twenty-two days.[6213] A protraction of healing and poorer results were also found in both laser tattoo removal in vegans (average healing time of twenty-three days) compared to omnivores (average healing time of nineteen days)[6214] and ablative laser skin resurfacing.[6215] This could be due in part to excess photodamage from eating more photosensitizing produce, but vegans also seem to have delayed healing of wounds unrelated to light exposure.

In a comparison of postsurgical scars from excision of skin cancers between vegans and omnivores, the vegans didn't seem to heal as well. Reduced collagen synthesis was suspected. Collagen is not only the major component of skin in general, but it's also the main connective tissue directly involved in wound healing.[6216] Impaired collagen synthesis could also explain why cosmetic fillers are longer-lasting in omnivores, since the mechanical stress of filler injection works to boost collagen synthesis,[6217] and why micro-focused ultrasound skin treatments seem to work better. Intense focused ultrasound is used to treat sagging skin by generating temperatures up to 140°F (60°C) to trigger a repair process that involves new collagen formation. The researchers suggested that less collagen production would explain why vegan patients experienced significantly less improvement.[6218]

Do those eating plant-based diets really make less collagen? Apparently so. Collagen synthesis rates appear to be about 10 percent lower in vegetarians.[6219] The question is *why*. In every single one of the

aforementioned studies that measured vitamin B_{12} levels, the vegan participants were found to be deficient (averaging < 200 pg/mL),[6220,6221,6222,6223,6224] and both human and animal studies show that B_{12} is important for collagen synthesis[6225,6226] and wound healing.[6227,6228] Homocysteine, a toxic by-product of B_{12} deficiency, appears to impair collagen cross-linking,[6229] which confers connective tissue mechanical integrity.[6230] It's critically important that everyone consuming plant-based diets include a regular, reliable source of vitamin B_{12}. (See here.)

Another potential contributor is increased protein needs during wound healing. For example, for those trying to heal pressure-induced skin ulcers, recommended protein intake goes from 0.8 g a day per kg of body weight (approximately 0.4 g per lb) up to 1.25 to 1.5 g/kg (about 0.6 to 0.7 g/lb).[6231] This explains why most of a dozen studies of protein supplementation for pressure ulcers found a greater reduction in ulcer size with supplementation.[6232] Vegans average about 1.0 g/kg a day, which is more than enough protein for day-to-day needs,[6233] but omnivores average about 1.3 g/kg, so they may already be getting the excess protein that could be helpful during wound healing.[6234] So, while recuperating from their next tattoo removal, I would recommend vegans up their legume intake.

COLLAGEN SUPPLEMENTS

Oral collagen supplementation has become quite the trendy treatment for skin aging,[6235] available in an array of pills, powders, and products from bars and gummies to collagen-fortified coffee and beer.[6236] Social media is said to be "inundated with paid ads marketing unsubstantiated claims."[6237] What claims, if any, can be substantiated?

I review all the studies on collagen supplementation for skin aging in my video see.nf/collagen. In short, most of the studies have been funded by collagen supplement manufacturers,[6238] and the overall quality of evidence has been considered by reviewers to be "limited, contradictory,"[6239] or "not particularly robust."[6240] A 2022 review titled "Myths and Media in Oral Collagen Supplementation for the Skin, Nails, and Hair" in the *Journal of Cosmetic Dermatology* concluded, "Dermatologists should be aware of the unsubstantiated proclamations of collagen made by companies … [that] surpass any evidence currently supported by the literature," and, given the

insufficient evidence, "collagen cannot be routinely recommended.…"[6241] The evidence is considered "particularly unconvincing," another review determined, when compared to methods more definitely shown to have a positive effect on skin collagen, such as sunscreen use, smoking cessation, and a healthier diet.[6242]

In see.nf/collagendiet, I describe how to stimulate your own collagen synthesis, for example, by ensuring a daily vitamin C intake of at least 95 mg,[6243] which is higher than the current recommendations.[6244]

Though we don't have evidence that collagen is superior to other proteins for skin aging,[6245] if you do want to try it, consumers are advised to contact the manufacturers to clarify sources. Most collagen supplements don't disclose this information—and for good reason.[6246] Terrestrial sources of collagen can include a witch's brew of duck feet, frog skin, kangaroo and rat tails, alligator bones, and horse tendons.[6247] Aquatic sources are mainly from the skins, bones, heads, scales, fins, and entrails of fish.[6248]

Recommended questions for manufacturers include, "What measures were used to protect against contamination or adulteration? If sourced from fish, were low-mercury fish used? If sourced from cows, what steps were taken to ensure that no brain or nervous system matter was included, in order to prevent prion disease?"[6249] In the United States, collagen is exempt from FDA prohibitions against using risky tissues, like brains, that are intended to protect consumers against bovine spongiform encephalopathy (mad cow disease).[6250]

For food safety, religious, ethical, and allergy reasons, there have been calls for non-animal sourcing.[6251] For example, 2 to 4 percent of the population is allergic to bovine collagen.[6252] To solve the mad cow conundrum, there have been calls to genetically engineer cattle without prions to "offer a safe source of collagen-based materials," but why not just get plants to make it? A technique has been developed to produce collagen from plants,[6253] but it has not yet reached commercial viability. It's hard to beat the cost of feet.

TOPICAL SKIN TREATMENTS

Over-the-counter "anti-aging" products constitute a billion-dollar industry.[6254] There is a "psychological effect from spending more," noted a

review on the myths of anti-aging skin care, but "don't be seduced by fancy packaging and high prices."[6255] Many products advertise dramatic results that are frequently exaggerated and misleading[6256] and are rarely supported scientifically.[6257] An independent product testing institute questioned the efficacy of anti-aging creams generally, finding that beneficial effects could only be picked up using sensitive instruments without becoming clinically detectable and suggested these products may not work any better than typical moisturizers.[6258]

Cross-sectional studies of Chinese[6259] and British women found that those who regularly used facial moisturizers were guessed to be about two years younger than women of the same age who didn't. However, a third, larger (Dutch) study did not. Regardless, snapshot-in-time studies can never establish cause and effect.[6260] Studies on moisturizers are limited, but they can improve the appearance of dry skin, which can otherwise look discolored, flaky, and rough.[6261] Moisturizers can hydrate the skin and may reduce the appearance of fine lines by 15 to 20 percent, called "the oldest trick [in] the cosmetic industry," but they may not do anything to treat the underlying cause.[6262]

DAILY SPF 15 FACIAL MOISTURIZER

Whether facial foundation, night cream, or anti-aging "serum," the formulations of most skin products are basically a moisturizer combined with purported active ingredients for marketing appeal.[6263] Which ingredients are *actually* active anti-aging agents? I bet you can guess which is the single most effective skincare component out there when I offer as a hint the reminder that up to 90 percent of the visible aging of someone's face is due to sunlight.[6264] From an anti-aging standpoint, the most biologically active ingredient in skin products is sunscreen.[6265]

Considered the single most important practice for maintaining youthful skin is the daily application of sunscreen and employing other protective measures, like wearing a hat. Everything else you can do for your skin pales in comparison, especially for those with pale skin.[6266] UV-A rays are primarily responsible for skin aging, whereas UV-B are the rays that cause sunburn. A broad-spectrum sunscreen covering both is recommended since both types of UV contribute to cancer risk.[6267] To prevent skin cancer, the

American Academy of Dermatology recommends sunscreen with an SPF of 30 or higher,[6268] but an SPF of 15 can prevent skin aging.[6269] How do we know? Because it's been put to the test.

Nine hundred adults were randomized to years of recommended daily sunscreen use or continuing with their own discretionary use. (It was considered unethical to withhold protection by giving people placebo sunscreen.) In the end, 77 percent in the recommended daily sunscreen group applied sunscreen at least three to four days per week compared with only 33 percent in the discretionary use group. Would that be enough of a difference to make a difference? Yes, there was significantly less skin aging in the instructed daily use group. In fact, they suffered no detectable increase in skin aging over the four-and-a-half-year study. The researchers concluded, "Regular sunscreen use retards skin aging in healthy, middle-aged men and women."[6270]

Although sunscreens are primarily intended to prevent further facial aging rather than reverse preexisting photodamage,[6271] some in the daily sunscreen use group did show an improvement in skin texture. The results are all the more striking given that the control group was told to continue to use sunscreen and hats whenever they thought it would be needed, suggesting people are poor judges or planners for excess UV exposure when left to their own devices. So, a daily facial moisturizer with an SPF 15 is recommended, even if it is cloudy or raining outside.[6272] Considered the "gold standard" for anti-aging skin care: "daily use of sunscreens in the daytime and retinoids at night.…"[6273]

NIGHTLY RETINOIDS?

While sunscreen can prevent further skin photoaging, tretinoin can reverse some of what's already been done. Also known as all-trans retinoic acid and sold under a variety of brand names, including Retin-A, tretinoin is a prescription-only form of vitamin A that can visibly improve mild to moderate photodamage, including fine and coarse wrinkles, freckles, and other pigmentation, and improve overall skin texture after months of regular use,[6274] though it can cause redness, stinging, burning, itching, and peeling in a high proportion of patients.[6275] There are gentler, less potent, over-the-

counter topical retinoids: retinaldehyde, retinol, and retinyl esters (acetate, palmitate, or propionate). I compare and contrast them in see.nf/retinoids.

Of all the nonprescription retinoid options, retinol may be the preferred choice,[6276] but tretinoin has by far the most robust track record of efficacy,[6277] so why not ask your doctor for a prescription? Because, as I detail in the video, long-term topical tretinoin use may increase your risk of an even more stinging side effect: premature death.[6278]

TOPICAL NICOTINAMIDE

What other skin cream components have been shown to help with skin aging? While placebo-controlled trials are the standard in most medical research, they are still all too rare for cosmetic products.[6279] This raises efficacy questions, so many are left with simply buying "hope in a jar."[6280] This also raises safety concerns. To this day, cosmetics contain an array of toxic chemicals. Of the more than 12,000 synthetic compounds used in cosmetics, less than 20 percent have been recognized as safe.[6281] Of course, this doesn't mean *natural* ingredients are necessarily harmless. Poison ivy is as natural as you can get, but you wouldn't want to rub it on your face.[6282] However, there are some relatively safe natural options with varying degrees of efficacy.

Topical nicotinamide, also known as *niacinamide*, is a form of vitamin B_3 that is nonirritating[6283] and has been described as "one of the best studied cosmeceutical ingredients for anti-aging,"[6284] but it looks like there are only three placebo-controlled human studies,[6285] which gives you an idea of the state of cosmeceutical science.

Skin photoaging is largely mediated by UV-induced free radical formation. One of the consequences of excess sun exposure is the oxidation of sugars and proteins in the skin into yellow-brown pigment that gives aging skin a yellowing, sallow appearance. Since nicotinamide is a precursor to two potent antioxidants, the hope is that this process could be interrupted,[6286] as revealed in the first study, titled "Topical Niacinamide Reduces Yellowing, Wrinkling, Red Blotchiness, and Hyperpigmented Spots in Aging Facial Skin."[6287]

It was a twelve-week, double-blind, placebo-controlled, split-face, randomized clinical study of middle-aged women. In a split-face study,

each subject is her own control. The active formulation (in this case, 5 percent nicotinamide in moisturizer) is rubbed on one side of her face and the placebo (straight moisturizer) on the other half, though neither she nor the researchers know which side is which until the code is broken at the end. This controls for skin type and administration technique, since different people apply facial products differently. However, people often use the same hand to apply creams to both sides of their face. So, unless specified that different gloves be worn or hands washed in between, there can be cross-contamination.[6288]

At the end of twelve weeks, there was a small (5 percent) reduction in wrinkles and fine lines and a slowing in the development in blotchiness, spots, and sallowness on the nicotinamide side of the face.[6289] A subsequent publication noted an improvement in skin elasticity as well.[6290] The magnitude of the effects may only be one-third to one-fifth as good as for tretinoin,[6291] but there were no reports of excess skin irritation.[6292]

The other two studies were similar split-face trials, but with 4 percent nicotinamide products. One study found no significant effect on facial wrinkles compared to placebo,[6293] but the other, which was limited to crow's-feet wrinkles around the eyes, found significant improvements in both subjective and objective measures by the end of the eight-week study. Sixty-four percent of the nicotinamide-side eye wrinkles underwent moderate or marked improvement compared to zero percent on the placebo side.[6294]

TOPICAL VITAMIN C

If skin aging is mediated by oxidative stress, why not just directly apply antioxidants like vitamin C? Topical application of antioxidants can lead to levels in the skin that are ten times what is achieved with oral dosing (at least in the skin of mice).[6295] According to a recent review on topical anti-aging skin care by a prominent Beverly Hills plastic surgeon, "At a minimum, patients should be encouraged to use daily sunscreen, a topical retinoid every night, and a topical antioxidant daily."[6296] But which antioxidant? Only one has been clearly shown to work.

Despite its ubiquity in skin care products, there is no evidence to support any role for topical vitamin E in skin aging, whether for wrinkles,

discoloration, or texture,[6297] and the one study on topical CoQ_{10} found that it also failed to work significantly better than placebo.[6298] There is, however, one type of vitamin C that has been shown to help.[6299]

Skin biopsy studies show that the topical application of a 5 percent solution of L-ascorbic acid (also known as ascorbic acid, the type of vitamin C found in food) significantly increases the expression of collagen in human skin compared to placebo, suggesting "functional activity of the dermal [skin] cells is not maximal in postmenopausal women and can be increased."[6300] A split-face study involving the application of three drops of a 10 percent L-ascorbic acid solution for three months found significant improvements over the placebo side of the face in fine and coarse wrinkles, sallowness, and skin tone (firmness).[6301] Not knowing which side was which, sixteen out of nineteen (84 percent) patients correctly guessed the vitamin C side as the one showing improvement.

Unfortunately, L-ascorbic acid is unstable in creams. It turns an unsightly brown when it oxidizes, limiting its shelf life.[6302] So, instead, the skin care industry uses more stable vitamin C esters or derivatives such as ascorbyl palmitate, ascorbyl stearate, magnesium ascorbyl phosphate, or ascorbic acid sulfate.[6303] Unfortunately, there is no evidence that these compounds have comparable effects, likely because they are poorly absorbed and only minimally convert to the active form. The good news is that you can make your own.

Although vitamin C concentrations as low as 3[6304] and 5[6305] percent have been shown to have anti-wrinkle effects in split-face or split-neck and arm studies, at least 10 percent is recommended. The 10 percent solution used in the aforementioned split-face study retails for a ridiculous $127 per ounce.[6306] You can make a DIY solution by simply buying L-ascorbic acid in bulk and mixing 3 g into 30 g of water at a cost of about a nickel per ounce, thousands of times cheaper. You can mix it in an eyedropper bottle. Drip just four or five drops on the palm of your hand, and use your fingertips to apply it over your face, neck, and upper chest daily. Be careful not to get it in your eyes, though.

Alpha Hydroxy Acids

There is a reason there's a long historical use of fruit purees as facial masks.[6307] Alpha hydroxy acids, also known as fruit acids, are used at high-strength concentrations in chemical peels, but lower concentrations are sold over the counter as exfoliants.[6308] I review the four placebo-controlled studies in see.nf/alpha. In sum, alpha hydroxy acids can help with past photodamage, but they may make future damage worse by increasing skin photosensitivity.[6309]

SKIN CANCER

More than a million new cases of skin cancer are diagnosed every year, affecting about one in three Americans in their lifetimes.[6310] Risk increases with age[6311] and the incidence has been on the rise.[6312] Should we get screened for skin cancer by getting periodic full-body exams? The Skin Cancer Foundation recommends annual physician exams,[6313] but the official U.S. Preventive Services Task Force position is that there is insufficient evidence to support any interval of skin screening.[6314] This is based in part on a national experiment in Germany.

In 2003, a total body skin exam screening campaign was started in the German state of Schleswig-Holstein. By 2008, melanoma mortality rates had dropped by nearly 50 percent.[6315] Given the apparent resounding success, the program was expanded nationwide in 2009. Sadly, five years later, there was no significant change in melanoma mortality. In fact, national rates had even crept up a bit, and the apparent gains in Schleswig-Holstein vanished back to baseline.[6316] Was the original drop just due to chance?[6317] More nefariously, some have suggested that German doctors, motivated by the financial incentive—a per-screening bonus of €15 (about $20)—started intentionally or unconsciously underreporting melanoma on death certificates to make the program appear effective.[6318] Either way, skin screening has not yet been shown to save lives.[6319]

Note that the USPSTF's lack of endorsement for regular medical skin screening is only in reference to the mass screening of asymptomatic healthy individuals. If you have a suspicious mole or are otherwise at heightened risk due to a personal or family history of skin cancer, you

should definitely bring it up with your healthcare provider. The ABCDEs of mole suspiciousness for melanoma, the deadliest form of skin cancer, are A for asymmetry, B for border irregularity, C for multiple colors, D for diameter (larger than a pencil eraser), and E for evolving, a change in size, shape, color, elevation, or symptoms (such as bleeding, itching, or crusting). Basically, any lesion that is new, changing, or unusual (compared to other moles) is suspect.[6320]

SLIP, SLOP, SLAP, SEEK, SLIDE

If universal screening isn't going to save us from skin cancer, what will? The same and best way to reduce the risk of all common cancers: primary prevention. In other words, preventing the cancer from emerging in the first place. Here's another mnemonic, Australia's SunSmart 5 S's program (featuring Sid the Seagull): slip on clothing, slop on sunscreen, slap on a hat, seek shade, and slide on sunglasses.[6321]

A single blistering sunburn on a child may double the risk of developing basal cell or squamous cell skin cancers later in life,[6322] whereas regular use of sunscreen during childhood has been estimated to reduce the incidence of these cancers by 78 percent.[6323]

Ideally, protective clothing should fully cover the arms and legs.[6324] For regular clothes without an ultraviolet protection factor (UPF) tag, densely woven, thicker, and darker cloth tends to be more protective. (Hold a garment up to the light and see whether it shines through.)[6325] Hats should shade the whole head.[6326] Wrap-around sunglasses can better shield the delicate skin around the eyes that may not be protected by sunscreen, and lip products with at least 30 SPF should be applied generously to fully cover the lips.[6327]

Oral Nicotinamide

After decades of use in the cosmetics industry to prevent skin aging,[6328] researchers decided to put nicotinamide to the test for skin cancer prevention. Normally, it would be difficult to fund studies on nonpatentable products that only

cost a few cents a day, but preliminary findings[6329] were so extraordinary that ONTRAC was born. Oral Nicotinamide to Reduce Actinic Cancer was a publicly funded, phase III (efficacy-determining) trial randomizing hundreds of people with personal history of skin cancers to 500 mg of nicotinamide or placebo twice a day for a full year. By the end, there were 463 new skin cancers in the placebo group versus 336 in the nicotinamide group. About 25 percent fewer cancers with no significant side effects, for just pennies a day.[6330] Details in see.nf/cancernic.

WHAT ABOUT SENSIBLE SUN EXPOSURE?

The UV rays in sunlight are considered to be a complete carcinogen, meaning they can not only initiate cancer but also promote its progression and spread.[6331] The incidence of melanoma, the scariest kind of skin cancer,[6332] has tripled over recent decades[6333] in part likely due to the increased use of tanning salons.[6334] Tanning beds and their UV rays are considered to be class 1 carcinogens, like tobacco, asbestos, plutonium, and processed meat.[6335] For more on tanning, check out see.nf/tanning.

Unlike natural sunlight, tanning bed lights emit mostly UV-A, which is the worst of both worlds: cancer risk without any vitamin D production.[6336] Sunlight supplies 90 to 95 percent of vitamin D for most people.[6337] In fact, as I detail in see.nf/sun, modeling studies suggest that low vitamin D levels from sunlight avoidance may kill more people[6338] than the skin cancer from sun overexposure.[6339] So, on balance, the benefits of "sensible sun exposure"[6340] might outweigh the risks, but why accept any risk at all when we can get all the vitamin D we need from supplements? In fact, the model got those estimates on preventing internal cancers with vitamin D from intervention studies involving giving people vitamin D *supplements*, not exposing them to UV rays.[6341] The sun debate is framed as needing to choose between the lesser of two evils: skin cancer or vitamin D deficiency. This framework ignores the fact that there's a third way: vitamin D supplements.

Black Salve Swindle

Skin cancers are usually just excised, but what about using "black salve" instead? Listed as a "fake cancer cure" by the FDA and similarly condemned by the American Academy of Dermatology, black salve is still promoted on the internet as a "natural alternative remedy for skin cancers." I detail how damaging and dangerous it can be in see.nf/salve.

Some cancer patients are duped by disinformation, but many who refuse conventional therapies described their oncologists as "impersonal," "'intimidating,' 'cold,' 'uncaring,' 'unnecessarily harsh,' 'thinking they were God,' and 'not even knowing [their] names,'" and becoming "adversarial" when questioned about recommended treatments. Few believed their doctors had their best interests in mind, and many said they would have been more likely to initially accept conventional treatment had they felt they had "caring physicians" who treated them with respect.[6342]

SUNSCREEN PROVEN TO PREVENT CANCER

As I noted before, there are randomized controlled trials that have shown that regular use of sunscreen can arrest signs of skin aging,[6343] including biopsy-proven reductions in UV-related skin damage.[6344] But, are there interventional trials proving that sunscreen can prevent cancer? Yes.[6345] In fact, it can actually reverse the progression of precancerous skin growths, causing them to spontaneously regress and vanish. I profile the mind-blowing study in see.nf/sunscreenuse. The body can sometimes heal itself once we stop bombarding it with so many cancer-causing rays.[6346]

PROPER SUNSCREEN USE

For maximum effectiveness, sunscreen needs to be applied properly. Several studies have demonstrated that this rarely happens,[6347] with as few as one in twenty-five complying with recommendations.[6348] In the same

video (see.nf/sunscreenuse), I detail the proper amount using the "teaspoon rule,"[6349] why SPF 50+ is often recommended[6350] even though SPF 15 should theoretically be enough to prevent cancer,[6351] how cloudy skies can sometimes be even worse,[6352] and timing of application before[6353] and after water[6354] and sand[6355] exposure.

It's Black and White

The average built-in SPF of Black skin (also known in the medical literature as "ethnic skin" or "SOC," skin of color)[6356] is 13, compared with only 3 for white skin.[6357] Though there have been no interventional studies on sunscreen effectiveness for skin cancer prevention in people with darker skin, SPF 13 is not considered sufficient sun protection, so the American Academy of Dermatology recommends regular sunscreen use with an SPF of 30 or higher for people of all skin shades.[6358] Unfortunately, only about 12 percent of non-Hispanic Blacks and 31 percent of Hispanics report regularly using sunscreen, compared to around 44 percent of non-Hispanic whites.[6359] Despite this, the incidence of melanoma, the deadliest skin cancer, is five times lower in Hispanics compared to whites and twenty-five times lower among Blacks. However, the mortality rate if melanoma does develop is higher among Blacks, presumed to be from delayed diagnosis.[6360]

Photoaging in darker skin is less likely to appear as wrinkles and more likely to appear as pigmentation issues, such as uneven skin tone, melasma (dark patches),[6361] and dermatosis papulosa nigra (small dark bumps on the face).[6362] To combat skin aging and cancer risk, transparent chemical sunscreens are often marketed to those with darker skin, since the mineral sunscreens (i.e., titanium dioxide and zinc oxide) often leave a white residue. However, there are

now micronized mineral sunscreens that are much less visible after application.

MINERAL RIGHT

What kind of sunscreen should you use? Cream-based is preferable to spray-on, since it's easier to see where you've applied the sunscreen.[6363] To help with adequate coverage, spray-on sunscreens should be rubbed around immediately after spraying.[6364] I don't recommend aerosolized sunscreens. They are flammable and can combust on the skin upon exposure to an open flame even after the sunscreen has dried.[6365] What's more, the safety of breathing in aerosolized sunscreen chemicals has not been adequately studied,[6366] though, frankly, the same thing could be said about rubbing them on your skin.

As I detail in see.nf/safestsunscreen, concerns about the systemic absorption of sunscreen chemicals were underscored by the 2019 FDA bombshell that none of them can be considered generally recognized as safe. Only two active ingredients got the green light, the two nonchemical "mineral" sunscreens titanium dioxide and zinc oxide. The revelation was based on a growing body of evidence that transdermal (through-the-skin) absorption of sunscreen chemicals was greater than we thought, raising "previously unevaluated safety concerns."[6367] Unevaluated, because previously we didn't think so much got into our bloodstreams.

TRIM THE FAT

Other than nicotinamide, how else might we protect against skin cancer from the inside out? Based on studies showing that high-fat diets accelerated skin cancer formation in mice[6368] and population studies showing higher cancer rates tied to higher-fat diets,[6369] the National Cancer Institute and a Veterans Affairs research team published striking results in *The New England Journal of Medicine* showing that randomizing those with a history of skin cancer to a lower-fat diet resulted in a tenfold drop in skin cancer rates.[6370] Details in see.nf/lowfatskin.

VARICOSE VEINS

Varicose veins are not just a cosmetic issue. They can be associated with feelings of pain, heaviness, and itchiness.[6371] Compression stockings were traditionally the standard therapy for management of symptoms,[6372] but over the last decade, the lack of evidence for compression efficacy combined with the development of minimally invasive endovenous ablation techniques has shifted treatment recommendations.[6373] (Details in see.nf/varicose.) However, neither treats the underlying cause.

Topical Vinegar

In see.nf/vein, I profile a study titled "The Effect of External Apple Vinegar Application on Varicosity Symptoms, Pain, and Social Appearance Anxiety: A Randomized Controlled Trial."[6374] Topical vinegar[6375] (not pee)[6376] can help with jellyfish stings, but not eczema.[6377] What about varicose veins? See the video for details, but the potential harms of applying undiluted vinegar[6378] probably outweigh the questionable benefits.[6379]

ANTI-VARICOSITY DIET

In Uganda, a survey found only six cases of varicose veins out of five thousand adults.[6380] Perhaps rural Africans had more than fifty times fewer varicose veins for the same reason that they had fifty times less heart disease, up to fifty times less colon cancer, and up to more than fifty times less of other "pressure diseases," such as diverticulosis, hiatal hernia, and hemorrhoids.[6381] Because their diet was so packed with whole plant foods, rural Africans were among the only known populations ever recorded eating more than 100 g of fiber a day, which is the amount that is considered normal for our species.[6382]

I mention in the Preserving Your Bowel and Bladder Function chapter and detail in see.nf/varicose how straining at stool can push blood flow back into the legs and cause the valves in the veins of our legs to fail.[6383]

The root cause of straining is the effort needed to pass unnaturally firm stools, but we can treat that cause by eating enough fiber-containing whole plant foods to create stools so large and soft that you could pass them effortlessly. Given the fiber connection, it's no surprise that Western vegetarians also have lower rates of pressure diseases like diverticulosis,[6384] hemorrhoids, and varicose veins,[6385] but that might not be the only reason. A study of elderly vegetarians found they also have a much lower incidence of varicose veins under the tongue, as well as fewer sublingual bleeding capillaries, a condition known as *caviar tongue*. Given the dilation of veins and thinning of blood vessel walls characteristic of scurvy, the researchers suspect the low rates of varicose veins in vegetarians may also have to do with their greater vitamin C intake.[6386]

NAIL HEALTH

According to the American Academy of Dermatology, nearly everyone will experience some sort of nail disorder during their lifetime. As we age, our nails grow more slowly, become more brittle, and can start to appear pale, dull, or opaque. Starting around age twenty-five, nail growth rates slow by about a half a percentage point a year, perhaps one of the reasons we are more likely to be affected by nail fungus as we get older, the most common of nail disorders.[6387] The prevalence of nail fungus, also known as *onychomycosis*, rises from about 2 percent in our youth to 20 percent over the age of sixty and affects around half of seventy-year-olds.[6388]

TREATING FUNGAL TOENAIL INFECTIONS

Nail fungal infections typically strike the toenails, causing nail discoloration, deformity, detachment, thickening, crumbling, and ridging. They are stubborn to treat, as the fungus can hide deep inside the nail, protected from the blood supply on one side and anything you want to put on topically from the other. So, even if you're able to beat it back, it often recurs due to residual infection.[6389]

Onychomycosis is most commonly treated with oral antifungal drugs[6390] because they are much more effective than topical antifungals, but they carry more side effects and drug interactions.[6391] Terbinafine, sold as Lamisil, is typically the drug of choice for treatment in the elderly.[6392] It can

cause a metallic taste in the mouth by the second month of treatment, and skin rashes are common and sometimes severe.[6393] Other common side effects include headache and gastrointestinal symptoms, with rare cases of liver, kidney, and heart failure.[6394] Cure rates in the elderly from oral antifungals are only about 64 percent, but that's a lot better than the topical drugs.[6395]

Oral antifungals are typically given for twelve weeks for toenail infections, whereas topical antifungals may take twelve months. (Fingernail fungus is usually treated in half the time.) Such long treatment courses can limit patient compliance, especially among those who want to use nail polish to cover it up, and, even after a full year of daily application, cure rates for most topical medications are only about 9 percent versus around 1 percent for placebo.[6396] There are some newer topical agents that can be applied once or twice a week that may work better, but, apparently, not significantly so.[6397] Given the poor response rate, topical treatment alone is generally only recommended in mild cases or where oral drugs are contraindicated.[6398] (For example, terbinafine is not recommended for people with liver disorders.[6399]) To increase the cure rates, oral and topical treatments can be combined.[6400] Based on in vitro data on the antifungal effects of an acidic pH,[6401] some recommend nightly diluted vinegar foot baths of half water and half vinegar before topical antifungal application.[6402]

What about other natural remedies? Diluted tea tree oil appears to help against the fungus that feeds on your scalp to cause dandruff[6403] and the athlete's foot fungus between your toes, so what about topical application for nail fungus?[6404] As I detail in see.nf/teatree, it was pitted head-to-head against the popular antifungal medication clotrimazole, sold as Lotrimin, in a double-blind, randomized, controlled trial and was found to be comparable in efficacy of cure, clinical assessment, subjective improvement, and even cost.[6405] Even better, though, is to treat the underlying causes.

Preventing and Treating Ingrown Toenails

While fingernails tend to become thinner with age,[6406] toenails can become thicker and harder, making them more

difficult to cut.[6407] To prevent toenails from becoming ingrown, when the side or corner of the nail digs into the adjacent flesh, toenails—especially on the big toe—should be trimmed straight across.[6408] Unlike the curve you get trimming your fingernails, the top of your toenails should make a straight line. You can round the corners,[6409] but the nail should always extend beyond the skin on both sides.[6410] Another main cause of ingrown toenails is ill-fitting footwear.[6411] Shoes that are that too tight or small can push the skin of your toe into your nail.

Minor ingrown toenails can be treated at home with cotton packing.[6412] As soon as you feel the corner of your toe getting inflamed, twist off a wisp of cotton from a cotton swab or a cotton ball. Insert it under the corner of your nail, and try to stuff it under and along the lateral edge of the nail to protect the underlying skin.[6413] Although it can be painful to get it in there, you should experience immediate relief when it's in place.[6414] Obviously, if it continues to get worse, see a healthcare professional.

PREVENTING FUNGAL TOENAIL INFECTIONS

First there's the pathogen. The leading culprit is the same fungus that also causes jock itch, ringworm, and athlete's foot.[6415] So, keeping feet clean and dry can help prevent the foot from being a fungal reservoir.[6416] Then, we can prevent fungal penetration of the nail by making sure nail grooming instruments are sanitized. Even sharing nail polish can be risky, as the fungus can live for months in top coat products.[6417] Artificial nails can put fingernails at risk,[6418] presumed to be because the acrylic nails trap dampness that would otherwise evaporate through the nail.[6419] (Due to the low-fat content of nails, they are normally about a thousandfold more permeable to water than skin.[6420])

Then, there's the host. Fungal nail infections may be a manifestation of poor peripheral blood circulation that would normally allow your body's natural defenses to keep the fungus from taking root in the first place. A study of four hundred patients found a greater than 50 percent reduction in

blood flow in patients with athlete's foot and nail fungus compared to patients without. So, fungal nail infections may just be a symptom of an underlying process, such as declining immunity or circulation, which can help explain why the eradication of these infections can be "unrealistic." This has led to a fatalistic response: "A more appropriate goal may be the amelioration of symptoms…."[6421] But, if circulation is a problem, why not instead try to improve the circulation?

We've known since the 1950s, from one of the first dietary cardiovascular disease reversal studies ever published, that you can effectively turn peripheral artery disease circulation on and off like a light switch within days just by switching people between a low-fat plant-based diet and the more conventional diet that contributed to the problem in the first place.[6422]

Separation Anxiety

Many over-the-counter products purport to improve nail quality, but little evidence supports these claims and the products can sometimes even make things worse. Cuticles serve a function. They are a barrier to pathogens and should be left in place, not cut or pushed back. The nail surface shouldn't be filed, as the thinning may make the nail prone to split, and sharp objects should not be placed under the nails, as they can breach the onychodermal band, the natural smile line that seals the nail bed against infection, which can increase the risk of onycholysis, the partial separation of the nail from the nail bed.[6423]

Acrylic nails can also be a predisposing factor for onycholysis, as the adhesive can be stronger than the natural bond between the nail and the nail bed.[6424] The accumulation of moisture beneath artificial nails can also make the nail more likely to detach. Nail hardeners are another potential cause because they contain up to 5 percent formaldehyde (also listed as "formalin" or "methylene glycol" on the

label),[6425] which can cause inflammation that can lead to nail separation.[6426]

HOW TO PREVENT BRITTLE NAILS

Brittle nails affect about one in five, with women affected about twice as frequently as men.[6427] Reported risk factors include dehydration, certain chemicals, and trauma.[6428] A common trope is that nail hardness depends on nail hydration. Nails become soft when overhydrated and are said to become brittle when they get too dry,[6429] leading to advice to soak brittle nails every day[6430] and apply nail moisturizing creams, oils, or ointments.[6431] When actually put to the test, though, the water content of brittle fingernails didn't seem significantly different than that of normal fingernails. In fact, the brittle nails had slightly more water. What did appear linked to the risk, however—tripling the odds of brittle nails—was professional manicures.[6432]

Rather than manicures leading to brittle nails, might those with brittle nails just be more likely to get manicures?[6433] Nail cosmetics, including nail polish removers, solvents, nail hardeners, cuticle removers, and premixed acrylic gels, as well as procedures such as nail wrapping and nail sculpturing, can weaken the very structure of the nail. You'd think nail hardeners would help, but, again, the formaldehyde in these products may do more harm than good in the long term.

At home, choose non-acetone nail polish removers (like acetate) and try to minimize use to once a week or less,[6434] as they are considered a major cause of brittle nails.[6435] Artificial nails can protect brittle nails, but the problem is that removal is always traumatic for the nail and prolonged use may weaken the nail by reducing oxygen transport.[6436] Finally, prevent trauma by avoiding filing the surface of your nails or subjecting them to repetitive stress, such as from typing.

BIOTIN FOR BRITTLE NAILS?

Biotin supplements for nail growth are popular,[6437] but, as we explored here, the same could be said about biotin for hair growth, and, in that instance, biotin was a total flop. Could the same be said about biotin for nails? We

don’t have a good sense, since there apparently hasn’t been a single placebo-controlled study published on the matter.[6438]

Where did anyone get the idea that biotin might help? Serious biotin deficiency is associated with poor nail quality,[6439] though this tends to only strike those who eat raw egg whites.[6440] Biotin works in ponies, affecting a 15 percent increase in hoof horn growth rate.[6441] (Their hooves are made out of the same stuff as our nails.) So, what about biotin in people?

There have been two uncontrolled before-versus-after studies that suggest 2.5 mg of biotin a day may help.[6442] One trial showed a 25 percent increase in nail thickness after six to fifteen months.[6443] There has only been one controlled trial, though. Once a day for four months, brittle fingernails were treated with a nail lacquer with or without taking daily 10 mg supplements of biotin. Nail appearance improved substantially in 80 percent of the biotin group versus 53 percent in the control group.[6444] Unfortunately, at that dose, biotin may disrupt laboratory measurements.

For scheduled blood tests, like thyroid function or pregnancy, you may want to stop the biotin one to five days before the blood draw, depending on how much you’re taking.[6445] The FDA was prompted to put out warnings about biotin after a case where biotin interfered with a test (troponin) that would have revealed a missed heart attack and the patient died.[6446] Those are the kinds of tests you can’t foresee.

A survey of dermatology outpatients taking biotin found that only 7 percent had ever heard about the FDA warning,[6447] and a nationwide survey of physicians also showed that there were significant professional knowledge gaps.[6448] A dose of 2.5 mg a day may be too low to interfere with lab results,[6449] so it may be worth a try for brittle nails even though we don’t have firm evidence that it will help.[6450]

PRESERVING YOUR TEETH

More than 65 percent of the U.S. population over the age of sixty-five have periodontitis.[6451] The word is derived from the Greek *peri-*, meaning “around,” *-odont*, meaning “tooth,” and *-itis*, meaning “disease.”

Periodontal disease is an affliction of the tissue surrounding and supporting our teeth, and a major cause of tooth loss.[6452]

Poor diet quality is associated with oral health problems such as periodontitis and tooth loss, and the relationship may be bidirectional. For example, as a pro-inflammatory food component, saturated fat could be contributing directly to tooth loss. Or, tooth loss could be contributing to eating more fatty foods like processed meat because they're easier to chew. In the same vein, the foods associated with fewer missing teeth—fruits and vegetables—are both anti-inflammatory and may require more chewing.[6453] Is a poor diet leading to poor dentition, poor dentition leading to a poor diet, or both?

LONG IN THE TOOTH

As we grow older, we already tend to eat less—and eat less healthfully. Between the ages of forty and seventy, food intake drops by about a quarter due to a declining appetite. We also start losing our taste buds, and sweet and salty tastes are often the first to slip. This can lead to diets particularly excessive in sugar and salt.[6454] Throw in a shift to preprocessed foods due to poor dentition, and you can imagine how this could kick off a vicious cycle, though longitudinal studies don't present clear evidence that tooth loss indeed leads to a loss in nutritional status.[6455] However, tooth loss is associated with premature death and dementia.

A systematic review and meta-analysis found that both periodontitis and tooth loss are predictors of a shortened lifespan. Not all studies accounted for confounding factors, such as smoking, which could easily increase the risk of both,[6456] but those that did control for these other considerations still found missing teeth to be associated with premature death.[6457] Dentition could just be a surrogate for overall health status or genetic robustness.[6458] For example, centenarians have better oral health than those in the same generation who died forty years previously, and so do the children of centenarians compared to their same-age peers.[6459] There is, however, a potential causal pathway by which periodontal disease could cut a life short.

Periodontitis is a chronic inflammatory bacterial disease that leads to the destruction of tooth-supporting structures, such as the gums and underlying ligaments and bone.[6460] These bacterial pathogens can invade the

bloodstream and trigger a systemic inflammatory burden.[6461] This could explain the association between missing even just a few teeth and the elevated risk of heart attacks,[6462] as well as connections between periodontal disease and other signs of vascular inflammation, such as erectile dysfunction.[6463] (By looking in your mouth, your dentist may find out more about you than you realize!) Does that explain the dementia link as well?

INDENTURED CONSERVANT

Systematic reviews and meta-analyses have found that tooth loss or periodontitis is associated with both cognitive impairment[6464] and dementia.[6465] Reverse causation might be an intuitive explanation—dementia leading to a decline in oral hygiene.[6466] But, prospective studies following people over time have found that tooth loss appears to predict future cognitive decline, and the more missing teeth, the higher the associated risk.[6467]

I detail a fascinating series of experiments in see.nf/overdentures, where, for example, in a study subtitled "New Teeth for a Brighter Brain," researchers found that replacing missing molars with crowns affects the size of your pupils, suggesting that a gap in the sensation of teeth pushing against each other adversely affects brain function.[6468] If you think that's wild, check out this one: Ten toothless individuals—nine out of ten of them cognitively impaired, six severely so—were given conventional dentures for a month before being fitted with overdentures, which are snapped onto titanium implants surgically screwed into the jawbone. The conventional dentures, held in place by adhesives and natural suction, did nothing to significantly alter cognitive function, but the ones securely attached to implants in the bone appeared to have a dramatic effect. The overdentures presumably transmitted the same kind of chewing pressure sensations to nerves in the jaw that the natural roots of teeth might. Nine out of ten of the subjects went into the study cognitively impaired, but eight out of ten left the study cognitively intact.[6469] This suggests that well-fitting, secure dental prostheses aren't just about improving self-confidence, social contact, and quality of life, but proper brain functioning as well. Even better, though, is to preserve the teeth you have.

Building a Better Mouthwash

If tooth decay is a bacterial disease, why not just use antibiotics to kill the cavity-causing bugs? Many such attempts have been made. However, undesirable side effects, such as antibiotic resistance, vomiting, diarrhea, and teeth-staining, have precluded their use.[6470] There are antiseptic mouthwashes with chemicals like chlorhexidine, which is considered to be the "gold standard" anti-plaque agent, but as I show in see.nf/mouthwash, there is a cheaper, safer, better option: using green tea as a mouthwash,[6471] with or without added amla.[6472]

DON'T SUGARCOAT IT

Our ancestors who lived more than 10,000 years before the toothbrush was invented had almost no cavities.[6473] Why? Because candy bars hadn't been invented yet, either. Now, dental cavities may be humanity's most prevalent disease,[6474] and, as I show in see.nf/sugar, sugar consumption is considered to be the one and only cause.[6475]

The recommended 3 percent cap on total daily intake of added sugars[6476] wouldn't even allow for a single average serving for young children of any of the top ten breakfast cereals most heavily advertised to them.[6477] Obviously, soda is off the table. One can would be nearly two days' worth of sugar.

The official position of the American Academy of Pediatric Dentistry was that frequent consumption of sugary drinks can be a significant factor in the initiation and progression of dental cavities[6478]—that is, it was the official position before it accepted a million-dollar grant from Coca-Cola.[6479] After the grant, its tune changed to "Scientific evidence is certainly not clear on the exact role that soft drinks play.…"[6480] As the Center for Science in the Public Interest's Integrity in Science Project put it, *"What a difference a million dollars makes!"*[6481]

If we were really interested in minimizing disease, the ideal goal would be to drop the intake of added sugars to zero.[6482] Though that may be able to

get rid of cavities, wrote a Kellogg's-funded researcher, "this ideal is impractical."[6483] The "dictatorial use of foods 'friendly to the teeth'" might promote "dietary celibacy" not "acceptable to all individuals."[6484]

Rather than recommending "draconian" reductions in sugar intake, the sugar industry responded that "attention would be better focused on fluoride toothpaste."[6485] That's the perfect metaphor for medicine's approach to lifestyle diseases: Why treat the cause when you can just treat the consequences?

Are Dental X-Rays Safe?

Every year, doctors may cause an estimated 29,000 cancers by dosing patients with X-rays during CT scans.[6486] What about dentists? Dental X-rays are the most common artificial source of contact with high-energy radiation,[6487] subjecting tens of millions of Americans a year to exposure.[6488] Don't the lead apron and thyroid (neck) shield protect your vital organs? All your vital organs except for one—your brain!

As I detail in see.nf/dentalxrays, dental X-rays appear to increase the risk of the most common type of brain tumor.[6489] There is little evidence to support irradiating asymptomatic patients in search of problems hiding in their mouths.[6490] Accordingly, dentists should only take X-rays when there is a patient-specific reason to believe there is a reasonable expectation the imaging will offer unique information that will influence diagnosis or treatment.[6491]

TOOTH-PRESERVING DIET

What is the role of diet in periodontal disease? I review the evidence in see.nf/periodontitis, including interventional studies showing that the superior periodontal health among vegetarians[6492] may be due to eating fewer pro-inflammatory foods[6493] or more anti-inflammatory components

like high-fiber diets.[6494] As I detail in see.nf/chewing, there was even a remarkable trial in which more than a thousand participants were randomized to decades of a healthy dietary intervention practically from birth. Those in the lower saturated fat and cholesterol arm ended up with better saliva flow, which is essential for the maintenance of oral health. This was thought to be a function of greater chewing required of fiber-rich foods.[6495] Similarly, foods requiring more intensive chewing have been found more effective at improving bad breath.[6496]

Brush with Greatness

Surprisingly, as I review in see.nf/flossing, the evidence is limited that adding flossing to a brushing regimen reduces gum inflammation,[6497] but it is still recommended on a daily basis.[6498] Researchers have compared unwaxed to woven to shred-resistant floss, and they all appear to have about the same plaque-removal efficacy.[6499] Should you floss before or after you brush? A randomized controlled trial on flossing sequence was performed to put to rest dueling intuitions. Flossing first won hands down.[6500]

GREENS FOR GUMS

When researchers took advantage of a *Survivor*-type reality TV show in which contestants agreed to live under Stone Age conditions to study the natural progression of dental disease without toothbrushing, they were surprised to find a lack of gingivitis. Normally, as I review in see.nf/plaque, plaque buildup is followed by gum inflammation, but perhaps this is only in the context of eating a lot of processed foods rich in sugar and low in anti-inflammatory, whole plant foods.[6501] Randomized, double-blind, placebo-controlled trials of the amount of lycopene in as little as one tomato a day, equivalent to about a daily tablespoon of tomato paste,[6502] found a significant reduction in gingivitis within just one week,[6503] as well as an improvement in gum bleeding in chronic periodontitis patients.[6504]

However, half the dose didn't appear to help, so it looks like you have to go the whole tomato.[6505]

A few plants—namely, greens and beets—have another secret weapon: nitrates. Beyond improving circulation, nitrates may also play an important antimicrobial role in our saliva,[6506] proven in a randomized, double-blind, placebo-controlled clinical trial to alleviate gum inflammation.[6507] Check out see.nf/chewing for the full story.

Oil Pulling My Leg?

Coconut oil is safe to put on your hair or your skin,[6508] but, according to the American Heart Association[6509] and the American College of Cardiology,[6510] you don't want to be eating it. In fact, you may not even want to be in the same kitchen when coconut oil is being heated. I don't know where people got the idea that it's safe to use for cooking. Coconut oil has one of the lowest smoke points and releases a variety of toxic emissions at typical frying temperatures.[6511] What about just swishing coconut oil around in your mouth?[6512]

I have a four-part video series starting with see.nf/oilpulling on a time-honored folk remedy that involves "pulling" oil back and forth between the teeth for minutes before spitting it out for a variety of purported "oral and systemic health benefits." There appear to be no such systemic benefits,[6513] and effects on oral health are mixed (good,[6514] bad,[6515] and neutral[6516]). The reason to avoid it completely is the very real risk of lipoid pneumonia, a potential consequence of aspirating small amounts of any oily substance into the lung.[6517] In fact, the reason some of the dental studies were performed on "a stored collection of human extracted teeth"—sounds like straight out of a horror movie—instead of on real-life subjects is that the researchers considered it "not ethically sound to conduct a human trial of [oil pulling] … with the knowledge that there

was a chance of inducing lipoid pneumonia in study volunteers."[6518]

DON'T END ON A SOUR NOTE

A meta-analysis of eighteen studies on the oral health implications of vegetarian diets showed that vegetarians have significantly fewer decayed, missing, and filled teeth.[6519] This isn't surprising given that vegetarians eat more antioxidants[6520] and anti-inflammatory[6521] foods. Those eating plant-based also have significantly lower rates of oral cancer in every study to date on the topic,[6522,6523,6524,6525] leading to a review on oral cancer prevention published in *The Journal of the American Dental Association* to conclude: "Evidence supports a recommendation of a diet rich in fresh fruits and vegetables as part of a whole-foods, plant-based diet.…"[6526] Vegetarians do appear to have an Achilles' tooth, though: an increased risk of dental enamel erosion,[6527] thought due to their consumption of more acidic fruits and vegetables, such as citrus and tomatoes.[6528]

As I cover in see.nf/sour, the solution is to rinse out your mouth with water after consuming sour foods or beverages[6529] and waiting to brush your teeth for at least thirty, and preferably sixty, minutes after consumption to allow your teeth to first remineralize, so as not to brush them in a softened state.[6530]

Is Fluoride Safe and Effective?

One of the studies that bucked the trend and showed that vegetarians had more cavities blamed the excess decay on the fact that vegetarians were significantly less likely to choose fluoride-containing toothpaste,[6531] which has clearly been shown to reduce tooth decay.[6532] Adding fluoride to drinking water is more controversial. Though characterized by the CDC as one of the top ten public health achievements of the twentieth century,[6533] growing evidence about the adverse effects of fluoride on brain development[6534] led to

the National Toxicology Program's draft conclusion that fluoride should now be "presumed to be a cognitive neurodevelopmental hazard to humans."[6535]

Ironically, it was the anti-fluoridationists who were accused of their "anti-scientific" attitudes, but now it's the pro-fluoridationists who may be ignoring evidence that doesn't conform to their beliefs.[6536] How can society get the cavity-preventing benefits of fluoride without the risks? Since the primary risk arises from systemic absorption, yet the primary benefits arise from topical contact with our enamel, we can safely reap the rewards by using fluoride toothpaste and mouthwashes.[6537] For an in-depth look into why I changed my mind on water fluoridation, see my five-part video series starting with see.nf/fluoride.

PRESERVING YOUR VISION

More than a million Americans are legally blind. The good news is that a healthy diet can help prevent all four of the most common causes of vision loss—macular degeneration, diabetic retinopathy, glaucoma, and cataracts.

MACULAR DEGENERATION

Age-related macular degeneration is the leading cause of blindness in the developed world.[6538] The macula is the central bull's-eye of the retina in the back of our eyes and is responsible for high-resolution vision. What makes it degenerate?

The retina, the inner rear lining of our eyeballs, transforms light into vision. This continuous feat requires a massive load of oxygen and energy, making the retina one of the most metabolically active tissues in the body—more so, gram for gram, than even the brain.[6539] The oxidative stress due to this firestorm of activity is compounded by the free radicals created by the sun's rays that are focused like a magnifying glass angling straight back

into the macula.[6540] This cumulative oxidative strain is thought to play the central role in age-related macular degeneration.[6541]

Eyes donated to science after death from people with age-related macular degeneration show increased oxidative stress[6542] and more free radical DNA damage than do the eyes from those without the condition.[6543] Even the bloodstream of those with age-related macular degeneration shows higher levels of oxidative damage, suggesting a systemic breach of antioxidant defenses.[6544] The pro-oxidants in cigarette smoke[6545] help explain why smokers have up to quadruple the risk of having the disease.[6546] To slow its progression, macular degeneration sufferers are strongly encouraged to quit cigarettes if they smoke and include in their diet a special mixture of antioxidant pigments that go straight to the macula.[6547]

The technical term for the macula is *macula lutea*, which comes from Latin *macula*, meaning "spot," and *lutea*, meaning "yellow." That's what it looks like when we doctors peer into the back of your eye with that bright light. The color comes from two yellow plant pigments that home onto the macula like a laser beam, achieving a concentration a thousand times higher than other tissues. Even just one or two millimeters off from the dead center of your vision, the pigment concentrations drop a hundredfold. Your body knows just where to put them. The two primary pigments, lutein and zeaxanthin, protect the retina from photo-oxidative damage by absorbing blue light.[6548]

The yellowing of our lenses when we develop cataracts may actually be our body's defense mechanism to protect our retinas. In fact, when cataracts are removed, the risk of blindness from macular degeneration may shoot up because we removed the protection.[6549] Instead of trading one type of vision loss for another, it's better to pigment the back of our eyes through diet instead of pigmenting the front of our eyes with cataracts. The pigment in the back of our eyes is entirely of dietary origin.

YELLOW CORN, GREENS, AND GOJIS

Where in our diet can we get these pigments? In an apparent attempt to distract from the cholesterol content of eggs, the egg industry scrambles to boast that eggs contain the pigments lutein and zeaxanthin that protect the retina from photo-oxidative damage.[6550] And it's true. Eggs can have up to

250 micrograms (µg), but a single serving of collard greens has closer to 18,500 µg and just one serving of kale tops the chart at nearly 44,700.[6551] Though yellow yolks might fool you, the two yellow pigments are found mostly in greens. (During autumn splendor, you can see some of the yellow pigments peek out of green leaves as the chlorophyll fades.)

One spoonful of spinach has as much of the pigments as eight eggs.[6552] For eye protection, the recommendation is to get 10,000 µg a day, which is about a third of a cup of spinach or forty eggs—more than three cartons a day. The plant pigments in eggs come from chickens that got it from pecking at corn or blades of grass. We can cut out the middle-hen and get the pigments straight from corn and greens. All the top ten sources of these critical, eyesight-saving nutrients in the USDA nutrient database are greens. Eggs don't even make the top one hundred. To get to eggs, you have to scroll down a couple of pages, and, according to the USDA, they come in right behind Cap'n Crunch with Crunch Berries (which is presumably on the list due to its yellow corn content).[6553]

This discrepancy pans out when put to the test. When study subjects ate around six high-lutein, free-range, certified organic eggs every week for three months, the pigmentation in their eyes hardly changed.[6554] Instead of getting the plant pigments from eggs that came from chickens that got them from pecking at plants, when researchers went straight to the source by offering these nutrients from plants directly—a cup of corn and a half cup of spinach a day—most individuals saw a dramatic boost in protective macular pigmentation within the first month.[6555]

Three months after the subjects stopped eating the corn and spinach, the levels of these pigments remained relatively high, indicating that once we build up our macular pigment with a healthy diet, our eyeballs really try to hold on to it. So, even if we go on vacation and end up eating more iceberg lettuce than spinach, our eyes will try to hold out until we get back.

Yellow corn has about seventy times more lutein than white corn,[6556] but spinach has sixty times more than yellow corn. Corn beats greens for zeaxanthin, though. The word comes from modern Latin *zea*, meaning "maize," and *xanthin*, "yellow coloring." However, a few food sources can crack corn. Orange bell peppers have eight times more zeaxanthin than corn,[6557] but goji berries reign supreme, with about twelve times more than orange peppers.[6558] In see.nf/gojis, I profile a double-blind, randomized,

placebo-controlled study that found that gojis may even help people already suffering from macular degeneration.

Goji berries may cost about twenty dollars per pound in natural foods stores, but they're even cheaper than raisins in Asian supermarkets, where you can buy them as "Lycium" berries. I encourage you to swap out raisins for goji berries—in your breakfast oatmeal, as a snack, in muffins, and anywhere else. As one review concluded, goji berries offer a "'whole food' dietary supplement for the maintenance of retinal health as well as for prevention and/or delay in progression of retinal diseases commonly seen in clinical practice."[6559]

PASS WITH FLYING COLORS

Lutein and zeaxanthin are both fat-soluble, so make sure you pair your greens with nuts, seeds, nut and seed butters, or any other Green Light source of fat. They'll taste better, and you'll maximize absorption of these important macular pigments. So, you can add walnuts to your pesto, whip up a creamy tahini-based salad dressing, top your sautéed kale with sesame seeds, or choose produce that has the fat baked in: avocados.

In see.nf/avocados, I run through all the experiments showing how pairing avocados with salsa or salads can dramatically increase the absorption of the carotenoids in vegetables.[6560] Another way to boost the bioavailability of the macular pigments in greens is to steam them,[6561] but heat isn't the only way to liberate lutein from greens. If you finely chop spinach, you can apparently double the amount of lutein released during digestion. And, if you really blend it up—a green smoothie, pesto, or some kind of pureed spinach dish, for instance—you may triple the bioavailability.[6562]

PLANT PIGMENTS PUT TO THE TEST

The Age-Related Eye Disease Study (AREDS) randomized thousands of men and women who had at least the beginnings of age-related macular degeneration to a combination of antioxidants and zinc versus placebos for more than five years[6563] and was able to decrease the risk of progression to advanced macular degeneration by 25 percent.[6564] The AREDS formulation quickly became the medical standard of care for those suffering from the

disease. In see.nf/areds, I detail all the changes in the formula since. Fish oil was tried and flopped, the zinc dose was lowered, and "vegetarian" levels of lutein and zeaxanthin[6565] beat out the original beta-carotene.[6566]

There is a consensus among professional eye health associations and guidelines that these kinds of supplements should be given to people with macular degeneration,[6567] but they have not been found effective for primary prevention. In fact, the Harvard Physicians' Health Study II found that those randomized to a multivitamin (Centrum Silver) developed *higher* rates of macular degeneration compared to placebo.[6568] To prevent the disease in the first place, a diet "high in green leafy vegetables" is recommended instead of supplements.[6569]

To protect your eyes, everyone is recommended to incorporate two to three servings of greens into your daily diet.[6570] Think of this as greens at every lunch or supper with bonus points for sneaking them into breakfast—perhaps in a green smoothie or a savory oatmeal dish. It may be especially important for white people to eat their green leafies, as they have significantly higher rates of age-related macular degeneration. This is likely due to eye color. Blue eyes let through a hundred times more light, so people with blue or gray eyes appear to be significantly more vulnerable to damage compared to those with brown or black eyes. (Green and hazel fall somewhere in the middle.)[6571]

I Can See for (Twenty-Seven) Miles

The macular pigments lutein and zeaxanthin not only protect our eyesight but may also improve it. Their peak light absorbance just so happens to be the wavelength of the color of our planet's sky. By filtering out that blue haze, those fortifying their retinas with a lot of greens are estimated to be able to distinguish distant mountain ridges up to twenty-seven miles farther than those with little macular pigment when standing atop a mountain on a clear day.[6572]

There have been nine randomized controlled trials investigating the effects of macular pigment

supplementation on visual function in normal healthy subjects. All have found significant improvements,[6573] including improving visual acuity, contrast sensitivity (important for low-light conditions),[6574] chromatic contrast (the vividness of colors), and photo-stress recovery time (the time needed to recover sight after a bright flash).[6575]

Are there any other foods that can improve vision in healthy people? Given the fact that cocoa powder can acutely boost cerebral blood flow,[6576] researchers compared the effects of eating a Trader Joe's dark chocolate bar (72 percent cocoa) versus a Trader Joe's milk chocolate bar (31 percent cocoa).[6577] Two hours after consumption, contrast sensitivity and visual acuity were significantly improved in the dark chocolate group compared to the milk chocolate group, meaning they were better able to pick out small, low-contrast targets. The researchers suggested it may be due to the enhanced availability of oxygen and nutrients afforded by the improvement in blood flow to the metabolically voracious retina.

The blood flow in the *choriocapillaris*, the massive network of tiny blood vessels that feed our retinas, may actually be the highest in the body.[6578] That may help explain why higher meat intake is associated with a significantly increased risk of developing macular degeneration.[6579] Those with higher cholesterol intake have up to 60 percent higher odds of early age-related macular disease, and higher saturated fat consumption bumps it up to 80 percent.[6580] Drusen, the spots of debris in the back of the eye that are the hallmark of macular degeneration, are actually cholesterol-rich deposits with a composition similar to that of atherosclerotic plaques in arteries.[6581] The level of oxidized cholesterol in drusen is so high that it would be lethal in most cell systems.[6582] Injecting LDL cholesterol into rats for seven days causes retinal changes "quite similar" to that of early-stage age-related macular degeneration in humans,[6583] but the current evidence

regarding the use of statin drugs to prevent or treat the disease in people is inconclusive,[6584] which would argue against a strong role of blood cholesterol in macular pathology.

FLOWER POWER

In addition to two to three daily servings of green leafy vegetables, berries are considered a healthy choice for conserving our eyesight.[6585] As I detail in see.nf/saffronvision, there are interventional studies showing that berries can improve various aspects of our vision,[6586,6587] but only one pigmented food has been put to the test for macular degeneration: the spice saffron. I run through all the studies in the video, but basically, a tiny daily pinch of saffron (20 mg) can cause a significant, yet modest, improvement in visual acuity in older adults with mild or moderate age-related macular degeneration.[6588]

Diabetic Retinopathy

Diabetes is another leading cause of blindness, as well as amputations and kidney failure. Thankfully, type 2 diabetes can be prevented and even reversed, as I discuss at length in my chapter on diabetes in *How Not to Die*.

GLAUCOMA

Glaucoma is now the leading cause of irreversible vision loss in the world. It's caused by the deterioration of the optic nerve that connects the eye to the brain. Most commonly, this is due to excessive pressure inside the eyeball. Up to 40 percent of glaucoma patients end up going blind in at least one eye.[6589] To prevent this from occurring, most treatments concentrate on trying to lower the intraocular pressure.[6590]

KALE GRAIL

Might greens be the go-to again? The nitric oxide that is boosted by vegetable nitrate consumption helps to balance pressure in the eyeball by reducing the overproduction of *aqueous humor* (the fluid that fills and inflates the eyeball) and improving outflow of any excess.[6591] The pharmaceutical industry has been working on coming up with Viagra-type drugs to increase the amount of nitric oxide in the eye,[6592] but we already have veggies that can get it up.

Only about one in ten white people eat even a single serving of dark-green leafy vegetables a *month*. To study the relationship between greens and glaucoma, researchers sought a cohort of Black women, of whom nearly nine out of ten regularly eat their greens.[6593] Compared to those eating a single serving of kale or collard greens once a month or less, those eating more than one serving a month had less than half the odds of glaucoma.[6594] It didn't seem to take much at all. At so few servings a month, even studies of white people might be informative, so Boston researchers looked to the Harvard Nurses' Health Study (97 percent white)[6595] and the Harvard Health Professionals Follow-Up Study (only 1 percent Black).[6596] Based on the more than 100,000 men and women followed for decades, higher nitrate intake (mostly from green leafy vegetables) was indeed associated with significantly lower risk of developing glaucoma.[6597]

NO HEAD STANDS

Is there anything else we can do? Aerobic exercise can at least transiently reduce intraocular pressure,[6598] and one study suggested that chronic conditioning can maintain lower pressures over the long term.[6599] However, bungee jumping,[6600] scuba diving,[6601] and inversion (head-down) yoga positions may have the opposite effect.[6602]

A study of nearly 30,000 runners found a dose-dependent effect, with farther distances and faster times associated with a lower incidence of glaucoma.[6603] Of course, such observational data are complicated by the specter of reverse causation. Instead of exercise maintaining people's vision, maybe those who maintain their vision are more likely to exercise. And, indeed, those with glaucoma do tend to exercise less than same-age

peers.[6604] There has yet to be a randomized controlled trial to put exercise to the test, but we do have interventional data on berries.

SWIM WITH THE CURRANT

Japanese researchers have shown that black currant pigments can slow down glaucoma vision loss. (Details in see.nf/currants.) This was accompanied by an increase in ocular blood flow, but no change in intraocular pressure, suggesting that berries might also work for "normal tension" glaucoma, the type in which the optic nerve deterioration proceeds despite normal eyeball pressure.[6605] Note that most "currants" sold in the United States are little raisins (*Vitis vinifera*) and not actual currants (*Ribes nigrum*), which were illegal to grow until recently, due to pressure from the lumber industry because they can carry white pine blister rust.[6606]

GINGKO?

As I detail in see.nf/gingkonic, one study found suggestive benefit of *Ginkgo biloba* extracts for open-angle glaucoma,[6607] and one[6608] of two[6609] found a significant benefit for closed-angle glaucoma. If you want to try it despite the underwhelming results, make sure you first discuss it with your healthcare professional due to a possible increase in bleeding risk from the herb.[6610]

NICOTINAMIDE

In the same video, see.nf/gingkonic, I detail a randomized, double-blind, placebo-controlled, crossover trial showing that the B vitamin nicotinamide may cut the risk of further visual field deterioration of glaucoma patients from 12 percent down to 4 percent within a matter of months.[6611] A 2022 study found a significant improvement in visual function compared to placebo with two months of an escalating nicotinamide dose, going from 1 g to 3 g a day, but it is not directly comparable since pyruvate, another important part of energy metabolism, was also added.[6612] See here for my discussion of cost, labeling confusion, and potential side effects of taking nicotinamide.

CATARACTS

Age-related cataract, the clouding of the normally clear natural lens of the eyes, typically starts between the ages of forty-five and fifty. It is the leading cause of blindness in low- and middle-income countries, but only responsible for about 5 percent of blindness in higher-income countries, thanks to the availability of cataract surgery, the current standard of care. These days, high-tech cataract surgery is a relatively quick, safe, and simple procedure, with rapid recovery. It involves the removal of the clouded lens and replacement with an artificial lens usually made out of silicone or acrylic.[6613]

Overall, about half of patients don't recover vision better than 20/40 after cataract surgery, but the most common complaint is *dysphotopsia*, light artifacts manifesting as streaks or flashes that can result from internal reflections within the implanted lenses. Anywhere between 33 and 78 percent of cataract patients are affected,[6614] and it typically doesn't improve without surgical replacement.[6615] The most serious sight-threatening complication is *endophthalmitis*, the introduction of infection into the eye. Though it's extremely rare—less than one in twenty-five hundred surgeries—it's concerning enough that bilateral cataract surgery is done in two separate operations instead of both at the same time to avoid the risk of going completely blind from infections in both eyes.[6616]

GREENS *AGAIN?*

How about preventing the cloudiness in the first place? Cataracts are a direct result of oxidative stress,[6617] free radical damage to the normally transparent crystallin proteins that make up the lenses in our eyes.[6618] The oxidative stress can come from hyperbaric oxygen therapy, the natural UV rays of the sun, artificial UV rays of tanning beds, or other forms of high-energy radiation.[6619] For example, all twenty-one studies of healthcare workers exposed to X-rays, such as those who do angiograms, found higher rates of cataracts, sixteen of which significantly so.[6620]

If cataracts are caused by oxidation, how about eating more antioxidants? The body concentrates vitamin C in the lens at levels fifty times higher than the blood to defend against oxidative attack.[6621] Experiments in which samples of eye fluid were taken during cataract

surgery after vitamin C supplementation confirm that changing what goes into our mouth can change what ends up in our eyes,[6622] but does that translate into lower risk?

Those eating diets with a higher total antioxidant content do tend to have lower risk of age-related cataract.[6623] The same could be said for the intake of some individual antioxidants—vitamin C, beta-carotene, and lutein and zeaxanthin—but not others, such as vitamin A, vitamin E, or alpha-carotene.[6624] For vitamin C, both intake and blood levels correlated with lower cataract risk.[6625] Those getting the amount of vitamin C found in about two oranges a day appeared to have approximately 40 percent lower risk.[6626] Researchers concluded that dietary vitamin C intake "should be advocated for the primary prevention of cataract," mirroring similar advice from a meta-analysis on dietary lutein and zeaxanthin and cataract risk: "[O]phthalmologists should counsel individuals to increase consumption of lutein-rich foods, such as dark-green leafy vegetables."[6627] Why not just recommend antioxidant supplements instead?

ANTIOXIDANT SUPPLEMENTS?

Details in see.nf/antioxmulti, but supplements containing vitamin C, vitamin E,[6628] and beta-carotene[6629] with or without[6630] zinc failed to affect the rate of cataract formation. Perhaps there's a threshold effect such that supplementation would only work in the context of dietary deficiency.[6631] For example, consider the case of lutein and zeaxanthin. They are the only carotenoids present in the human lens,[6632] so perhaps it's no surprise that beta-carotene failed to help.[6633] Lutein and zeaxanthin supplementation also failed, but only among those getting enough in their diet. Those with the lowest baseline intake did appear to benefit from supplementation.[6634] Presumably, those with an inadequate baseline intake of greens would also benefit from just eating more greens.

MULTIVITAMIN SUPPLEMENTS?

Taking supplements just as an "insurance policy" is a common sentiment heard in the context of multivitamins, but as I note in see.nf/antioxmulti, the results for cataract prevention are mixed. For example, one study showed that those randomized to Centrum for about a decade had a 34 percent

lower risk of developing or worsening one kind of cataracts, but a 100 percent higher risk (a doubled risk) for developing or worsening a different type of cataract. The contrasting effects, concluded the researchers, "prevent us from making recommendations…."[6635]

SEEING CLEARLY

In addition to antioxidant-rich foods,[6636] eating more anti-inflammatory foods is also associated with lower cataract risk.[6637] As well, the aging toxin AGEs (see here) may accelerate cataract formation by cross-linking lens proteins.[6638] That may help explain why the consumption of meat (including poultry) has been associated with increased cataract risk.[6639] In contrast, those eating at least about an ounce a day of daily legumes have less than half the odds of posterior cataracts, but the researchers didn't adjust for meat consumption, so it's hard to know if this is just an indirect benefit of eating less meat.[6640]

The European Prospective Investigation into Cancer and Nutrition is a large enough study to get more granular. The study compared the rates of cataract development in "high" meat eaters, "low" meat eaters, and pescatarians versus those eating vegetarian and those eating vegan. The researchers went out of their way to choose health-conscious subjects to help factor out smoking, exercise, and other non-diet variables, so the "high" meat-consuming group was defined as just one serving a day (100 g) or more.[6641] Yet even compared to health-conscious light-meat consumers, those cutting back on meat even further (eating less than 100 g a day) had a 15 percent lower cataract incidence.

Compared to the one-serving-or-more-a-day meat eaters, those cutting out all meat except for fish (the pescatarians) had a 21 percent lower risk, those cutting out *all* meat (the vegetarians) appeared to drop their risk by 30 percent, and those going a step further and also eliminating eggs and dairy (the vegans) had 40 percent less risk of developing cataracts.[6642] Similar stepwise reductions of risk can be seen with other diseases, such as diabetes, hypertension, and obesity, as one's diet gets more and more centered around plants.[6643] A subsequent study out of Taiwan confirmed that those eating no meat were significantly less likely to develop cataracts

compared to those eating on average just about a half serving of meat a day.[6644]

Why do vegetarians have higher rates than vegans? It might be the dairy. We've known that galactose, the breakdown product of the milk sugar lactose, can cause cataracts from studies dating back to 1935[6645] with titles like "Cataracts Produced in Rats by Yogurt."[6646] Galactose buildup in the eye causes an injurious swelling of the lens.[6647] Thankfully, human livers have a greater capacity to detoxify galactose than do rat livers.[6648] There are children born with genetic defects who can't handle it as well (and subsequently develop cataracts),[6649] but might a lifetime of consuming dairy increase the risk of cataracts even in those with normal detoxification enzyme activity?[6650] After all, drinking milk into adulthood is an evolutionarily novel behavior.

Across the general population, milk consumption does not appear to increase the risk of cataracts, but some people may be more susceptible.[6651] People are born with different capacities to detoxify galactose. Among those with normal, but lower, levels of the galactose-detoxifying enzyme *galactokinase*, high-lactose intake from milk and other dairy products may quadruple the risk of developing cataracts later in life.[6652] This has been used to help explain why women have higher cataract rates than men, since women tend to have weaker galactokinase activity.[6653]

PRESERVING YOUR DIGNITY

I'm breaking with the alphabetical sequence by placing this section at the end.

HOW TO DIE A GOOD DEATH

We have all sorts of detailed data about dying, but little about the experience of death. For the minority who die while receiving palliative care, death could probably be described as good, but there is a suspicion that the experience is bad for the majority who die in hospitals or nursing homes.[6654] Unfortunately, that's where most people die.[6655]

In spite of widespread preference to die at home, in almost all populations most deaths occur in institutions. Approximately 80 percent of Americans say they would prefer to die at home,[6656] yet fewer than 30 percent do.[6657] Highly medicalized institutional deaths have consequences not just for the patient but for their bereaved caregivers as well. Not only do patients with cancer who die in a hospital tend to experience more physical and emotional distress and worse quality of life at the end of life but their caregivers suffer five times the odds of developing post-traumatic stress disorder and nearly nine times the odds of severe, prolonged, disabling grief. Now, that was from an observational study.[6658] It's not like the patients were randomized to die in different locations, so this doesn't prove cause and effect, but it certainly raises concerns.

When researchers have looked into the care of dying patients in hospitals, it hasn't been pretty. Basic interventions to maintain patients' comfort were often not provided, contact with dying patients was minimal, and the distancing and isolation worsened as death approached. For example, in one heart-wrenching case report, a fifty-two-year-old woman with metastatic cancer that had spread to her liver had gross abdominal distension and was jaundiced, very breathless, but alert. Her eyes were swollen and she shed yellow tears. The patient received *no care* from the nurses delegated to attend to her. Yet in the nursing log, it was recorded that attention had been given to her personal hygiene, pressure areas to prevent bed sores, oral hygiene, and eyes—but it was all a lie. The only attention she got was to receive a commode from a nursing assistant. Contact time totaled six minutes over the four and a half hours the researchers kept track.[6659]

What would a good death look like? It looks like retaining control, dignity, and privacy. Having pain relief, emotional support, and respect for your wishes. Choosing where and how you spend your last days. Being able to say goodbye, and being able to leave when it is time to go and not have life prolonged pointlessly.[6660]

The best bet to ensure that your death is yours is access to hospice care. Palliative care involves comfort measures to relieve symptoms and improve quality of life that can be utilized at any stage of a serious illness, whereas hospice is *just* comfort measures, embodying a shift of focus from curing the disease to improving the quality of one's last days.[6661] About half of

Medicare patients receive some hospice care, but for many (28 percent), they are enrolled mere days before death.[6662]

Hospice is often framed as "giving up," but, ironically, when you compare hospice versus nonhospice patient survival, the patients in hospice actually tend to live longer. Patients who choose hospice care live on average about a month longer than similar patients who do not choose hospice.[6663] In one study, people with lung cancer randomized to early palliative care lived two and a half months longer.[6664] That's the kind of survival benefit you might get with a standard chemotherapy regimen.[6665] In fact, that's one of the ways hospice could extend survival in cancer patients: by avoiding the risk of overtreatment with chemo and its related toxicity.[6666]

PHYSICIAN AID IN DYING

There are limits to palliative care. Even under hospice, where one would assume such care to be excellent, there are those who spend their last months in uncontrolled pain.[6667] And this unbearable suffering, despite our best efforts, leads to requests by patients to end their lives prematurely.[6668] Physician-assisted suicide, or perhaps more accurately *physician-assisted dying*[6669] or *medical aid in dying*, allows the terminally ill to end their lives through the voluntary self-administration of a lethal dose of medication expressly prescribed by a physician for that purpose.[6670] As I discuss in see.nf/aid, any physician aid in dying is illegal and punishable by law in forty U.S. states. In contrast, VSED is legal throughout the United States: Voluntarily Stopping Eating and Drinking.[6671]

THE BENEFITS OF VSED

In an ideal world, every patient with a life-limiting illness would receive optimal hospice and palliative care comfort measures such that no one would ever wish to hasten their own death. Unfortunately, the reality is that some with terminal illness continue to suffer despite our best efforts,[6672] leading increasing numbers of patients to explore VSED to escape intolerable suffering.[6673] In Europe, as many as 1 to 2 percent of deaths are attributable to this practice.[6674]

VSED can be defined as a conscious decision to voluntarily and deliberately choose to stop eating and drinking with the primary intention of hastening death because of the persistence of unacceptable suffering.[6675] In see.nf/vsed, I discuss all the benefits: dying at home, no waiting period for approval, it's legal, you can change your mind, and you don't need anyone's permission. Just knowing there's a "way out" can provide relief from feelings of desperation and entrapment, engendering a feeling of control that may itself be therapeutic.[6676] It can also prevent people from contemplating a more violent way out or feeling pressured to end their lives prematurely while they still can.[6677]

WHAT IS VSED LIKE?

What is it like to die from voluntarily stopping to eat and drink? There are a lot of anecdotes floating around describing death from VSED as peaceful, painless, and dignified.[6678] Fortunately, there have been several independent studies to evaluate these claims,[6679] which I explore in see.nf/vsed.

The average time of death after stopping eating and drinking is about seven days, though 8 percent lived for more than two weeks. The last days of life were rated as peaceful, with low levels of pain and suffering, even more so than a physician-assisted death.[6680] Most hospice workers said they would consider VSED themselves should they become terminally ill.[6681]

The state of terminal dehydration may even have some analgesic (painkilling) effect,[6682] presumed to be due to the release of endorphins, which act as natural pain blockers.[6683] So, concluded a systematic review published in a palliative care journal, VSED may reflect all twelve principles of a "good death," with an emphasis on retaining dignity and control.[6684]

One of the most famous accounts of VSED is a doctor's description of his own mother's death in the *Journal of the American Medical Association*.[6685] I asked permission from the journal to reprint two particularly poignant paragraphs for you here. It was happy to oblige—for $12,867.28. So, I just put them in my see.nf/vsed video instead. (Make sure to have a box of tissues at hand.)

The Dementia Trap

There are other side benefits to the dehydration process.[6686] There is less worry about incontinence, catheters, or bedpans, and less nausea and vomiting as our digestive secretions dwindle. Fewer respiratory secretions mean less coughing and choking and fewer drowning sensations. Dehydration can also decrease swelling, which can be a problem with end-stage cancer. That can relieve pain by taking pressure off the nerves. Mental awareness may also decline, which can also bring some relief, but it can also present a serious ethical dilemma. What if you become delirious, forget you ever made the decision, and start asking for something to drink? I cover this in my video see.nf/dignity, as well as how to create advance directive documents to specifically address the issue of hand feeding should you want to avoid end-stage dementia.

YOU ARE IN CONTROL

Thanks to the Fourteenth Amendment, everyone in the United States has the right to refuse medical care.[6687] Critics contend that food is different because it's a necessity.[6688] But, if you can refuse to be put on a respirator to save your life, the counterargument goes, then you should be able to refuse food and drink. (After all, nothing is more necessary than breathing!) In see.nf/dignity, I run through other common criticisms and potential pitfalls, including how to manage the associated thirst. The bottom line is that VSED appears to provide most patients with a peaceful and gentle death.

IV. Dr. Greger's Anti-Aging Eight

INTRODUCTION

Anti-aging quackery is an age-old phenomenon, but the convergence of three factors has been blamed for the recent explosion: the seventy-two-million-strong wave of aging baby boomers, online availability and advertising, and the passage of the 1994 Dietary Supplement Health and Education Act (DSHEA).[6689]

ANTI-AGING SCAMS

When surveyed, most people incorrectly believe that supplements must be approved for safety by a government agency such as the FDA before they can be sold to the public or, at the very least, must include a warning on the label about potential side effects. Nearly half even believed supplement manufacturers had to show some sort of effectiveness.[6690] None of that is true, though, thanks to DSHEA. The act removed the burden of proof for quality control, safety, or efficacy from the supplement manufacturers, and the market blew up from a $4 billion industry with 4,000 products before DSHEA's passage to a $40 billion industry with an excess of 50,000 products.[6691] By 2012, sales of dietary supplements in the United States were averaging more than $100 per person per year.[6692]

By law, over-the-counter medications must meet standards for safety, efficacy, and quality control, but dietary supplements are exempt.[6693] Prior to DSHEA, supplements were regulated like food additives, so manufacturers had to show that the products were safe before they were

brought to market, but not anymore. What's the harm? Watch my video see.nf/dshea.

Because of the lack of government oversight, there is no guarantee that a supplement bottle even contains what's listed on its label. In one study, only two out of twelve supplement companies were found to have products that were labeled accurately.[6694] FDA inspectors have even found that seven out of ten supplement makers violated Good Manufacturing Practices, which are considered the *minimum* quality standards,[6695] such as ingredient identification and basic sanitation. Not 7 percent, but 70 percent in violation.

The problem isn't limited to fly-by-night phonies lurking in some dark corner of the internet either. The New York State attorney general commissioned DNA testing of seventy-eight bottles of commercial herbal supplements sold by GNC, Walgreens, Target, and Walmart, and four out of five bottles didn't contain *any* of the herbs listed on their labels. Instead, the capsules often contained little more than cheap fillers, such as powdered rice and "houseplants."[6696]

At least you hope it's just houseplants. Some supplements are tainted with pharmaceuticals—sometimes even banned substances that had already been yanked from the market. As I note in see.nf/adulterated, recalled supplements may pop right back on store shelves, sometimes with even *more* banned ingredients.[6697] As a founding fellow of the Institute for Science in Medicine put it, "Fines for violations are small compared to the profits."[6698]

PAYING TO CUT YOUR LIFE SHORT?

A nationally representative sample of thousands of Americans over the age of sixty found that 70 percent reported using dietary supplements.[6699] Perhaps that should be 100 percent, since the Institute of Medicine's official recommendation is for everyone fifty and older to take a B_{12} supplement (or consume foods fortified with B_{12}),[6700] but the most common supplement taken was a multivitamin. What might that do for our lifespan?

As you can see in see.nf/multi, there have been nine randomized controlled trials of multivitamin and multimineral supplements, randomizing more than 50,000 men and women to typically years of such

supplements, and no overall benefit to mortality was found.[6701] "[W]e believe that the case is closed," read an editorial published in the *Annals of Internal Medicine* titled "Enough Is Enough: Stop Wasting Money on Vitamin and Mineral Supplements."[6702] Instead of trying to get our nutrients from pills, concluded a 2021 review on vitamin and mineral supplements, we should "move to more plant-based diets, as advised now internationally."[6703]

At least multivitamins appear to be safe.[6704] The fact that they were not associated with mortality was heralded as good news, after results from the Iowa Women's Health Study had found multivitamin use associated with a higher risk of premature death.[6705] However, there are a few supplements for which it appears people are actively paying to live a shorter life. Meta-analyses of randomized controlled trials have found that high-dose vitamin A, beta-carotene,[6706] and extended-release niacin[6707] can all increase mortality risk compared to placebo.

One way that any supplement could harm more than a user's wallet is through a fascinating glitch of human psychology called *self-licensing*.[6708] In see.nf/glitch, I explore why smokers smoke more[6709] and dieters eat more[6710] when randomized to take "supplements" that were actually placebos.

WHAT VITAMIN D CAN AND CANNOT DO

What about those so-called life extension formulas? Researchers fed mice human-equivalent doses of combinations of the highest-quality purported longevity supplements incorporating more than a hundred components, and not a single one extended lifespan. One mixture even cut their lives short. (The researchers suspect it was the fish oil that was at least partially responsible for the reduced lifespan.)[6711]

One supplement was shown in randomized controlled trials to extend human life: vitamin D.[6712] So why isn't it part of my Anti-Aging Eight? Vitamin D has been touted as a veritable cure-all,[6713] but as I note in my video see.nf/dpanacea, when actually put to the test in randomized controlled trials, vitamin D supplementation was found to be ineffective for the prevention and treatment of most conditions against which it's been tested.[6714] It failed to help with cardiovascular disease,[6715] type 2 diabetes,[6716]

multiple sclerosis,[6717] obesity,[6718] or prostate cancer.[6719] It's the old story of reverse causation and confounding. Sick people don't tend to go out in the sun, and low vitamin D levels may just be a marker for inactivity.[6720] Just because low vitamin D levels are correlated with high disease rates doesn't mean the low vitamin D levels are *causing* the disease.

There are a few exceptions. Besides the obvious vitamin D–deficiency diseases of softened bone—rickets and osteomalacia[6721]—vitamin D supplements have been found to be effective for preventing exacerbations of asthma[6722] and chronic obstructive pulmonary diseases like emphysema in people with low baseline vitamin D levels.[6723] Although vitamin D was ineffective for preventing depression,[6724] it does appear to be helpful for treating it,[6725] and the converse was true for acute respiratory tract infections—effective for preventing them[6726] but apparently not for treating them.[6727]

VITAMIN D FOR DEFYING DEATH?

The vast majority of observational population studies also show that those who have higher vitamin D levels in their blood have a lower risk of premature death.[6728] Once put to the test, though, will life extension flop, too? Sufficient D is certainly not necessary for a long life.[6729] A study of centenarians found appallingly low vitamin D levels. In fact, they were mostly undetectable using standard testing.[6730] But might taking vitamin D supplements help our chances at a longer life?

A Mendelian randomization study found that those born with genetically predetermined lifelong low D levels did tend to live shorter lives,[6731] but interventional trials looking at intermediate risk factors for our leading killer, such as artery stiffness[6732] or function, failed to show benefits for vitamin D supplements.[6733] However, what we really want are randomized, double-blind, placebo-controlled studies looking at the endpoint that matters most: premature death. Not to worry—there have been sixty-five of them![6734]

The reason I've made videos telling people to take vitamin D supplements to live longer (see.nf/dlongevity) is a Cochrane review of the first fifty-six such trials published in 2014. But by 2019, seventeen additional randomized controlled trials were published, with some so massive that they were able to tip the balance.[6735] For example, the VITAL

study randomized more than 25,000 men and women to five years of vitamin D, fish oil, both, or neither (placebos). Neither vitamin D[6736] nor fish oil[6737] was able to prevent major cardiovascular events or cancer, and neither prevented premature death. Critics argue that only a small percentage (12.7 percent) of the study subjects started out deficient in vitamin D,[6738] and all participants—even those in the placebo group—were allowed to take additional vitamin D on their own. It was not deemed ethical to randomize those who might be deficient to abstain from a vital nutrient of which they might not otherwise get enough. This is a common problem with vitamin D trials.[6739] In the VITAL trial, more participants in the placebo group took their own vitamin D than did those in the actual vitamin D supplementation group, presumably because they tested low.[6740] You can imagine how this would dilute the results.

Adding the results of VITAL to the mix, along with all the large new studies that failed to find a mortality benefit, the updated meta-analysis found that the reduction in mortality risk no longer reached statistical significance.[6741] Taking vitamin D_3 supplements did seem to reduce the risk of dying from cancer, though. The effect was small, such that you'd have to supplement 250 people for a year to prevent a single cancer death.[6742] One could argue that this reduction in the risk of dying from the second most common killer could translate into life extension for those at reduced risk of dying from killer number one, heart disease (or for those at particularly high cancer risk), but there isn't enough evidence to confirm this supposition. At the current rate, as many as a thousand new trials of vitamin D supplementation are set to be reported over the next decade, so things may change.[6743] But, as of the time of this writing, there have been more than five dozen randomized controlled trials, and the latest, largest meta-analysis of such studies shows no statistically significant mortality benefit overall.[6744] So, while I went into this book expecting I'd recommend them for lifespan extension, vitamin D_3 supplements didn't make the list, but there are eight things that do.

NUTS

According to the World Health Organization, the constituents of a healthy diet are vegetables, fruits, legumes like beans, lentils, and chickpeas, nuts, and whole grains, while cutting down on added sugars, salt, and saturated and trans fats, which are found predominantly in junk foods, meat, and dairy.[6745] Meta-analyses of prospective studies have shown reduced overall mortality risk for each of those healthy components. Each additional daily serving of vegetables was associated with a 4 percent lower risk of premature death, with 6 percent lower risk for each additional daily serving of fruits, 8 percent lower risk per serving of whole grains, 10 percent lower risk for a single daily serving of legumes, and 15 percent lower risk for eating even a daily half serving of nuts. The primacy of nuts for mortality risk reduction is underscored by the fact that a half serving of nuts is only about 15 g (0.5 oz), whereas servings of the other four groups were all larger, up to 100 g per serving. Of all the dozen or so defined food groups, nothing beats nuts for reducing the associated risk of dying before one's time.[6746]

HEALTH NUTS

Few foods, concludes a review in a top-rated nutrition journal, have experienced such "vindication" as nuts.[6747] Nut consumption is associated with a lower risk of dying from stroke, heart disease, respiratory disease, infections, diabetes, and even cancer—more than half of our top ten killers.[6748] (One study found that patients with stage 3 colon cancer who ate nuts at least twice a week had more than double the chance of surviving an average of six and a half years compared to those who never partook.[6749]) So, it isn't surprising that eating nuts is associated with a lower risk of dying prematurely across the board. In a study of those aged 84 to 107, eating nuts every day was associated with as much life extension as regular donut consumption was associated with lifespan contraction.[6750] The title of an editorial in the *Journal of the American College of Cardiology* suggested succinctly: "Eat Nuts, Live Longer."[6751] Nuts are one of the very few foods that, just on their own, may literally add years to your life.[6752]

Based on studies tracking the eating habits and deaths of about a half million people over time,[6753] inadequate nut consumption may be responsible for the premature deaths of millions every year around the world.[6754] What does this mean for us on a personal level? Eating nuts at least twice a week appears to halve mortality risk compared to almost never eating them.[6755] So, two handfuls of nuts a week could be the longevity equivalent of jogging for four hours.[6756] Looking at it another way, not eating nuts may risk doubling our chances of dying prematurely. But there's a difference between relative risk and absolute risk.

A healthy, middle-aged person's risk of dying in the next decade may only be about 2 percent. That's a one-in-fifty chance of dying over the next ten years—but only if they don't eat nuts.[6757] If they do eat them, their risk of dying may fall to just 1 percent. So, it's accurate that risk was cut in half, from 2 percent down to 1 percent, but our absolute risk of dying only fell by a single percentage point. That may not sound as impressive, but to me, dying with so much life left seems like such a tragedy that it would be worth making lifestyle changes to drive down that risk as low as possible, especially when one such strategy is a simple, delicious dietary tweak.

This is all assuming that the link between nut consumption and mortality is cause and effect. There are many potentially confounding factors. People who consume nuts tend to exercise more, smoke less, and eat less meat and more vegetables and fruits, for example. But, after controlling for these factors, the mortality benefits appear to persist.[6758] Randomized controlled trials have certainly shown that nuts can improve some of the key risk factors for some of our leading killers, such as cholesterol[6759] and, in the case of walnuts, artery function.[6760] No other food group was found to lower LDL cholesterol as effectively.[6761] Even then, though, there may be displacement effects. When researchers asked study participants to incorporate hundreds of calories of nuts into their daily diet, the subjects ended up just naturally decreasing their intake of animal protein, saturated fat, and sodium,[6762] which would be expected to help regardless of any benefits from adding nuts.[6763] It's not just that people are eating nuts instead of meat, though. The drop in heart attack risk among more frequent nut eaters is just as strong or even stronger among vegetarians.[6764]

How many nuts should we eat for maximal benefit? Remarkably, most of the survival advantage can apparently be achieved by eating only about

three servings of nuts a week, which is just an average of 12 g a day,[6765] and no further reduction of mortality risk was found above a little more than a daily 0.5 oz or 15 to 20 g a day.[6766] So, at most, that's a palmful—for instance, nine hazelnuts (filberts), ten walnut halves, thirteen cashews, seventeen almonds, or twenty-five peanuts.[6767]

How Many Nuts Are Too Much?

Surprisingly, not a single one of dozens of studies adding an average of hundreds of calories of nuts a day for fifteen weeks to people's diets resulted in significant weight gain.[6768] However, there is a limit. Do not regularly eat more than a cup of nuts a day for the same reason we should avoid consuming multiple cups of spinach, beet greens, or Swiss chard, more than a few starfruits,[6769] multiple cups of rhubarb,[6770] or even spoonsful of chaga mushroom powder[6771] a day: oxalates.

Refer to see.nf/oxalaterisk to see who is at particular risk and see.nf/oxalatefood for other risky doses, including sixteen glasses of iced tea a day[6772,6773] and regularly eating in excess of a cup of cashews[6774] or almonds,[6775] or a combination of five handfuls of almonds and six tablespoons of chia seeds a day.[6776] See here for a caveat about getting too much selenium in Brazil nuts.

WHICH NUT IS HEALTHIEST?

What about peanut butter? Details in see.nf/pblongevity, but basically, the longevity benefits associated with nuts (including peanuts) do not appear to extend to peanut butter, perhaps due to the lack of intact cellular structures that deliver a bounty of prebiotic goodness to our friendly gut flora. (See here.) The healthiest nut, however, is probably walnuts. Not only do they have some of the highest antioxidant[6777] and omega-3[6778] levels, but walnuts

are the only nuts known to significantly improve artery function,[6779] and they beat out others in suppressing cancer cell growth in vitro.[6780]

While nut consumption in general has been associated with lower risk of impaired agility and mobility in older men and lower risk of impaired overall function in older women,[6781] in the Harvard Nurses' Health Study, only walnuts were significantly associated with healthy aging after controlling for confounding factors.[6782] Of all the nuts investigated in the PREDIMED study, the researchers discovered the greatest benefits associated with walnuts, particularly when it came to cancer.[6783] Individuals eating more than three servings a week of walnuts appeared to cut their risk of dying from cancer in half. A review of the available evidence concluded that "the far-reaching positive effects of a plant-based diet that includes walnuts may be the most critical message for the public."[6784]

GREENS

Nuts seem to beat out vegetables in terms of food groups associated with a longer life, but that was compared to vegetables *in general*. Green leafy vegetables can match nuts for potentially decreasing the risk of premature death,[6785] and consumption of greens is also associated with lower risk of heart disease, stroke, and a few types of cancer and may even help prevent some of the leading causes of age-related vision loss.[6786] (See the Preserving Your Vision chapter.) Greens can also boost our immunity, slow our metabolism, and protect our body against the effects of air pollution, one of the leading causes of death worldwide.

BOOSTING GUT DEFENSES WITH BROCCOLI

Our greatest exposure to the outside world is through our gut. When you take into consideration all the little folds in our intestinal lining, its total surface area is about half the size of a badminton court.[6787] Yet the lining is extremely thin, at just fifty-millionths of a meter. In other words, the barrier between our bloodstream and the outside world is many times thinner than a piece of tissue paper. If the lining of our gut were any thicker, it would be difficult for nutrients to pass through. Our skin needs to be waterproof so

we don't start leaking, but our intestinal lining must allow for both nutrients and fluids to be absorbed. Since we have such a fragile layer separating our inner core from the outer chaos, we need a good defense mechanism in place to keep out the bad.

Enter our immune system, specifically, our intraepithelial lymphocytes, which are special types of white blood cells that have two functions: serving as our gut's first line of defense against pathogens and conditioning and repairing the thin intestinal lining.[6788] The "Ah receptor" covers these lymphocytes and activates the cells.[6789] This crucial receptor is significantly upregulated in centenarians, whereas its loss leads to premature aging (at least in mice).[6790] For years, scientists were unable to find the key that fit into the Ah receptor lock. If only we could uncover how to activate these cells, we might be able to boost our immunity.[6791] That key, it turns out, is found in broccoli. For more details, go to see.nf/gutdefenses.

The immune boost we get from consuming broccoli and other cruciferous vegetables not only protects us against pathogens found in food but also against pollutants in the environment, like car exhaust or tobacco smoke. Because dioxins and certain other pollutant chemicals exert their toxic effects through the Ah receptor system, cruciferous compounds may block them.[6792] Lest you think concerns over toxic chemicals floating around whiff of overblown hippie paranoia, in reality they are likely the fifth leading cause of death.[6793]

BILLIONS OF YEARS LOST EVERY YEAR

According to the preeminent Global Burden of Disease Study, air pollution is the fifth leading killer of humanity, wiping out about four million people a year[6794] from lung cancer, emphysema, heart disease, stroke, and respiratory infections.[6795] Ironically, one respiratory infection—COVID-19—may have saved lives in some parts of the world. In the early months following the lockdown in China, the decrease in air pollution was so great that as many as 30,000 air pollution fatalities *a month* may have been averted in that country alone. In other words, the air quality in China was so bad that COVID-19 may have ended up *saving* around a thousand lives a day.[6796]

Nine out of ten people live in areas that violate the World Health Organization's air pollution guidelines.[6797] It's estimated that improving air quality to those standards would increase the average global lifespan by more than two years. So, every year, polluted air appears to shave off billions of years of life expectancy.[6798] Traffic-related air pollution exposure has also been associated with premature skin aging[6799] and dementia.[6800] What can we do about it?

In 2014, China declared a "war against pollution," and their pollutant particle levels have since dropped by 29 percent, potentially adding years onto their average life expectancy.[6801] Elsewhere, however, such strict policy actions "might not be politically acceptable" as they "might indirectly affect the comfort of the population."[6802] Until we have better vehicle inspections, public transport, bus lanes, bicycle lanes, and perhaps even urban tolls to fund air cleanup efforts, what can we do to protect ourselves?

Personal strategies to minimize effects of air pollution include limiting physical exertion outdoors on high air pollution days and near heavy traffic areas.[6803] A randomized, crossover trial of older men and women found that walking along busy streets "curtails or even reverses the cardiorespiratory benefits of exercise."[6804] Close-fitting particulate respirators, such as N95 face masks, should even be considered on high pollution days.[6805]

Thanks in part to our changing climate, even if we uproot our families and move out to the countryside, worsening forest fires can bring pollution home, almost no matter where you live and breathe. Home air purifiers are increasingly recommended during fire smoke events,[6806] as numerous studies have shown that they can lower particulate exposure and benefit respiratory and cardiovascular health.[6807] I'd recommend HEPA filter models and avoiding air cleaning technologies that may emit harmful by-products,[6808] such as electrostatic precipitators (ionizers)[6809] and negative ion generators.[6810]

Diet contributes to more than twice as many deaths as air pollution, though.[6811] Fortunately, we may be able to bring the power of diet to combat the effects of polluted air.

DIETARY DETOX

I detailed how cruciferous vegetables can boost the activity of the detoxifying enzymes in our liver (see here) such that heavy broccoli eaters have to drink more coffee to get the same caffeine buzz.[6812] We also have detoxification enzymes lining our airways. Studies show that people born with less effective ones have an exaggerated allergic response to diesel exhaust, suggesting that these detox enzymes actively combat the inflammation caused by pollutants in the air.[6813] Might broccoli boost the activity of those enzymes, too?

Given that the cruciferous compound sulforaphane is the "most potent known inducer" of a major class of detox enzymes, researchers tried to see if it could combat the pro-inflammatory impact of pollutants.[6814] Details in see.nf/pollutiondetox, but basically, by squirting both diesel exhaust and flu viruses up people's noses, researchers discovered that eating a cup or two of broccoli could offer the best of both worlds—less inflammation from the pollution[6815] and an improved antiviral immune response.[6816] Broccoli was also found to cut inflammation levels in smokers[6817] and dramatically accelerate the clearance of carcinogenic pollutants like benzene from the body.[6818]

What About Broccoli Supplements?

What if you don't like the taste of cruciferous veggies but still want their benefits? Researchers put BroccoMax, a leading commercially available broccoli supplement, to the test. Its manufacturer boasts that each capsule of BroccoMax contains the equivalent of half a pound of broccoli. Each day, study participants were given either six capsules or about a cup of broccoli sprouts. In the end, the supplement hardly worked at all, while the sprouts boosted blood levels about eight times higher and about eight times cheaper.[6819] Newer enzyme-treated broccoli sprout extract

supplements claim comparable bioavailability, but they, too, were found to pale in comparison to the real thing.[6820]

GREEN IS FOR SLOW

One of the ways caloric restriction may extend the lifespan of animals is by slowing their metabolism.[6821] Like a candle, burning with a smaller flame may allow us to last longer. Thanks to the nitrates in green leafy vegetables, we may be able to achieve a similar metabolic benefit by eating a big salad every day.

The nitrate naturally found in leafy greens and beets improves the efficiency of our mitochondria, the little power plants within our cells, boosting athletic performance by extracting more energy from each breath.[6822] That's why a single shot of beet juice enables free divers to hold their breath for thirty seconds longer than usual, for instance.[6823] See what else vegetable doping can do for athletic performance in see.nf/nitrates. No drug, supplement, steroid, or any other intervention has been shown to do what vegetable nitrates can do.[6824]

Top Ten Common Food Sources of Nitrates

1. Arugula
2. Rhubarb
3. Cilantro
4. Butter Leaf Lettuce
5. Spring Greens (e.g., Mesclun Mix)
6. Basil
7. Beet Greens
8. Oak Leaf Lettuce
9. Swiss Chard
10. Beets

Beets barely even reach the top ten list of common nitrate-rich foods, though. Eight of the top ten are greens, and, with four times the nitrate content of beets, arugula comes out on top with a whopping 480 mg of nitrate per 100-g serving.[6825]

Overall, green leafy vegetables contribute to 80 percent of our nitrate intake.[6826] So, if we eat a lot of greens, might we be able to slow our metabolism since our body would be able to function so much more efficiently, effectively drawing more energy from each calorie? Indeed, researchers found that the resting metabolic rates of study participants slowed by an average of about 4 percent after they consumed a dose of nitrate equivalent to a few servings of greens or beets.[6827] That's nearly a hundred calories of slowing a day.[6828] The researchers conjectured that this may be a way our body evolved to use vegetables to help preserve energy during lean times in our ancient past. Either way, slowing our metabolism may have benefits for our longevity[6829] and explain why those who eat more greens tend to live longer than those who eat less.[6830]

VEGETABLE NITRATES TO COMBAT MUSCLE AGING

Nitrate supplementation can significantly increase exercise tolerance[6831] and performance,[6832] not only because it enables our body to extract more energy from oxygen[6833] but because it helps to dilate our arteries so they can deliver more oxygenated blood to our muscles[6834] and even directly improves muscle function (contractility) through an unknown mechanism.[6835] Nitrate-rich diets have been associated with improved muscle strength and physical function, leading researchers to conclude that "vegetables may be an effective way to limit any age-associated declines in muscle function." Causality, however, can't be inferred due to the cross-sectional nature of the data.[6836]

Catch see.nf/nitrateaging for more, but there have been acute interventional studies, such as one in which older men and women with an average age of seventy-one were given a beet juice supplement equivalent to about a cup of cooked greens. The participants experienced a significant boost in knee extension (quads) power and velocity. Based on the steady annual rate of muscular decline, the extent of the nitrate enhancement was said to be "functionally equivalent to acutely reversing the effects of several

decades of aging."[6837] A similarly aged group consuming a similarly sized dose also significantly improved upper body strength recovery (forearm hand grip).[6838]

VEGETABLE NITRATES TO COMBAT ARTERY AGING

In an editorial titled "Cardiac Aging and the Fountain of Youth," a Mayo Clinic research chair commented on the results of an "impressive array of experiments suggesting that this dream of reversing cardiac aging might not be as mythical as we had once believed."[6839] Spiking the water of old mice with nitrates was able to reverse age-related heart and artery stiffness,[6840] but what about people?

A meta-analysis of a dozen randomized, controlled human trials found that between two-thirds of a cup to two cups of cooked greens' worth of nitrates significantly improved artery function as measured in the arms[6841] or legs,[6842] and, as I detail in see.nf/nitrateaging, this translates into clinical benefit, for example, enabling peripheral artery disease patients to walk 18 percent longer without pain.[6843]

The healthiest way to get your nitrate fix is to eat a big salad every day. People randomized to eat a green leafy salad with arugula and spinach lowered their blood pressures within hours, compared to eating a greens-free salad of cucumber, green beans, and cherry tomatoes.[6844] You could take nitrate- and nitric-oxide-boosting supplements, but they have a questionable record of safety[6845] and efficacy.[6846] What about a juice like V8, which includes beets and spinach juice as ingredients? It must not have much of either, because you'd need to drink nineteen quarts of it a day to reach your daily nitrate intake target.[6847] (Details in see.nf/nitratetarget.)

FEEDING YOUR ORAL MICROBIOME

When all the studies are put together, nitrate-rich vegetables are found to significantly lower blood pressure on average,[6848] but some studies show no benefit whatsoever.[6849] To understand this variability and why eating greens is especially important as we age, you must first understand the nitrate activation step that happens in your mouth, thanks to good bacteria on your tongue. I explain the whole fascinating process in see.nf/scrape, but the

bottom line: Foster the growth of nitrate-metabolizing bugs by eating nitrate-rich vegetables regularly,[6850] don't use antiseptic mouthwash,[6851] and clean your tongue daily[6852] (unless you have heart valve problems, a pacemaker, or anything else that puts you at risk for endocarditis).[6853]

HOW TO KEEP NITRATES FROM TURNING INTO NITROSAMINES

Note that the nitrate strategy may only work in the context of a healthy diet.[6854] Adding saturated fat (in the form of meat and dairy) to a vegetable-rich Mediterranean diet was found to raise blood pressure, not lower it.[6855] Furthermore, the nitrate strategy may only be *safe* in the context of a healthy diet.

The activation step that occurs on our tongue is the conversion of nitrates into nitrites. *Nitrites?* Isn't that what's added to cured meats? Why are nitrates and nitrites from vegetables okay, while the very same compounds from meat are linked to cancer?[6856] Because nitrites on their own are not carcinogenic; they *turn into* carcinogens. Nitrites only become harmful when they become nitros*amines* and nitros*amides.* For them to do that, amines and amides must be present, both of which are found in abundance in animal products.

So, adding nitrites to meat leads to the formation of carcinogens. (In the case of "uncured" bacon, you may see "fermented celery juice" or something similar in the ingredients list; that's just a deceptive way to add nitrites without using the word "nitrites.")[6857] The threat from processed meat is so great that the second-largest prospective study ever on cancer and diet determined that reducing consumption of processed meat to less than 20 g a day, a portion smaller than a matchbook, would prevent more than 3 percent of all deaths in Europe.[6858] The largest prospective study of diet and health in U.S. history—the NIH-AARP study of more than half a million Americans—found that the fraction of preventable deaths may be even higher. For instance, suggested the researchers, if the highest consumers of processed meat would reduce their intake to the equivalent of less than half a bacon strip a day, 20 percent of heart disease deaths among U.S. women could be averted.[6859] It's no surprise that the American Institute for Cancer

Research recommends that we simply "avoid processed meat such as ham, bacon, salami, hot dogs and sausages."[6860]

So, nitrite-laden processed meats are a no-go, but what if the amines and amides in unprocessed meat mixed with the nitrites from activated vegetable nitrates? Remember, on their own, nitrites aren't carcinogenic; it's only when they're turned into nitrosamines and nitrosamides in the presence of amines and amides. So, for example, what if you eat a big salad, then, two or three hours later, eat unprocessed meat? The swallowed nitrites off your tongue from the salad-nitrate that got pumped back into your mouth could then mix in your stomach with the amides and amines from the meat. Researchers put this possibility to the test by having volunteers drink nitrate-rich water with a daily meal of cod, salmon, pollack, or shrimp. (Seafood is high in amines.) The level of carcinogenic nitrosamines flowing through their bodies shot up during the week they were asked to eat fish and fell back down once they cut out the seafood.[6861] A similar reaction was found in another study, with unprocessed chicken and turkey breast instead of seafood.[6862] This explains why having omnivores drink a single bottle of beet juice can lead to a significant rise in these carcinogenic compounds in their urine within twenty-four hours.[6863]

On the other hand, the vitamin C and other antioxidants naturally found in plant foods help block the formation of these carcinogens in our stomach.[6864] This helps explain why intake of nitrate and nitrite from processed meats has been linked to cancer, but no increased risk has been found for intake of nitrate or nitrite from plants.[6865] It may take more than a side serving, though. In the seafood study, the research subjects ate some vegetables with their fish, but evidently not enough to block carcinogen formation.[6866] So, those wanting to take full advantage of nitrate-rich vegetables may want to center all their meals around whole plant foods.

SALAD DAYS

In 1777, General George Washington issued an order that American troops should forage for wild greens around their camps "as these vegetables are very conducive to health, and tend to prevent … all putrid disorders."[6867] Since then, however, most Americans have declared their independence from greens. Today, only about one in twenty-five even reach a dozen

servings throughout the course of an entire month,[6868] whereas I advise getting more than a dozen servings a week.

Greens have been suggested as one of the Okinawan secrets for longevity.[6869] Eating greens at least nearly every day may be one of the most powerful steps we can take to extend our lifespan. A study titled "Healthy Lifestyle and Preventable Death" identified six lifestyle factors that were associated with cutting in *half* the risk of dying over a period of twelve years for men and women in their sixties and seventies. Beyond nondietary factors, such as not smoking and walking an hour or more a day, the sole criterion for dietary quality the researchers used was "eating green-leafy vegetables" at least "almost daily."[6870]

Of all the food groups analyzed by a Harvard University research team, greens were associated with the strongest protection against major chronic diseases,[6871] including up to about an associated 20 percent reduction in risk for heart attacks[6872] and strokes[6873] for each additional serving per day.

So no wonder that of all the different types of fruits and vegetables, the best evidence for reducing mortality risk overall is seen with the consumption of green leafy vegetables.[6874] Imagine if there were a pill that could prolong your life and only had good side effects. Everyone would be taking it! It would be making billions of dollars for the lucky drug company that created it. All health plans by law would have to cover it. People from every walk of life and every corner of the globe would be clamoring for it. But when that "pill" is just eat-your-greens, people's eyes just glaze over.

IMPORTANT CAVEAT: Greens and Warfarin

If you are on warfarin (also known as the drug Coumadin), be sure to speak with your physician before you increase your intake of greens. The drug works by hampering the enzyme that recycles vitamin K, which is involved in blood clotting. If your system gets an influx of fresh vitamin K, which is concentrated in greens, you may undermine the effectiveness of the drug.[6875] You should still be able to

enjoy your greens, but your doctor will need to titrate the dose of the drug to match your regular greens intake.

BERRIES

For all the national dietary guidelines from around the world, the most common key message is simple: Eat more fruits and vegetables.[6876] But not all fruits and vegetables are the same. Those who think berries are the berry best live longer, but those who are bananas over bananas do not.[6877] I've already talked about the benefits of berries for cognition in the Preserving Your Mind chapter, for immunity in the Preserving Your Immune System chapter, and for eyesight in the Preserving Your Vision chapter. Rarely in research are berries separated out from the generic fruit category,[6878] but combining the three prospective studies on eating berries and overall longevity, it's clear that those with high berry consumption tend to live significantly longer than those with low intake.[6879] Tastes great *and* may help us live longer? That's what plant-based eating is all about.

JAM-PACKED WITH ANTIOXIDANTS

Berries appear to reduce all-cause mortality risk as much as green leafy vegetables.[6880] Greens are the healthiest vegetables, and berries the healthiest fruits—in part due to their respective plant pigments. Leaves contain chlorophyll, the green pigment where the firestorm of photosynthesis takes place, so greens have to be packed with antioxidants to deal with the free radicals that are formed. Meanwhile, berries evolved to have bright, contrasting colors to attract fruit-eating critters to help disperse their seeds, and the same molecular characteristics that give berries such vibrant colors may account for some of their antioxidant abilities.[6881]

Apples and bananas are America's favorite fruits, with antioxidant power of about 60 and 40 units, respectively (in modified FRAP assay daμmol antioxidant units). Mangos are the preferred fruit everywhere else and have much more antioxidant punch at around 110 units. (If you think about how much more colorful mangos are on the inside, this makes sense.)

But none of these fruits is a match for berries: Per cup, strawberries have about 310 units; blueberries, 380; raspberries, 430; cranberries, 490; and blackberries, a staggering 680 antioxidant units. There are some Dr. Seuss–sounding berries in the Arctic tundra, like red whortleberries, that have even more antioxidant power, but when it comes to what is readily available in the store, it's blackberries for the win. Selecting blackberries over strawberries may give you twice the antioxidant bang for your berry.[6882]

Super-Dupe-Er Fruit

Açaí berries have anti-aging effects in mice,[6883] though they don't prolong the lifespan of *C. elegans*.[6884] Açaí does improve the survival of fruit flies fed a high-fat diet, but what might it offer people?[6885] I profile the disappointing clinical results in see.nf/acai. Even the antioxidant effects are overblown. Those who hawk supplements love to talk about how açaí consumption can "triple antioxidant capacity" of your blood. If you look at the study they cite, though, you'll find that the antioxidant capacity of participants' blood did actually triple after eating açaí—but the same tripling was achieved in the control group consuming plain applesauce.[6886]

DEAD AND BERRIED

As I noted here, the stomach acts as a bioreactor.[6887] The fat in muscle starts to oxidize (turn rancid) from the moment an animal is slaughtered, but when meat hits the acid bath of the stomach, a burst of free radicals is generated.[6888] Within hours of consumption, oxidized fat by-products like malondialdehyde (MDA) are created and then absorbed into the bloodstream,[6889] where they can damage proteins and mutate DNA.[6890] But berries can help.

Polyunsaturated fats are most susceptible to oxidation, which explains why a digested chicken leg results in six times more MDA equivalents than

beef or pork and salmon results in fourteen times more. What about high polyunsaturated plant foods like pecans? Add handfuls of pecans to people's diets, and MDA levels go *down*.[6891] Why? Because whole plant foods come prepackaged with antioxidants to protect against oxidation. On average, plant foods have *sixty-four times* more antioxidants than animal foods. Even iceberg lettuce has more antioxidants than meat, and it's 96 percent water.[6892] That's why most of the oxidized fat we get in our diet comes from meat products and fatty processed foods.[6893]

If antioxidants in plants can counter fat oxidation in the stomach, what about just eating plants and meat together? It worked in pigs. When pigs were fed a mixture of oil and beef, they had a fivefold increase in MDA equivalents, but when they were fed the same oily beef with fruits and vegetables (plums, apples, and artichoke hearts), the meal appeared to only double MDA levels.[6894] Researchers in Italy decided to try this in humans by having people eat a McDonald's Big Tasty Bacon and fries with or without one and a half glasses of fermented berry juice (red wine). Within four hours of eating the Big Tasty Bacon and fries without the wine, there was a significant rise in oxidized LDL cholesterol in the blood, but not after the same McDonald's meal was paired with merlot.[6895] The same neutralization of the effects on oxidized fats and cholesterol in the blood was found with two glasses of red wine with a double cheeseburger.[6896]

The one food group with more antioxidant power than berries is spices. Herbs and spices have been used in meat preservation to reduce rancidity for thousands of years.[6897] Researchers prepared a spice mix composed of about a teaspoon of paprika, one and a half teaspoons of oregano, a half teaspoon of garlic powder, a half teaspoon of ginger, and about a quarter teaspoon each of black pepper, cloves, cinnamon, and rosemary to a half pound of ground beef. Compared to the burgers without the spice mix, the spiced burgers cut the MDA flowing through the subjects' systems approximately in half (as measured in their urine).[6898] Just adding about a half teaspoon of turmeric to a half pound of ground beef can cut its MDA content by around 20 percent. Although black pepper alone doesn't seem to help, combining the turmeric with even just an eighth of a teaspoon of black pepper appears to double turmeric's effect.[6899]

Turkey is a tougher challenge. Although red wine could fully quiesce the fat oxidation of a double cheeseburger, it was able to drop MDA blood

levels by only 40[6900] to 75 percent after consumption of turkey cutlets. However, if you presoak the cutlets in red wine in addition to drinking it with the meal, you can fully defuse the MDA bump.[6901] The same with a concentrate of cranberries, blackberries, blueberries, raspberries, Chilean guava, and Chilean wineberries. Mixing the berries into ground turkey meat cut the MDA spike from turkey burgers nearly in half, and drinking two cups of the berry combination in beverage form with the meal was able to fully quash the rise in MDA.[6902]

Rather than making berry burgers, what about just eating a side salad? Researchers combined about a quarter pound of turkey breast with a half cup of a Mediterranean-type salad made up of tomato, raw pink onion, black olives, extra-virgin olive oil, and fresh basil into an in vitro digester and were able to reduce the formation of oxidized fats in half. A full cup of salad stopped the oxidation completely. Testing the different salad components separately, the most potent appeared to be the onion and the olive oil.[6903]

Unlike tuna fat or fish oil supplements, which can quintuple the MDA formation from digesting turkey meat, the antioxidants in extra-virgin olive oil can cut it in half.[6904] There can be a paradoxical effect at higher concentrations, though. At a concentration of 2.5 percent, which is about a half teaspoon of oil for a 3-oz serving of turkey breast, extra-virgin olive oil has a powerful antioxidant effect. But at 5 percent (a full teaspoon) or 10 percent, it had a pro-oxidant effect, making MDA formation from digesting turkey even worse.[6905] No such paradoxical effect has ever been reported with whole plant foods. Only about one in five Americans eats salad on a given day, though.[6906] How about just a simple cup of joe?

Given the sad state of the standard American diet, coffee is actually one of the leading sources of antioxidants.[6907] Turkish coffee is like the matcha of the coffee kingdom in that you drink the powdered beans, and a cup of it can cut the MDA levels in your bloodstream caused by a meat meal by more than half, comparable to the effect of red wine. Instant coffee is the least potent. It would take four and a half cups of instant coffee to have the same effect as one cup of Turkish.[6908]

To quantify just how many plant foods it would take to neutralize the free radicals produced in the stomach after consuming animal foods, researchers created the Postprandial Oxidative Stress Index, defined as “the

capacity of a plant derived food in grams to completely (100%) inhibit MDA formation from 200 g turkey meat incubated in SGF [simulated gastric (stomach) fluid] for 180 min at 37°C" body temperature. How much tomato would you have to put on that turkey sandwich to not end up with mutagenic oxidized fat in your blood? Thirty-one slices, which is about five tomatoes' worth. Spinach has, gram for gram, six times more free radical–quenching power, but it is so light that you'd need three cups of spinach, which might topple the sandwich but could be doable as a large side salad. Having one large apple would also do it, but berries would be the best. Even just an eighth of a cup of blackberries would sop up the free radicals created by the turkey meal in the stomach, or a quarter cup of blueberries, a half cup of raspberries, or a full cup of strawberries.[6909]

Fatty fish like tuna or salmon would be worse than turkey because of the polyunsaturated fat content in fish, and beef and pork would be better. The worst of the worst would be a combination of poultry (turkey) and fish fat (tuna oil), which creates five times more oxidized fat in the stomach than turkey alone. Still, that's nothing that less than a cup of blackberries couldn't handle.[6910] So, whenever you eat meat or fatty junk food, you should make sure your stomach also has potent plants in it at the same time to deal with the pro-oxidant aftermath.

If you're going to buy bulk vitamin C to make your own DIY facial youth serum (see here), why not just sprinkle some on a meal? Because it could make things worse. Straight vitamin C in the stomach can convert the ferric iron (Fe^{3+}) in meat into ferrous iron (Fe^{2+}), which causes toxic hydroxyl radical,[6911] resulting in a net pro-oxidant effect at all vitamin C doses tested when mixed with high-fat beef during digestion.[6912]

No Wild Goose Chase

As a Western-trained physician, I had never heard of amla, which is dried, powdered Indian gooseberry fruit. I was surprised to find more than seven hundred articles on it in the medical literature and even more surprised to find papers with titles like "Amla, a Wonder Berry in the Treatment and Prevention of Cancer." Arguably the most

important plant in Ayurvedic medicine, amla is used traditionally for everything from a hair tonic to a snake venom neutralizer.[6913] I eat it because it's apparently the single most antioxidant-packed whole food on Earth.[6914] See what four cents' worth can do to the antioxidant power of a smoothie in see.nf/breakfast.

In the Ayurvedic lexicon, amla is considered "the best medicine to increase the lifespan"[6915] and a "potent aphrodisiac," but the evidence to support these claims derives from fruit flies.[6916] The Elens-Wattiaux mating chamber I detail in see.nf/amla has since been replaced with the "Copulatron." But when you read about aphrodisiac effects, you're probably not thinking *more maggots.* What effects have been documented in people?

A lifespan-extending effect wouldn't be surprising given the cholesterol-lowering benefits of amla[6917] I note in the video. Amla has also been shown to reduce triglycerides,[6918] improve blood fluidity, reduce markers of oxidative DNA damage[6919] and systemic inflammation,[6920] improve blood sugar control in diabetics,[6921] and may decrease the effects of stress on the heart.[6922] As noted in see.nf/dyspepsia, it can also work as well as antacids for calming an upset stomach, in addition to significantly reducing heartburn and regurgitation.[6923] See my Amla section in *How Not to Die* for tips on buying and using it.

CHASE RAINBOWS

Leading health organizations such as the American Heart Association and the American Institute for Cancer Research encourage people to "eat the rainbow," a wide spectrum of naturally colorful foods.[6924] Beyond the fact that 94 percent of Americans don't even reach the minimum recommended number of servings of fruits and vegetables (five to thirteen, depending on gender, age, and activity), there is a "phytonutrient gap." We are missing out on the colors. If the average American should eat about ten servings a

day, that could be visualized as two from each color category, yet about eight out of ten Americans fall short of every color. The worst is the purple/blue group, our source of anthocyanin pigments, for which more like nine out of ten are deficient.[6925] Blueberries are the main source in the U.S. diet, yet people average only about a single blueberry a day.[6926]

Anthocyanin comes from the Greek *anthos*, meaning "flower," and *kyanos*, meaning "blue."[6927] The same pigments color red, blue, and purple berries, but their names still hint at their floral origins—for example, the petunidin in blueberries or the peonidin in cranberries.[6928] Able to cross the blood-brain barrier, anthocyanins are thought to be responsible for the cognitive benefits of berries in terms of improving brain perfusion, memory, executive function, processing speed, attention, and overall cognitive performance.[6929] They may also benefit our eyesight.

In the Preserving Your Vision chapter, I talked about their potential for helping with macular degeneration, glaucoma, and cataracts, but berries also can benefit our vision in other ways. Randomized, double-blind, placebo-controlled trials have shown that berry anthocyanins can significantly improve both objective and subjective signs and symptoms of eye strain,[6930] as well as improving light[6931] and dark[6932] adaptation. Anthocyanins appear to be important for regenerating a receptor protein known as "visual purple" in our retina that helps convert light into electrical signals for the brain, speeding up how fast our vision can adjust to changing light levels.[6933]

As discussed in the Inflammation chapter, berries have systemic anti-inflammatory effects throughout the body, though they can also suppress inflammation directly within the gut.[6934] Ninety percent of patients with ulcerative colitis responded to bilberries, with most achieving remissions within six weeks; disease activity surged back, however, once the berries were stopped.[6935] Part of this may derive from the prebiotic effect of anthocyanins on the gut flora. Eating berries increases the number of good bugs and decreases the number of bad ones.[6936] For example, eating blueberries every day increases the number of *Lactobacilli* and *Bifidobacteria*.[6937] Similar effects have been shown for black currants[6938] and tart cherries.[6939]

Anthocyanins have also been found to improve short- and long-term blood sugar control,[6940] in part by improving insulin sensitivity,[6941] so it's no

surprise that higher berry intake is associated with a lower risk of developing type 2 diabetes.[6942] A famous pair of Harvard studies chalking up millions of person-years of data found that just two or more servings a week was associated with 23 percent lower risk.[6943]

Berries may also acutely improve artery function,[6944] which could help explain why higher anthocyanin intake is associated with a significantly lower risk of dying from cardiovascular disease[6945] and, by extension, all causes put together.[6946] A bowl of blueberries can even mediate much of the arterial dysfunction induced by smoking a cigarette. Smoke just one, and the ability of your arteries to relax naturally drops by 25 percent within two hours.[6947] But if you eat two cups of blueberries a hundred minutes before smoking, that same cigarette causes less than half the damage. (Of course, all the damage could be prevented by not smoking in the first place.)

We suspect it's largely the anthocyanin component since purified anthocyanins alone can improve artery function,[6948] though not as well as whole berries.[6949] At doses over 300 mg a day, anthocyanins can also lower LDL cholesterol.[6950] That translates into as little as a single daily serving, like a half cup of high-anthocyanin berries such as blueberries.[6951] Even just daily consumption of blueberry tea—powdered blueberries in a teabag steeped for five minutes—can lower cholesterol, though it took three months for the tea to start having a significant effect.[6952]

Anthocyanins are cleared from our bloodstream within about six hours, so, by the afternoon, the berries you had on your oatmeal may have run their course.[6953] In my mind, berries make the perfect dessert for any meal. There are other anthocyanin-containing fruits, like plums, pomegranates, and red or black grapes. Anthocyanins can also be served in your main course, thanks to red onions, blue potatoes, red cabbage, or purple barley. I like to air-pop purple popcorn for a snack or air-fry purple sweet potato fries for a side. For a drink, what do you think makes hibiscus tea as ruby red as Dorothy's slippers? Anthocyanins may also be responsible for the blood-pressure-lowering benefits of hibiscus.[6954] In animal models, the anthocyanins in black rice help ameliorate the accelerated aging induced by galactose in mice,[6955] and those in purple wheat prolong the lifespan of *C. elegans* by about 10 percent.[6956]

CHERRIES, CRANBERRIES, GOJIS, AND GRAPES

For about half a century, we've known that tart cherries are so anti-inflammatory that they may be used to successfully treat gout, a painful type of arthritis, as I mentioned in the Inflammation chapter.[6957] Cherries can also reduce inflammation in healthy people, as indicated by decreasing C-reactive protein levels.[6958] Overall, eleven out of sixteen interventional trials on the consumption of cherries, both tart and sweet ones, found a decrease in inflammation, and a drop in oxidative stress was found in eight out of ten studies, a decrease in exercise-induced muscle soreness and loss of strength in eight out of nine, a drop in blood pressure in five out of seven, improvements in arthritis in five out of five, and improved sleep in four out of four (presumably due to the melatonin content, see.nf/melatoninfoods). Most of these studies were less than two weeks in duration and involved giving people the equivalent of 45 to 270 cherries a day.[6959]

When not in season, tart cherries can be found canned in water and sweet cherries can be found in the freezer section. (I still like to suck on frozen dark cherries like little popsicles—a trick my mom taught me.) In *How Not to Die*, I recommend using the drained liquid from canned cherries in a hibiscus punch recipe and mixing cherries into your morning oatmeal with cocoa powder for a chocolate-covered cherry-like sensation.

As we saw in the Preserving Your Bowel and Bladder Function chapter, cranberries have benefits for urinary health for both men and women. Cranberries can increase the lifespans of flies[6960] and worms[6961] and slow the age-related decline in insulin production in rats,[6962] but they haven't been put to the test for mammalian longevity.

I highlighted goji berries in the Preserving Your Immune System and Preserving Your Vision chapters. Also known as *wolfberries*, goji berries have long been considered a "potent anti-aging agent" in traditional Chinese medicine and have been used to counteract premature hair graying, for example.[6963] There is little scientific evidence to confirm such effects, though. Goji berries do extend the lifespan of *Drosophila*, but fruit being good for fruit flies isn't exactly revelatory.[6964] However, they have at least four times the antioxidant activity of other dried fruits, like raisins or dried cranberries that you might otherwise sprinkle on your oatmeal or add to

your trail mix.[6965] Goji berries also have anti-inflammatory effects in vitro (on cells from umbilical cords),[6966] as well as in randomized, double-blind, placebo-controlled trials of whole people,[6967] and may even help with weight loss, as I detail in my Inflammation Quenchers chapter in *How Not to Diet*.

Whatever you now do with raisins, do it with gojis instead. Domesticated more than 6,000 years ago,[6968] the grapevine is now the single largest fruit crop grown in the world.[6969] What can they do for us? A meta-analysis of more than fifty randomized controlled trials involving thousands of study participants found that various grape products can cause a small (five-point) drop in LDL cholesterol, but raisins did not seem to work.[6970] This may be because most raisins are made from "white" grapes, the ubiquitous pale green Thompson grapes. In a head-to-head comparison between red grapes and green ones, eating about three cups a day of red grapes for eight weeks significantly reduced LDL cholesterol, but the same amount of green grapes did not.[6971]

Similarly, raisins were not able to acutely improve artery function,[6972] but a cup and a quarter of various fresh grapes, including red and blue-black ones, can even blunt the arterial dysfunction caused by a McDonald's Sausage McMuffin with Egg meal.[6973] Chronic improvement in artery function was also demonstrated in a randomized, double-blind, placebo-controlled trial (using powdered red grapes).[6974]

Grape Seed Extract Supplements

The McMuffin mediation study included grapes with seeds, which harbor the bulk of the polyphenols in the fruit. Only 1 percent is found in the pulp and 5 percent in the juice. The skins of grapes hold 30 percent of the polyphenols, but the seeds contain the remaining 64 percent.[6975] Unfortunately, it can be hard to find seeded grapes these days. What about just taking grape seed extract supplements? I review the available studies for you in see.nf/gse. The bottom line? Stick to the seeded grapes. I've found the best odds of finding seeded grapes are at Asian markets, where you

might be lucky enough to find Concord-like Kyoho grapes (from the Japanese *Kyoho¯ budo¯*, meaning "giant mountain grape"), dark purple globes with tasty large oval seeds.

XENOHORMESIS AND microRNA MANIPULATION

Xenohormesis and microRNAs represent cross-kingdom communication pathways between plants and animals that we may be able to use to our advantage.

XENOHORMESIS

Hormesis can be thought of as the "that which doesn't kill you makes you stronger" principle.[6976] Physical activity is the classic example:[6977] You put stress on your muscles and heart, and are all the healthier for it, provided there is sufficient recovery time. Mild stresses like exercise can trigger a protective response that leads to strengthened defenses in the long run.[6978]

In the sixteenth century, the Swiss physician Paracelsus, the "father of toxicology," coined the Latin phrase *sola dosis facit venenum*, which is translated as "only the dose makes the poison."[6979] This aphorism is typically summoned to explicate how some of the most helpful or harmless substances (like water) can be toxic at high enough concentrations, and, conversely, how even some of our most poisonous substances (like cyanide) can be harmless at sufficiently infinitesimal doses. The field of toxicology adopted this threshold dose-response model, where at low enough concentrations, there may be no effect, but above that, the hazard is proportional to the dose. Hormesis added a new wrinkle, forcing toxicology to challenge this assumption.[6980]

Hormesis takes the notion "too much of a good thing can be bad" and turns it on its head by suggesting that, sometimes, a little of a bad thing can be good.[6981] Hormesis comes from the Greek term *hormáein*, meaning "to excite."[6982] Rather than a linear model in which there are small effects at

small doses and the same but larger effects at larger doses, hormesis describes a biphasic response characterized by one effect at a low dose and the opposite effect at a higher dose. For example, herbicides kill plants, but in tiny doses they can actually boost plant growth, presumably by stressing the plant into rallying its resources to successfully fight back.[6983]

What began as a biological curiosity used in a misguided nineteenth-century attempt to vindicate homeopathy[6984] is now undergoing a resurgence of interest.[6985] In the 1980s, as few as a single study a year were published on hormesis in the scientific literature. Now, on average, more than one paper is published every day.[6986] This is in large part due to interest in the role of hormesis to combat aging.[6987]

BASK IN THE GLOW?

Hormesis was first shown to extend life more than a century ago when low doses of radiation were found to increase the lifespan of beetles[6988] by presumably ramping up DNA repair.[6989] That which didn't kill them made them stronger. I run through the wild ride of a story in see.nf/radiation, including studies suggesting longer lives among atomic bomb survivors[6990] and experiments done more than a mile down into the Earth to counter the cosmic rays bombarding us every second.[6991] "Nothing in life is to be feared," Marie Curie, who won the Nobel Prize for pioneering work in radioactivity, is quoted as saying, "it is only to be understood."[6992] Of course, this is coming from a woman who died of bone marrow failure from radiation exposure,[6993] such that her remains had to be interred in a lead-lined coffin.[6994] Watch the video, but the bottom line is that we don't know enough about low-level radiation to exploit any hormetic effects without potentially being exposed to unacceptable risks. There are, however, salutary ways to harness hormesis for health and longevity.

NO PAIN, NO GAIN

We all know that exercise is ultimately good for us, but, nonetheless, it places inseparable stress on the body.[6995] Ultramarathon runners generate so many free radicals during a race that they can damage the DNA of a significant percentage of their cells.[6996] But, within a week, they don't just go back to the baseline level of DNA damage; they have significantly *less*

damage, presumably because they had revved up their antioxidant defenses.[6997] So, exercise-induced oxidative damage may ultimately be beneficial. In other words, classic hormesis, where low levels of damage can upregulate protective mechanisms and ultimately leave you better off. For those interested in how not to undermine the benefits of athletic recovery, check out see.nf/exercisehormesis.

WHAT DOESN'T KILL PLANTS MAY MAKE US STRONGER

Hormesis may be why dietary restriction can lead to lifespan extension.[6998] The mild stress placed upon the body by not eating enough may activate a wide variety of protective pathways, ramping up anti-inflammatory and antioxidant defenses.[6999] Your body is preparing itself for the coming famine it thinks is about to occur.

In the Caloric Restriction chapter, I'll explore ways to exploit the benefits of dietary restriction to extend life and prevent disease, but chronically restricting food intake is not a realistic health strategy for many. Given the powerful evolutionary drive to eat, it's hard for most people to cut food intake by even 10 or 20 percent.[7000] A more feasible alternative may be to activate dietary restriction–induced stress response pathways by other means. One such possibility is *xenohormesis*, derived from the Greek *xenos*, meaning "stranger," "foreigner," or "other." Xenohormesis refers to the bestowal of stress resistance from stressed plants to the animals who eat them.[7001] In other words, instead of exposing ourselves to the stressor to trigger our body's defenses and shore up protection against future stressors, why not let plants take the hit?[7002]

Couch potatoes don't have anything on real potatoes. Plants live the ultimate sedentary lifestyle. Because they can't move, they've had to evolve a whole other way to respond to threats, and they do so biochemically. They manufacture—from scratch—a dizzying array of compounds to deal with whatever's coming their way.[7003] For example, if we get too hot, we can move into the shade, but if plants get too hot, they're stuck. They *are* the shade!

Plants have had nearly a billion years to create a whole chemistry set of protective substances, some of which can play a similar role in us. After all, where do most vitamins come from? Plants make them for their own needs,

and we hijack them for broadly analogous cellular roles in our own body.[7004] There is also a shared set of "vitagenes" conserved through evolution to encode an array of repair and maintenance processes, such as heat-shock proteins that confer fitness and survival benefits.[7005] Nature programs marvel how closely we're related to chimps, but we share about a fifth of our genes with a banana[7006] even though it's been more than a billion years since we had a shared ancestor—before the human and the banana split.[7007] Nature didn't reinvent the wheel for critical cellular processes, such as basic metabolism and preserving DNA integrity. Plants and animals even share some of the same stresses.

We get attacked by bacteria, and so do plants and fungi.[7008] When bacteria muscle in on a particular fungus, it creates a molecule called penicillin—provided free for us—and when a fungus muscles in on a particular bacterium, it produces rapamycin as an antifungal to slow its growth, inhibiting the target of rapamycin (TOR) pathway conserved in fungi, plants, and animals, including us.[7009] Remember, that's the same "engine of aging" enzyme pathway that can be tweaked to extend lifespans. (See here.)

When plants get infected, they produce the compound in aspirin, which can come in handy when we get infected ourselves. Plants heal wounds, and so do we, using similar signaling systems.[7010] Plants have DNA they need to protect from free radical damage, so they cook up complex antioxidants that we can use for ourselves instead of reinventing the wheel. In a sense, the crispers in our fridges are like nature's medicine cabinet.

We can just let the plants get stressed because, incredibly, the stress response molecules in plants may activate the same protective responses in us.[7011] The majority of known health benefits of edible plants may be attributable to the pharmacologically active substances of plants' sophisticated stress responses, off which we can then piggyback. For example, I've often mentioned polyphenols, a class of phytonutrients for which there's a huge medical literature on health-promoting effects.[7012] Plants produce polyphenols to protect themselves,[7013] and we may be able to expropriate and commandeer them for our own similar purpose.[7014]

Xenohormesis explains how environmentally stressed plants produce bioactive compounds that can confer survival benefits to those of us who consume them. Drought-stressed strawberries, for example, have more

antioxidants and other phytonutrients. Have you ever eaten a wild strawberry? The taste is incomparable to the flat flavor facade of the cultivated kind. The healthiest grapes often grow in relatively dry, sun-exposed, infertile soil.[7015] Studies show that commonly consumed fruits and vegetables can be nutritionally enhanced by light, water, nutrient deficits, cold stress, or being nibbled on by bugs.[7016] That may help explain why the levels of phytonutrients are estimated to be 10 to 50 percent higher in organic vegetables compared with conventionally grown ones.[7017] Organic grape juice, for instance, contains more polyphenols and resveratrol than conventional grape juice.[7018] Similarly, soups prepared from organically grown vegetables contain levels of salicylic acid that are nearly six times higher than soups prepared from nonorganic ingredients.[7019]

If you starve plants, they do the same thing mammals do: activate preservation pathways. So, let the plants face the adversity to create the molecules that trigger cell stress resistance, alter metabolism, and improve disease resistance. Then, we can just capture them for the same uses in our own body. The fact that many phytonutrients act as "dietary restriction mimetics," in that they mimic the physiological effects of dietary restriction, may be no coincidence. The plants produce these compounds to save their own green butts from scarcity. So, instead of having to starve, thanks to xenohormesis, we may be able to let plants bear the brunt and enable us to harness their hardships as a means to promote our own health.

PLANT POKES

The flip side of xenohormesis is that plant compounds themselves can act as a source of hormetic stress that ends up bolstering us. If you remember from the Oxidation chapter, green tea's rallying of antioxidant and DNA repair defenses appears to be a consequence of its mild *pro*-oxidant qualities.[7020] It ends up doing a lot of good by being a little bad. The constant small jabs with every sip rev up our defenses to better protect us when a more serious insult comes along. It's like minor irritations that build up callouses on our hands to fortify our resilience. The end result? Interventional studies on rodents show that green tea extends their lifespan,[7021] and observational studies on human populations show that tea drinkers may average lives that are years longer.[7022,7023]

Remember the broccoli story from the same chapter?[7024] How the cruciferous compound sulforaphane is the most potent natural inducer of Nrf2, a "guardian of healthspan and gatekeeper of species longevity"? Our body wouldn't ramp up the detoxification enzymes in our liver every time we ate broccoli if it didn't consider broccoli to be a threat at some level. It's like how applying the hot pepper compound capsaicin on our skin can trigger heat receptors and fool our body into sweating and flushing its way to actually bring down our internal body temperature.[7025] Our body seems to picture each floret of broccoli as a miniature medieval mace and responds by battening down the hatches. We may then reap the rewards of this veggie vigilance and enjoy a longer life as a result.

It's no surprise that our body is finely tuned to react defensively to so many compounds in plants. After all, plants don't want to be eaten. Sulforaphane is thought to be created in plants to dissuade nibblers with its bitterness. Allicin, the garlicky compound in garlic, is presumably made for the same purpose. At petri dish concentrations exceeding that which could be achieved by even garlic-lover levels of consumption, certain garlic compounds can be toxic to mammalian cells (obtained from human foreskin,[7026] so no applying raw crushed garlic to your skin),[7027] but at culinary levels our body evolved to handle, subtoxic dosing in pasta sauce can induce the adaptive stress responses thought responsible for garlic's health benefits.[7028] Whether some of our healthiest plants are actually mildly toxic[7029] or our body merely treats them as such, the end result is the same: health through hormesis.

POWER PLANTS

There are thousands of phytonutrients that will never make it onto the side of a cereal box, yet may play a role in reducing the risk of chronic diseases—and those are just the ones we know about.[7030] The terms *phytonutrient* and *phytochemical* refer to natural compounds found in plants that can affect our health. (*Phyto-* comes from the Greek *phyton*, meaning "plant.") They are not considered "essential" nutrients like vitamins, as we can technically survive without them. Instead, they have been called "lifespan essential," meaning they're necessary for the longest possible life.[7031] In this way, they are like dietary fiber—critical for optimal health and longevity,

but not technically essential, as coma patients can survive for years on an intravenous mixture of sugar water, electrolytes, amino acids, vitamins, and a few essential fats and trace minerals.

How many people are dying these days of vitamin deficiencies, like scurvy, compared to the number dying from phytonutrient deficiencies? An estimated 7.8 million premature deaths are attributed annually to the inadequate consumption of fruits and vegetables, not getting at least eight servings a day.[7032] Millions of lives hang in the balance, the balance being the scales that hang in the produce aisle.

In the United States alone, if you add up all the fatal cancers, strokes, heart attacks, and other deaths that could have been averted by simply eating more fruits and vegetables, it comes out to about 450,000 deaths every year.[7033] There is a phytonutrient deficiency pandemic that could be wiped out with a few more daily servings of plants. Yet, the pandemic is getting worse, not better. Over the last few decades, dietary quality has continued to deteriorate. Consumption of both fruits and vegetables (excluding potatoes) has dropped by more than half,[7034] and intake of legumes, also an important source of phytonutrients,[7035] has dropped by about 40 percent. At the same time, saturated fat consumption is on the rise. Only about 1 in 250 people even meet 80 percent of the American Heart Association's recommendations for a healthy diet.[7036]

Perhaps people just don't understand the power of plants. Consider the first phytochemical, isolated in 1804 from the poppy plant: morphine.[7037] In the fourth century, the first handbook of emergency medicine was published in China and recommended wormwood for malaria.[7038] Seventeen hundred years later, this discovery was immortalized in a Nobel Prize in medicine for the phytochemical *artemisinin*, now included in the most effective combination therapies against the scourge of malaria.[7039] In my video see.nf/herbs2drugs, I dive into other powerful examples.

POLYAMORY

Polyphenols are among the front-runners in developing dietary approaches to fight age-associated diseases. More than 8,000 different polyphenols have been identified, but only a small proportion have had their health effects cataloged.[7040] Still, there is such a critical mass of data in favor of the

protective benefits[7041] of these "lifespan essentials" that recommended daily intakes of polyphenols have been proposed.[7042] I review what they can do and why in see.nf/polyphenols, where I also note the one source of flavonoids associated with an *increased* mortality: grapefruit, chalked up in part to grapefruit's suppression of a set of detoxification enzymes in our intestines.[7043]

NATURAL GEROPROTECTORS

Geroprotectors are substances that increase longevity and/or have other anti-aging properties.[7044] More than two hundred have been found. (See geroprotectors.org.) Some of the most powerful ones that even beat out synthetic compounds are natural plant extracts of simple herbs and spices, like celery seed.[7045] There are phytonutrients that can increase the maximum lifespan of animals by as much as 78 percent.[7046]

Plant extracts that have been shown to increase the lifespan of lower organisms include açaí, apples[7047] (including boring Red Delicious),[7048] asparagus, blueberries, cinnamon, cocoa, corn,[7049] fenugreek seeds, grape skins, holy basil leaf,[7050] peach, pomegranate, rose, and turmeric.[7051] Fewer improve the lifespan of mammals like mice, and those that do—like lemon—are tested on inbred strains chosen for their rapid aging.[7052]

Many of the "superfoods" that can extend the lives of enfeebled mice have no significant effect on robust, long-living ones, and those that do may be a result of inadvertent dietary restriction.[7053] For example, mice fed a turmeric compound lived longer than control group mice, but they weighed about 3 percent less, suggesting they were eating less.[7054] (Maybe they weren't curry fans.) The dietary restriction alone could potentially account for the longevity. When researchers subsequently fed mice iso-calorically instead of ad libitum, effectively forcing those groups of mice to eat the same amount, the turmeric benefit appeared to vanish.[7055]

Speaking of dietary restriction–induced life extension, might the hormetic or xenohormetic benefits of phytonutrients undermine the longevity dividends of the stress of caloric restriction? A mixture of synthetic antioxidants completely blunted the life extension from a 20 percent diet restriction in mice,[7056] but if you give polyphenols from blueberries, pomegranates, and green tea to intermittently fasted mice, they

live even longer than had they just fasted intermittently.[7057] The longevity benefit was potentiated by phytonutrients. The researchers suggest that although alternate-day fasting in mice may have a net beneficial effect on lifespan, it also may entail harmful stresses that can be successfully countered by polyphenol intake.

PLANTS, NOT PILLS

If phytonutrients can be so healthful, why not just take plant extract supplements rather than go to all the trouble of eating the plants themselves? Besides the misidentification, contamination, and adulteration issues rife within the poorly regulated supplement market[7058] we've discussed, there is a question of dose. Taking polyphenol supplements can result in blood levels nearly an order of magnitude higher than that of a polyphenol-rich diet.[7059] When it comes to hormesis, less may be more.

For a series of examples of how isolated phytochemicals and plant extracts can be life-extending at one dose but life-shortening at a higher one, check out see.nf/dosing. After all, many flavonoids function as "nature's pesticides," protecting plants from predators like us.[7060] We coevolved to counter these defenses, and thanks to hormesis, a smidgen of toxin can actually be beneficial, but a profusion of toxin can be toxic. To paraphrase a quote from a review on the anti-aging effects of polyphenols: It's easier to overdose on supplements than on salad.[7061]

SYNERGY WITHIN PLANTS

Some phytonutrients are so potent that functional doses can be encapsulated in a capsule, allowing for placebo-controlled trials of whole foods. For example, the sesame seed phytonutrient sesamin extends the lives of *C. elegans*[7062] and fruit flies.[7063] To see if it might have clinical effects, researchers pitted 2.5 g a day of ground black sesame seeds stuffed into capsules against placebo. Within one month, less than a teaspoon of sesame seeds a day drove down systolic blood pressures by eight points in middle-aged men and women. If sustained, that alone would decrease the risk of stroke by more than 25 percent.[7064]

The downside of whole-food studies is you're never quite certain which component—or components—may be responsible. Was it the sesamin or

other sesame phytonutrients, such as sesamol, sesamolin,[7065] or anthrasesamones A, B, C, D, E, or F?[7066] In a certain sense, who knows, but who cares, as long as it works. It's hard to patent produce, which is perishable and relatively unprofitable, so Big Pharma and supplement companies (which are often one and the same) use a reductionist approach to try to uncover the "magic bullet" active ingredient(s) of foods. But this ignores the concept of synergy. Sometimes, the whole food is greater than the sum of its parts.

For example, check out what happens when you pit various fractions of pomegranate polyphenols against prostate cancer cells in vitro. One subfraction reduced cancer cell growth by 30 percent compared to control, and another subfraction didn't help at all; the cancer grew as if it wasn't even there. So, mixing both together, you might expect the effect to land somewhere between the two, maybe 15 percent inhibition with the ineffectual fraction washing out the better one? But, no. Put them together, and you get *70 percent* lower cancer growth.[7067] Thirty percent + 0 percent = 70 percent. That's synergy, where 1 + 1 is greater than 2. A pomegranate extract supplement that includes only one of the fractions would miss out on most or all of the benefit.

When cranberry fractions were pitted against colon cancer cells, the discrepancy was even more extreme.[7068] Separately, two polyphenol fractions only suppressed cancer cell growth by 15 percent at most, but, when they were combined into the total polyphenol complement of cranberries, colon cancer growth was suppressed by as much as 90 percent. Similar synergistic effects against human cancer cells in vitro have been found in components of ginger root,[7069] grape skins,[7070] rosemary leaf,[7071] and tomatoes.

In see.nf/tomatosynergy, I give a remarkable account of synergy in action. Basically, supplements of the red tomato pigment lycopene have repeatedly failed to successfully prevent[7072] or treat[7073] prostate cancer, but tomato sauce seemed to help.[7074] This makes sense, given studies showing how tomato components that are noneffective[7075] or worse[7076] *individually* can suddenly show anticancer effects when combined. For phytonutrients, plants are better than pills. To quote a past president of the American College of Lifestyle Medicine, "The active ingredient in broccoli is broccoli."[7077]

Each plant not only has thousands of different phytonutrients, but very different phytonutrient profiles.[7078] So, there may be synergistic effects when eating different foods together, too.[7079] The reason it's better to get vitamin C in citrus form than pill form is that you won't miss out on all those citrus phytonutrients, like lemonin, limonol, or tangeretin, that may interact, work together, and complement one another. But you'd also miss out on them if you instead ate an apple. Comparing apples and oranges is like, well, comparing apples and oranges.

At least all fruits are fruits, whereas vegetables can be any other part of the plant. Roots harbor different phytonutrients than shoots. Carrots are roots, celery is a stem, dark green leafies are leaves, peas are pods, and cauli*flower* is true to its name, a collection of flower buds. Combining foods across different categories appears to increase the likelihood of synergy.[7080] The combined antioxidant power of raspberries and adzuki beans together, for example, is greater than just the sum of one plus the other. Neither soy phytonutrients nor green or black tea components alone decreased the tumor load or metastasis of human prostate cancer implants in mice, but soy and tea together did.[7081] Hot pepper extracts alone appeared to have little effect on the growth of cervical or breast cancer cells, but mixed with green tea, the cancer killer power rose tenfold in the case of cervical cancer and a hundredfold for breast cancer over green tea alone.[7082]

These are interesting proof-of-principle studies, but they have limited human relevance if the cancer-stopping concentrations used in the petri dishes couldn't be achieved in the bloodstream through normal dietary consumption. To resolve this issue, researchers exposed breast cancer cells from different patients to six different plant compounds individually, then all together at the level you might find in your bloodstream after eating foods like broccoli, grapes, soybeans, and turmeric. While individual plant compounds had little or no effect on their own, in combination, dietary blood levels significantly suppressed breast cancer cell proliferation by more than 80 percent, inhibited cancer cell migration and invasion, stopped the cancer cells in their tracks, and eventually killed them all off. All the while, this "phytochemical super-cocktail" had no deleterious effects on the normal, noncancerous cells used as control.[7083]

A 10 percent tomato diet reduced the prostate cancer tumor burden of rats by 33 percent, and a 10 percent broccoli diet reduced the amount of tumors by 42 percent.[7084] Put them together, though, and a diet enhanced with both tomato and broccoli cut tumor levels by more than half. A spouse wrote to the editor of the *Harvard Men's Health Watch*, saying their husband, having heard about lycopene, wants to have pizza for his prostate but they don't think it's a healthy food. The doctor replied with the suggestion of a "cheese-free pizza (with broccoli instead of pepperoni, please)."[7085]

GARDEN VARIETY

Though there are generic plant compounds like vitamin C that are found scattered throughout the plant kingdom, there are also specific phytonutrients produced by specific plants to perform specific functions—both in their organs and in ours.[7086] We miss out on these if we're stuck in a fruit and vegetable rut, even if we're eating many servings a day.

Airline pilots experience high rates of DNA damage due to being bombarded with radiation from the galaxy without the protection of the full atmosphere. A study found that pilots eating a greater mixture of phytonutrients had less chromosomal damage, but the researchers didn't control for total fruit and vegetable intake.[7087] Maybe the greater variety was just a proxy for greater quantity. Those randomized to eat fourteen servings of fruits and vegetables a day for even just two weeks show a reduction in oxidative DNA damage compared to those randomized to eat only four servings a day,[7088] but what about a study in which the number of servings is held constant and you just increase the diversity of the produce? That's exactly what a group of researchers in Colorado did.

Both diets had the same number of daily servings (eight to ten), but the high botanical diversity diet included fruits and vegetables from eighteen different families versus emphasizing just five in the low diversity diet. Only those randomized to the high diversity diet experienced a significant reduction in DNA damage.[7089] The researchers concluded that "smaller amounts of many phytochemicals may have greater potential to exert beneficial effects than larger amounts of fewer phytochemicals." Observational studies have also found that fruit and vegetable variety is

associated with lower inflammation[7090] and better cognition[7091]—again, independent of quantity. Does this mixing and matching of a variety of plant foods actually translate into a concrete difference for patients?

Check out see.nf/foodcombining for a wild experiment involving secretly giving cancer patients a combination of a fruit, a vegetable, a spice, and a leaf—about one one-hundredth of a pomegranate, less than one floret of broccoli, less than an eighth of a teaspoon of turmeric, and about a sixth of a tea bag's worth of green tea a day, hidden in capsules and randomized against placebo. Surely such tiny amounts couldn't affect the progression of cancer, right? Wrong.[7092] As I show in the video, the cancer was significantly slowed down.

Based on an update of the most extensive report on diet and cancer ever published, the foundation of cancer prevention is a diet centered around plants—whole grains, vegetables, fruits, and beans—while cutting down on alcohol, soda, meat, and processed junk.[7093] As I documented in *How Not to Die*, a completely plant-based diet may even shrink the tumor, not just slow down its growth, but there's no reason we can't do both with a plant-based diet chock full of particularly powerful plants.[7094]

microRNAS

If you thought the interspecies communication between the plant and animal kingdoms with xenohormesis was interesting, hold on to your hat. The "Central Dogma" of molecular biology has been challenged by a revolutionary twenty-first-century discovery: microRNAs.[7095]

Allow me to transport you back to high school biology. If you remember, our genetic code is stored in our DNA. Those are the instructions for creating and maintaining our body. There's no point in just having a set of blueprints if they can't be communicated to the builders to become manifest in the real world. RNA is that messenger. Messenger RNA transcribes a stretch of DNA code (called a gene) and has it translated into the finished product, a structural protein or an enzyme. The Central Dogma describes this flow of information as one gene to one messenger RNA to one protein. Then along came a shocking discovery from the Human Genome Project.

Only about 2 percent of our DNA actually codes for proteins. So, what does the other 98 percent do? When I was in medical school, the more than one billion letters of seemingly purposeless DNA[7096] were dismissed as "noise," "garbage sequences,"[7097] or "junk DNA," perhaps just accumulated genetic schmutz from throughout our evolutionary past.[7098] That would seem a little wasteful, though. A parallel from astrophysics was drawn to this mystery: dark matter,[7099] the apparent fact that we can't account for about 85 percent of the matter in the universe.[7100] The mystery of the dark matter of our genome was solved in 2001:[7101] Most of our DNA violates the Central Dogma by being actively transcribed into *noncoding* RNA—that is, RNA that doesn't code for proteins.[7102] Then what does it do?

We now know that there are more than a hundred types of noncoding RNAs, but let's focus on the OG: microRNA.[7103] It takes a stretch of DNA thousands of letters long to encode the average messenger RNA.[7104] In contrast, microRNAs are only about twenty letters long. For example, the first microRNA ever discovered was twenty-two letters long in the four-letter RNA alphabet: UUCCCUGAGACCUCAAGUGUGA.[7105] What exactly do microRNAs do? They are generally created to glom on to messenger RNAs to prevent them from being translated into proteins.[7106]

If DNA is the blueprint and messenger RNAs are the construction workers translating those instructions into building parts of a house, microRNAs are like regulatory bureaucrats who intercede and keep particular workers from carrying out their duty. This is a good thing. Without building inspectors, minimum safety standards could be flouted. And different elements need to be timed properly. It makes sense to hold off the roofers until well after the foundation is poured.

Understanding microRNA regulation is particularly insightful[7107] because a single microRNA can block more than a thousand different messenger RNAs.[7108] So, one microRNA can effectively silence more than a thousand different genes. In my building analogy, one simple instruction can put all the second-floor workers on hold until the first-floor workers finish construction. Then, there are regulators who regulate the regulators, other noncoding RNAs that stop the microRNAs from stopping the messenger RNAs,[7109] but let's not even go there.

Just when the complexity seemed overwhelming, researchers realized that even though there are a trillion possible microRNA twenty-letters-long

combinations made from the four-letter RNA alphabet, only a few thousand microRNAs seem to be active in the human body.[7110] And, in any given cell, the five most abundant microRNAs average half the overall microRNA pool in the cell.[7111] However, in 2007 things got a lot more interesting.

MicroRNAs have been found circulating in at least twelve different human bodily fluids.[7112] (When I read that, I had to stop and think, *Wait. Can I even name a dozen bodily fluids?*) We didn't think this possible since we have enzymes that chop up any floating RNA outside our cells (as a precaution against viruses, which often come bearing RNA). It turns out they're being transported in *exosomes*, tiny bubble-like vessels that pinch off from cells. We used to think these budding blebs were just a waste disposal device for the cells.[7113] (Why do scientists seem to just jump to junk when they don't understand something?) But, in 2007, we discovered that they were packed with microRNA.[7114] Our cells were communicating with each other! In this way, a liver cell could send out microRNAs to regulate the genes in a lung cell, which could then regulate a brain cell, or vice versa. They could even talk to the next generation by depositing their microRNA load into a sperm or egg cell.[7115]

What's the upshot of all this? It is now safe to say that microRNAs probably regulate virtually every biological process, playing essential roles in virtually every aspect of health.[7116] Mice genetically engineered to be unable to make microRNAs never even make it past the embryo stage.[7117] Diseases of all shapes and sizes have been linked to the dysregulation of microRNAs.[7118] But the good news is that there is something we can do about it. MicroRNA expression can be modified through diet.[7119]

microRNAS AND AGING

What does this have to do with aging? As a major regulator of all cellular pathways,[7120] it would make sense for microRNAs to play a role, but the connection has special salience. The very first microRNA was discovered in the humble roundworm *C. elegans*.[7121] Guess what it did? Regulated its lifespan. Reducing the activity of the simple microRNA reduces lifespan and accelerates tissue aging, whereas overexpressing it significantly extends life. It turns out that the target of the microRNA was a DAF-16 suppressor gene.[7122] DAF-16 is the worm equivalent of the FOXO gene, which can

confer immortality to certain primitive animals[7123] and is one of the most important genetic determinants of extreme longevity in humans.[7124] By blocking the repression of this longevity gene, the microRNA had a lifespan-extending effect. Knowing the expression patterns of just a few microRNAs in *C. elegans* can effectively predict the longevity of individual animals.[7125]

To study the effects of microRNAs on mammalian lifespan, a series of lifestyle interventions were set up in mice. One group of mice was put on a high-fat diet, and they lived for 101 weeks. A second group was put on a high-fat diet with added voluntary exercise, and they lived for 114 weeks. The next group was put on a low-fat diet, which brought them up to 127 weeks. A fourth group was put on a low-fat diet plus exercise and lived for 131 weeks. Group five was put on caloric restriction on a high-fat diet and lived for 137 weeks. And, finally, mice were put on caloric restriction on a low-fat diet and lived for 153 weeks, a lifespan more than 50 percent longer than those in the regular high-fat group. Using this approach, the researchers found that ninety-two microRNAs were correlated with lifespan, including eighty-four in an inverse manner. In other words, the microRNAs generally appeared to be suppressing longevity genes, so certain microRNA levels were up to 90 percent lower in the longest-living group.[7126] However, there are exceptions.

For example, miR-17 (short for microRNA-17) directly extends the lifespans of mice. Transgenic mice created to overexpress miR-17 live longer and healthier lives, proving that microRNA isn't just correlated with a longer life but directly causes it (in part by repressing mTOR, which I explored starting here).[7127] Such "longevi-miRNAs" may account for the parabiosis findings.[7128] Remember the mad scientist experiments (see here) of rejuvenating old animals by sewing them to younger cagemates and hooking together their circulations? That effectively proved that there are blood-borne determinants of aging. Perhaps microRNAs fit the bill.

In humans, dozens of circulating microRNAs are upregulated as we age, and dozens are downregulated.[7129] The blood levels of seven microRNAs may be able to differentiate Alzheimer's patients from healthy controls with up to 95 percent accuracy.[7130] If these dynamics are all just genetic, then microRNA levels could still be useful as biomarkers or diagnostics, but they might be harder to tweak to control our fate. But, no, a study on identical

twins who died about a decade apart found they had highly discordant microRNA levels, suggesting that nongenetic factors, such as diet and lifestyle, are pivotal in microRNAs related to life expectancy.[7131]

EXERCISE POWER OVER microRNAS?

More than 6,000 patents have been filed on the potential use of synthetic microRNA mimics and inhibitors to fight aging and disease,[7132] but, to date, no such drugs have been approved.[7133] Is there anything we can do naturally?

MicroRNAs may be one of the reasons randomized controlled trials have shown that exercise can prevent cognitive decline in older adults[7134] and improve cognition for those already suffering from Alzheimer's disease.[7135] There are microRNAs that are reduced in Alzheimer's (like miR-132[7136] and miR-338[7137]) but boosted by exercise,[7138,7139] and, conversely, there are microRNAs that are overexpressed in Alzheimer's (like miR-7[7140] and miR-766[7141]) but reduced by exercise.[7142,7143] The picture isn't completely clear, though. MiR-146a has consistently been found to be elevated in the blood,[7144] brain,[7145] and cerebrospinal fluid[7146] of Alzheimer's disease patients. And, although acute resistance training[7147] and chronic basketball training[7148] were found to reduce circulating levels of the microRNA, rowing training[7149] and marathon running[7150] were found to increase them. So, we still have much to tease out about the possible role that microRNAs play in the way physical activity can improve mental activity.[7151]

MODULATING microRNAS WITH MEALS

MicroRNAs may also be a mediator of the benefits of polyphenols.[7152] A dozen different phytonutrients have been shown to change the expression of dozens of microRNAs in vitro.[7153] As we know, one problem with petri dish studies is that sometimes concentrations are used that far exceed that which can be achieved through regular dietary consumption, but a few foods have been put to the test. For example, a study showing that extra-virgin olive oil with a high polyphenol content has a different microRNA impact than lower-polyphenol olive oil suggests that the polyphenols may be playing an active role.[7154] Nuts—either one to two handfuls of walnuts a day for a

year[7155] or a single handful of a combination of almonds and walnuts for eight weeks—also change the levels of an array of microRNAs in the bloodstream.[7156] But to what end?

There are well-known inflammiRs, inflammatory microRNAs like miR-155, that are suppressed by a variety of flavonoids—genistein in soy, quercetin in apples and onions, allyl isothiocyanate in onion family vegetables, curcumin in turmeric, and apigenin in parsley, celery, and chamomile tea.[7157] MiR-155 also plays a role in cancer. For example, miR-155 is implicated in the development of acute myeloid lymphoma, the deadliest form of leukemia and the most common acute leukemia among adults. In a study titled "Alleviating the Progression of Acute Myeloid Leukemia (AML) by Sulforaphane Through Controlling miR-155 Levels," not only could miR-155 levels be dropped by about 80 percent by the cruciferous vegetable compound in vitro, but this led to a significant drop in cancer cell viability.[7158] Unfortunately, broccoli sprouts, the most concentrated source of sulforaphane, have yet to be tested on AML patients to assess clinical outcomes.

Flavonoids have been found to suppress the proliferation of tumor cells by both suppressing oncogenic (cancer-causing) microRNAs and boosting tumor suppressor microRNAs.[7159] Long-term soy consumption in breast cancer patients had this effect,[7160] perhaps helping to explain why soy consumption appears to help prevent the development of breast cancer in pre- and postmenopausal women,[7161] as well as improve survival in breast cancer patients and reduce the chances of the cancer coming back.[7162] This may also help explain the upregulation of tumor suppression microRNAs in vegetarians and vegans compared to omnivores,[7163] and the subsequent lower cancer risk,[7164] though meat consumption can affect microRNAs, too.

Rectal biopsies taken before and after a month of eating three daily servings of beef or lamb found significant upregulation of oncogenic microRNA clusters in rectal tissue. Adding resistant starch to the diet was able to reduce, but not completely eliminate, this effect.[7165] Similarly, the cooked meat carcinogen PhIP, found particularly in grilled, broiled, fried, and barbecued chicken, causes estrogen-like effects on microRNAs implicated in the initiation and progression of breast cancer.[7166] MicroRNA modulation has also been used to explain why saturated fat increases insulin resistance, though, so far, this has only been demonstrated in rat muscle.[7167]

Beyond potentially contributing to the lower cancer[7168] and diabetes[7169] rates among those eating plant-based, diet-induced microRNA changes may also contribute directly to life extension. A study on circulating microRNA expression in the Loma Linda blue zone, where healthy Adventist vegetarians live about a decade longer than their fellow Californians, found half a dozen microRNAs related to aging differentially expressed between vegetarians and nonvegetarians that potentially provide mechanisms for the longer plant-based life expectancy. Interestingly, for one of the anti-aging measures, semi-vegetarians and vegans both beat out ovo-lacto vegetarians, those who eschew meat but eat eggs and dairy. Semi-vegetarians were defined as eating meat at least once a month, but no more than once a week. The researchers suggest that they might have ended up eating fewer animal products overall than the vegetarians who more regularly ate eggs and dairy.[7170]

XENO-microRNAS

Intercellular microRNA communication is conserved throughout the evolutionary tree of life, raising the possibility of cross-kingdom gene regulation. In the eighteenth century, life was classified as belonging to either the plant kingdom or the animal kingdom.[7171] In the nineteenth century, single-celled organisms like amoebas got their own kingdom,[7172] and with further improvements in microscopy, bacteria got one as well. (These days we're up to seven kingdoms—algae and fungi each got their own, as did bacteria-like organisms originally described as extremophiles, living in previously thought uninhabitable zones like hot springs.[7173])

With a common language of microRNAs, might inhabitants of different kingdoms communicate with one another? In 2011, we learned that microbiome microRNAs could modulate the gene expression of their host.[7174] For example, there are gum disease bacteria that secrete vesicles filled with microRNA shown to penetrate host cells, apparently to suppress our immune response.[7175] Sneaky! Then, in 2016, we learned that we have our own microRNA counterinsurgency program. Fecal microRNAs produced by our intestinal lining cells infiltrate our gut bacteria, regulate their gene expression and growth, and may be essential for the maintenance of a healthy microbiome.[7176] If there is microRNA manipulation happening

between the simplest and most complex organisms on Earth, what about cross-talk with an intermediate—the plant kingdom?

The nerd's cartoonist, Randall Munroe at xkcd.com, used a comic captioned "Really, *every* gathering is a family reunion" to remind us that ultimately, we're all related. If you go far enough back, each of us can trace back to a common ancestor, all the way back to the very first *Homo sapiens* to whom we're all related. So, the cartoon shows a party scene with stick figures labeled "me," "2nd cousin," "14th cousin," and "35th cousin," and also a pet cat, labeled "17,000,000th cousin." Yes, if you go back far enough, you and Fluffy actually had a real flesh-and-blood common ancestor. The cartoon also has a houseplant labeled "50,000,000,000th cousin."[7177] Using molecular clock–dating techniques on shared DNA deviation, it's estimated that plants and animals diverged 1.576 billion years ago, give or take 88 million years.[7178] So, even you, Fluffy, and the ficus shared an ancestor. Family reunion indeed.

Recognition of the ubiquitous presence and activity of microRNAs in plants followed soon after their discovery in animals.[7179] Cotton plants, for example, use microRNAs to silence the virulence genes of a pathogenic fungus.[7180] What influence might plant microRNAs be having in another cross-kingdom interaction—with us? Just like we share many microRNAs with other animals, some microRNA sequences in plants have such close overlap with animal microRNAs that scientists suspect they're actually the same microRNA, conserved through 1.5 billion years of evolution.[7181] Regardless, matching up the sequences of plant microRNA to human messenger RNA, there appear to be at least a thousand different human genes that plant microRNAs could target.[7182]

Plant-based diets contain thousands of biologically active microRNAs.[7183] While the scientific community has historically chalked up the benefits of fruits, vegetables, and herbal medicines to the presence of phytonutrients, it may be their microRNAs playing a role.[7184] Isolated phytonutrients have often failed to fully replicate the effects of the whole foods from which they were extracted. This failure has been attributed to the synergistic symphony of interactions between the various components working together. As we've seen, one way that phytonutrients like polyphenols affect our physiology is by manipulating our microRNA

expression, but perhaps plant microRNAs are silencing our genes directly.[7185]

The exploration of the potential for cross-kingdom gene regulation with "xeno-microRNAs"[7186] from plants is currently considered among the most exciting topics in all of science.[7187] Broadly, the concept of cross-kingdom genetic manipulation is nothing new. After all, RNA and DNA from viruses have been hijacking human cells since time immemorial. But, if food-derived microRNAs are altering our gene expression, that certainly offers new meaning to the phrase "you are what you eat."[7188]

DIETARY microRNAS

Dietary microRNAs would mean that food may provide information as well as nutrition—information that could effectively switch our genes on or off.[7189] Some researchers have conceptualized dietary microRNAs as "dark nutrients," in another nod to dark matter, claiming that they play a "significant role in human health."[7190] Yes, plant microRNAs have been shown to enter human cells and alter our gene expression,[7191] but let's take a step back. Would microRNAs in our diet even survive cooking or digestion?

Some processed plant products, such as olive oil and beer, seem to have lost their microRNAs in the production process.[7192] What about microRNA loss on the stove? We used to think cooking destroyed genetic material, but more recent experiments show that some plant microRNAs can take the heat.[7193] Some, such as miR-159 in broccoli, remain stable after cooking,[7194] while those like artichoke microRNA-319 are partially destroyed.[7195] And the levels of other microRNAs, like those found in cooked beans and brown rice, rise even higher after cooking, presumably by being liberated into the cooking water.[7196] Mammalian and avian microRNAs in meat, dairy, and eggs survive cooking and processing, based on studies of pork and poultry sausages,[7197] ham,[7198] salami, hard-boiled eggs, cheese, and pasteurized milk. There was little change in microRNA levels between raw beef and beef roasted until well done;[7199] however, they would still have to survive the acid bath of the stomach.

Again, the conventional wisdom was that microRNAs would be destroyed during digestion,[7200] but if you dunk them in acidic gastric fluid,

the majority of plant and microRNAs appear to survive for at least six hours.[7201] In the small intestine, though, there are RNases, enzymes that chew up naked RNA. How might they survive that gauntlet? They may not have to. A study in mice found that the stomach itself appears to be the primary site of dietary microRNA absorption into the bloodstream.[7202] Alternately, microRNAs may travel wrapped in protective exosomes.

From plants, exosome-like vesicles have become known as "edible nanoparticles," and they can be filled with microRNAs.[7203] A pound of fruit can contain 1 g of these little delivery vehicles.[7204] This packaging has been proposed as a solution to the microRNA bioavailability problem.[7205] In that form, they could be absorbed by our intestinal lining, repackaged into exosomes, then released into our circulation.[7206] The proof is in the pudding, though. When we eat microRNAs, do they show up in our bloodstream?

Unlike typical animal microRNAs, the tips of plant microRNAs are tagged with a methyl group.[7207] (See here.) This not only makes them more resistant to digestion but it allows researchers to differentiate them from preexisting microRNAs circulating in animals.[7208] Feed mice some cruciferous vegetables, and cruciferous vegetable microRNAs peak in their bloodstream within six hours and can be picked up in multiple organs.[7209] Corn microRNAs peak in the bloodstream of pigs fed fresh corn between six and twelve hours after consumption.[7210] Most plant microRNAs are carried in exosomes,[7211] which can even transport RNA into the brain.[7212] The cruciferous microRNAs were found circulating for more than thirty-six hours.[7213] What about in people?

Researchers found that as many as 5 percent of all detectable microRNAs circulating in people's bodies may be from plants. The first report of plant microRNAs circulating in humans was published in 2012, the consistent finding of rice microRNAs in bloodstreams of Chinese consumers.[7214] Just as fish-eating seals have circulating fish microRNAs and cows have plant microRNAs from foraged crops and grasses, most of the plant microRNAs in us are from fruit and vegetable species.[7215] Plant microRNAs have been found throughout the human body, including the brain, breasts, kidneys, liver, and lungs, as well as in breast milk, amniotic fluid, and umbilical cord blood.[7216] Are these just incidental findings, or are dietary microRNAs doing anything to us or for us?

Hundreds of different microRNAs have been found in the edible nanoparticles of common fruits and vegetables.[7217] In a proof-of-principle study, edible nanoparticles from grapes were fed to mice. They were taken up into intestinal cells, changed gene expression, and protected the mice from gut inflammation.[7218] Similar experiments with carrot, ginger, and grapefruit nanoparticles found a range of beneficial regulatory effects, but how do we know it was necessarily the microRNAs?[7219]

MicroRNAs are such simple molecules that we can make them from scratch. So, researchers synthetically made strawberry microRNA-156, rice microRNA-168, and cabbage microRNA-874 to isolate out microRNA-specific effects. And, indeed, they were found to have anti-inflammatory effects on human cells. RNA extracts of blueberries, raspberries, and apple peels had a similar effect. To make sure this was not a generic RNA effect, an RNA extract from beef was tested and it failed to dampen inflammation.[7220]

One plant microRNA found circulating in people is microRNA-156a. Decreased levels were found in the blood and blood vessels of patients with cardiovascular disease, suggesting it might have a protective effect. But where is microRNA-156a concentrated? In green vegetables. Give people a salad, and you can see a bump in 156a within an hour. Might lower levels of 156a in heart disease patients just be a proxy for low levels of greens intake? To find out if it was actually cause and effect, researchers exposed human artery endothelial cells to pure (synthesized) microRNA-156a and showed that it targets a sticky protein called *junctional adhesion molecule-A* that abets in the attraction of inflammatory immune cells into the artery wall to trigger atherosclerotic plaques. And indeed, boosting microRNA-156a reduced the attachment of inflammatory cells to artery lining cells.[7221] So, the protective effect of green vegetables on cardiovascular disease[7222] may be more than just a nitrate effect.

A similar story was found with breast cancer and microRNA-159a, which is found in abundance in broccoli.[7223] Lower blood levels correlated with higher breast cancer incidence and tumor progression. MicroRNA-159a wasn’t just a broccoli biomarker, though, but an active player, targeting a cancer-promoting gene called transcription factor 7. When mice

implanted with human breast tumors were fed straight microRNA-159a, they experienced a dramatic decrease in tumor weight and growth. So, the protective effects of cruciferous vegetables on breast cancer[7224] may be more than just a sulforaphane effect.

HERBAL microRNAS

Might some of the effects of herbal medicines also be ascribed to plant microRNAs? In see.nf/herbalmirnas, I review the evidence on microRNAs in ginseng,[7225] licorice,[7226] red sage (*danshen*),[7227,7228] and another traditional Chinese herb, honeysuckle, which appeared to have remarkable efficacy in hospitalized COVID patients.[7229] Unfortunately, as I explain in the video, like so many impromptu pandemic trials, the study left a lot to be desired. The bottom line is that microRNAs may shed some light on how plants can be so powerful (including why some poisonous plants are so poisonous![7230]).

APPLE OF DISCORD

The concept that dietary miRNAs could be therapeutic has been called "compelling, fresh, and revolutionary."[7231] However, the first reports were met with suitable skepticism,[7232] which have since evolved into a fierce controversy.[7233] Many subsequent attempts at replication failed to unambiguously confirm the initial findings,[7234] leaving the medical literature littered with editorials with titles like "Diet-Derived MicroRNAs: Unicorn or Silver Bullet?"[7235] and "Dietary Non-Coding RNAs from Plants: Fairy Tale or Treasure?"[7236] I run through the tug-of-war controversy in see.nf/discord. Though it continues to be an exciting area, the biological role of dietary plant microRNAs remains far from being firmly established.[7237]

EATING ANIMAL microRNAS

What about eating or drinking animal microRNAs present in meat, milk, and eggs?[7238] Animal-derived microRNAs can sometimes be absorbed in much more significant amounts than plant microRNAs.[7239] The problem is it's much more difficult experimentally to distinguish between dietary

animal microRNAs and the ones our own animal body makes, since they can be nearly or completely identical.[7240]

One way researchers have tried to solve this conundrum is to genetically engineer "knockout" mice, in which the gene for a particular microRNA is "knocked out," inactivated or deleted. For example, researchers made microRNA-451 knockout mice drink the blood of wild mice, chickens, and pigs. When they then found microRNA-451 circulating in their bloodstreams and carrying out its regulatory function, they knew that ingested animal microRNAs could indeed affect physiology.[7241]

Vampiric mice aside, how could confirmatory experiments be carried out in people? This is an important question since there are a number of pro-inflammaging and cancer-promoting microRNAs in animal products that are a 100 percent match with the same microRNAs in humans.[7242] Even if you couldn't differentiate meat microRNA from me microRNA, you could at least test to see if you get a rise in blood levels after consumption. Tracking three shared cow microRNAs in people after eating beef failed to show a bloodstream bump,[7243] though, if you remember, that rectal biopsy study did at least show microRNA changes down in the colon after red meat consumption.[7244] Chicken microRNAs from egg consumption, however, can be detected in the human bloodstream after intake.

In the USDA-funded study published as "MicroRNAs in Chicken Eggs Are Bioavailable in Healthy Adults and Can Modulate mRNA Expression in Peripheral Blood Mononuclear Cells," volunteers were fed hard-boiled eggs. Within nine hours, blood levels of microRNA-181a and microRNA-181b rose to about 150 percent and 300 percent above baseline, respectively, reflecting their relative abundance in eggs. This was accompanied by a suppression of the validated gene target of miR-181b in their white blood cells. To verify that chicken microRNAs actually make it into the human bloodstream after egg consumption and don't just indirectly bump up endogenous microRNA levels, the researchers were able to track the entry of a chicken-specific microRNA into their circulation.[7245]

DRINKING ANIMAL microRNAS

The greatest evidence for the potential for cross-kingdom gene regulation comes from the dairy literature. Of all body fluids tested, milk contains the

largest load of microRNAs.[7246] Milk is a secretory product of mammary gland epithelial cells, which discharge miRNA-packed exosomes into the milk.[7247] Based on the human breast milk literature, most are immune-modulatory,[7248] especially during the first six months of lactation.[7249] We've long known that breast milk contains antibodies and other protective agents missing from baby formula to provide passive immunity and help with immune system development, but microRNAs may add additional urgency to the entreaty that breast is best.[7250]

Babies aren't just breastfed but breast-programmed.[7251] Milk is no longer perceived just as food for infants but rather as a highly sophisticated communication system orchestrating early development.[7252] For example, we've known for more than a decade that something in milk prevents allergies. Rat milk, but not rat formula, prevents allergies in rat pups.[7253] MicroRNAs may help explain why breastfeeding seems to protect against childhood asthma[7254] and pediatric infections and results in higher intelligence compared to formula feeding.[7255] If milk microRNAs can so manipulate an infant's physiology, what happens if we drink milk after weaning as an adult, or even drink milk from another species?

The milk of pandas and pigs, humans, and cows and water buffalo share a few common highly expressed microRNAs,[7256] but cow's milk also contains large quantities of hundreds more,[7257] as many as 1,500 different microRNAs.[7258] Because most milk microRNAs are encapsulated in exosomes, they are resistant to heat. While most exosomes and their cargo are destroyed by boiling or ultra-high-temperature processing (used to make shelf-stable creamers), commercial pasteurization leaves a significant proportion of milk microRNAs intact.[7259] Most then survive conditions of digestion in adults.[7260]

To prove that milk microRNAs from one species can make it into the circulation of another species who drinks it, milk microRNAs were tagged with a fluorescent label as a tracker. Loaded into cow's milk, the microRNAs ended up distributing and accumulating in the spleens, livers, hearts, and brains of mice. In vitro, human cells take them up and have multiple genes upregulated and downregulated as a result.[7261] Of course, mice suckling from cows is ludicrous. Primates, on the other hand …

Government-funded researchers at the University of Nebraska had men and women drink different quantities of dairy milk—one, two, or four cups. Considerable amounts of milk microRNAs appeared in their blood in a dose-dependent manner, peaking within four hours after consumption and affecting target gene expression. The bovine microRNAs tested were identical to human microRNAs, though. How do we know that drinking milk doesn't somehow boost the endogenous production of our own microRNAs instead of crossing over from the digestion tract into our bloodstream? The levels of a control microRNA not found in milk were unaffected,[7262] but more robust evidence came from subsequent studies using highly sensitive PCR techniques that could detect tiny differences between bovine and human microRNAs. And indeed, blood concentrations of bovine-specific microRNAs end up circulating throughout our body within hours of milk consumption,[7263] providing compelling evidence that dairy milk exosomes from commercial pasteurized milk right off store shelves can end up in the tissues of human consumers.[7264] What consequences may this have?

The most abundant microRNA in milk is microRNA-148a, and it's a key inhibitor of crucial suppressors to the engine-of-aging enzyme mTOR that I talked about in the Aging Pathways section.[7265] After all, what does an infant need more than accelerated aging? This may be even more apparent in dairy cows, whose newborns double their birthweight in forty days, more than four times faster than our infants.[7266] Cows have been selectively bred for lactation performance, which incidentally appears to have exaggerated microRNA-148a expression.[7267]

The species-specific growth stimulation programmed by milk microRNAs was meant to be confined to infancy. The concern is that continuous exposure to growth-promoting exosomes of pasteurized milk may confer substantial risk for the development of chronic diseases—from acne and obesity to diabetes and cancer.[7268] MicroRNA-148a, for instance, directly stimulates prostate cancer growth in vitro,[7269] which may help explain why dripping milk on human prostate cancer cells boosts their growth rate by more than 30 percent.[7270] Maybe that's why a systematic review of observational studies reported that an overwhelming majority of

them—nineteen out of twenty—found a link between milk consumption and increased risk of developing prostate cancer.[7271] MicroRNA-21, one of the earliest identified cancer-promoting "oncomiRs,"[7272] is also a signature microRNA of dairy milk.[7273]

MicroRNAs may also help explain the difference in associated mortality between fresh milk and fermented milk in two large Swedish studies. Significant increases in mortality risk in men and women were associated with the consumption of fresh milk, but not soured milk.[7274] Bacteria fermentation of milk can lead to exosome and microRNA breakdown,[7275] though this did not appear to affect prostate cancer risk, which seemed to be elevated by both milk and yogurt consumption.[7276]

A recent review titled "Cow's Milk May Be Delivering Potentially Harmful Undetected Cargoes to Humans" suggested that dairy recommendations need to be reconsidered in light of the fact that an estimated thirty-five trillion bovine exosomes are floating around in each glass of milk.[7277] Given the role of exosomes in pasteurized milk to boost mTOR activity, some researchers have concluded that "milk exosomes should not reach the human food chain,"[7278] as milk "is not a suitable food for adults."[7279] In other words, milk is for babies.

PREBIOTICS AND POSTBIOTICS

The human colon may represent the most biodense ecosystem in the world.[7280] Though many may believe that our stool is primarily made up of undigested food, about 75 percent is pure bacteria[7281]—trillions and trillions, in fact, about half a trillion bacteria per teaspoon.[7282] As Neil deGrasse Tyson put it, "More bacteria live and work in one linear centimeter of your lower colon than all the humans who have ever lived."[7283]

Do we get anything from these trillions of tenants taking up residence in our colon, or are they just squatting? They pay rent by boosting our immune system, making vitamins for us, improving our digestion, and balancing our hormones. We house and feed them, and they maintain and protect their house, our body. Prebiotics are what feed good bacteria. Probiotics are the good bacteria themselves. And postbiotics are what our bacteria make.

Our gut bacteria are known as a "forgotten organ,"[7284] as metabolically active as our liver and weighing as much as one of our kidneys.[7285] They may control as many as one in ten metabolites in our bloodstream.[7286] Each one of us has about 23,000 genes,[7287] but our gut bacteria, collectively, have about three *million*.[7288] About half the cells in our body are not human.[7289] We are, in effect, a superorganism—a kind of "human-microbe hybrid."[7290]

What we eat plays the dominant role in determining our gut microbiome, based on studying stool samples from around the world, those who eat different habitual diets, and what comes out of fraternal versus identical twins.[7291] Change your diet, change your gut flora, within days or weeks, for good or for ill.

THE GOOD, THE BAD, AND THE BUGLY

Having coevolved with us and our ancestors for millions of years,[7292] the relationship we have with our gut flora is so tightly knit as to affect most of our physiological functions.[7293] Yet our microbiome is probably the most adaptable component of our body. Gut bugs like *Escherichia coli* (*E. coli*) can divide every twenty minutes.[7294] The more than ten trillion bugs we churn out every day can therefore rapidly respond to changing life conditions.[7295] Every meal, we have the opportunity to nudge them in the right direction.

Thousands of years ago, Hippocrates is attributed as saying that all diseases begin in the gut[7296] or, more ominously, "death sits in the bowels."[7297] Of course, he also thought women were hysterical because of their "wandering uterus."[7298] ("Hysteria" comes from the Greek *husterikos* for "of the womb.") So much for ancient medical wisdom. The pendulum then swung to the point of incredulity when the medical community refused to accept the role of one gut bug, *Helicobacter pylori*, as the cause of stomach and intestinal ulcers.[7299] Out of frustration, one of the pioneers chugged a brew of the bugs from one of his ulcer patients to prove the point, before finally being vindicated with the Nobel Prize in 2005 for his discovery.[7300]

In some ways, the pendulum has swung back, with overstated causal claims about the microbiome's role in a wide range of disparate diseases that are casually bandied about.[7301] Perhaps the boldest such claim dates

back more than a century to Élie Metchnikoff, who argued that senility and the disabilities of old age were caused by "putrefactive bacterial autotoxins" leaking from the colon. He was the first to emphasize the importance of the gut microbiome to aging.[7302] He attributed healthy aging to gut bacteria that fermented carbohydrates into beneficial metabolic end products like lactic acid and associated unhealthy aging with putrefaction, the process in which bacteria degrade protein into noxious metabolites as waste products.[7303]

There is no shortage throughout history of old-timey crackpots with quack medical theories, but Metchnikoff was no slouch. He was appointed Louis Pasteur's successor,[7304] coined the terms "gerontology"[7305] and "probiotics,"[7306] and won the Nobel Prize in medicine to become the founding "father of cellular immunology."[7307] More than a century later, some aspects of his theories on aging and the gut are now being vindicated.[7308]

YOUNG AT GUT

Full-term, vaginally delivered, breastfed babies are said to start out with the gold standard for a healthy microbiome, which then starts to diverge as we age.[7309] The microbiomes of children, adults, the elderly, and centenarians tend to cluster together,[7310] such that a "microbiomic clock" can be devised.[7311] Dozens of different classes of bacteria in our gut so reliably shift as we age[7312] that our age can be guessed based on a stool sample within about a six-year margin of error.[7313] If these changes turn out to play a causal role in the aging process, then, hypothetically, our future high-tech toilet may one day be able predict our lifespan as well.[7314]

The transition from adulthood into old age is accompanied by pronounced changes to the microbiome.[7315] Given large interpersonal differences, there is no "typical" microbiome of the elderly,[7316] but the trends are in the very direction Metchnikoff described: a shift from the fermentation of fiber to the putrefaction of protein.[7317] This deviation from good bugs to bad is accompanied by an increase in gut leakiness, the spillage of bacterial toxins into the bloodstream, and a cascade of inflammatory effects. This has led to the proposal that this microbiome shift is a "primary cause of aging-associated pathologies and consequent premature death of elderly people."[7318]

As profound a change in microbiome composition from early adulthood into old age, there's an even bigger divergence between the elderly and centenarians.[7319] When researchers analyzed centenarian poop, they found a maintenance of short-chain fatty acid production from fiber fermentation.[7320] For example, in the Bama County longevity region in the Guangxi province of China, fecal sample analyses found that centenarians were churning out more than twice as much butyrate as those in their eighties or nineties living in the same region. If you recall, butyrate is an anti-inflammatory short-chain fatty acid critical for the maintenance of gut barrier integrity. At the same time, there were significantly fewer products of putrefaction, such as ammonia and uremic toxins like *p*-cresol. The researchers concluded that an increase of dietary fiber intake may therefore be a path toward longevity.[7321] An abundance of fiber feeders also distinguished healthy individuals ninety years and older from unhealthy nonagenarians.[7322]

CENTENARIAN SCAT

Interestingly, the microbiomes of Chinese centenarians shared some common features with Italian centenarians, suggesting that there could be certain universal signatures of a longevity-promoting microbiome.[7323] For example, centenarians have up to about a fifteenfold increase in butyrate producers.[7324]

A study of dozens of semi-supercentenarians (those aged 105 to 109) found higher levels of health-associated bacteria, such as *Bifidobacteria* and *Akkermansia*.[7325] In vaginally delivered, breastfed infants, *Bifidobacteria* make up 90 percent of colon bacteria, but the level may slip down to less than 5 percent in adult colons and even less in the elderly and those with inflammatory bowel disease.[7326] But centenarians carry more of the good bacteria in their gut.[7327]

Bifidobacteria are often used as probiotics, but anti-aging properties may exist in their *post*biotics. *Bifidobacteria* are one of the many bacteria that secrete "exopolysaccharides," a science-y word for slime.[7328] That's what dental plaque is, the biofilm created by bacteria on our teeth.[7329] Exopolysaccharides produced from a strain of *Bifidobacteria* isolated from centenarian poop were found to have anti-aging properties in mice,

reducing the accumulation of age pigment in their brains and boosting the antioxidant capacity of their blood and livers.[7330]

Akkermansia muciniphila is named after the late Dutch microbiologist Antoon Akkermans[7331] and from Latin and Greek for "mucus-lover." The species is the dominant colonizer of the protective mucus layer in our gut that is secreted by our intestinal lining.[7332] Unfortunately, that mucus layer thins as we age,[7333] a problem exacerbated by low-fiber diets. When we eat a fiber-depleted diet, we starve our microbial selves. Our famished flora, the microbes in our gut, have to then compete for limited resources and may consume our own mucus barrier as an alternative energy source, thereby undermining our defenses.[7334,7335] Mucus erosion from bacterial overgrazing can be switched on and off on a day-to-day basis in mice supplanted with human microbiomes with fiber-rich and fiber-free diets.[7336] You can even show it in a petri dish. Researchers successfully re-created layers of human intestinal cells and showed that dripping fiber (from plantains and broccoli) onto the cells at dietary doses could "markedly reduce" the number of *E. coli* bacteria breaching the barrier.[7337] Aside from eating fiber-rich foods, *A. muciniphila* helps to directly restore the protective layer by stimulating mucus secretion.[7338]

A. muciniphila is a likely candidate for a healthy aging biomarker,[7339] as its abundance is enriched in centenarians[7340] and it is particularly scarce in elders suffering from frailty.[7341] A comparative study was undertaken of the microbiomes of people in their seventies and eighties experiencing "healthy" versus "non-healthy" aging, defined as the absence or presence of cancer, diabetes, or heart, lung, or brain disease. *Akkermansia*, the species most associated with healthier aging, were three times more abundant in the fecal samples of the healthy versus non-healthy aging cohort. Among centenarians, a drop in *A. muciniphila* is one of the microbiome changes that seems to occur about seven months before death, despite no apparent changes in the physical status, food intake, or appetite at the time.[7342] To prove a causal role in aging, researchers showed that feeding *A. muciniphila* to aging-accelerated mice significantly extended their lifespans.[7343]

CAUSE, CONSEQUENCE, OR CONFOUNDING?

A recurring recommendation from centenarian poop studies is the promotion of high-fiber diets,[7344,7345,7346] one of the most consistently cited pieces of lifestyle advice in general for extreme longevity and health.[7347] An alternative proposal is a fecal transplant, from a cocktail of centenarian stool. Both approaches assume a cause-and-effect relationship between fiber-fueled feces and long lives, but there remains much controversy over whether age-related microbiome changes are cause, consequence, or confounding.[7348]

Aging is accompanied by *dysbiosis*, an unhealthy imbalance of gut flora characterized by a loss of fiber-fed species.[7349] Rather than a changing microbiome contributing to the aging process, it's easier to imagine how aging could instead be contributing to a changing microbiome. Loss of taste, smell, and teeth with age could lead to decreased consumption of fiber-rich foods, replaced by salted, sweetened, easier-to-chew processed foods.[7350] The drop in the quantity and diversity of whole plant foods—the only naturally abundant source of fiber—could result in a dysbiosis[7351] that leads to early death and disability. Or, the decline in diet quality could directly dispose to disease, with the dysbiosis just an incidental marker of an unhealthy diet.

There are also ways aging can be connected to dysbiosis independent of diet. While the rates of antibiotic prescriptions in childhood and through middle age have dropped in recent years, prescription rates among the elderly have shot up.[7352] Even non-antibiotic pharmaceuticals can muck with our microbiome. A study pitting more than a thousand FDA-approved drugs against forty representative strains of gut bacteria found that 24 percent of marketed drugs inhibited the growth of at least one strain.[7353] Reduced physical activity could also contribute to sluggish, stagnant bowels that could leave our gut bugs no other choice but to turn to protein for putrefaction once preferred prebiotics are used up.[7354] Nursing home residents are often fed the kind of low-fiber diet that can contribute to the "decimation" of a healthy microbiome.[7355] So, while researchers have interpreted the link between dysbiosis and frailty as a poor diet leading to poor gut flora leading to poor health,[7356] the arrows of causality could potentially go in every which direction. Maybe there's even a chicken-or-

the-egg feedback loop in play.[7357] With so many interrelated factors, you can imagine how hard it is to tease out the causal chain of events.

These questions crop up all the time in microbiome research. For example, the microbiomes of centenarians aren't just better at digesting fiber. They're better at detoxifying industrial pollutants, such as petrochemicals; food preservatives like benzoate and naphthalene, used in petroleum refinement; and haloalkanes, widely used commercially as flame retardants, refrigerants, propellants, and solvents. None of these detoxification pathways was found in the microbiomes of the Hadza, one of the last hunter-gatherer tribes in Africa.[7358] Did the enhanced detoxification in centenarian guts (compared to younger individuals) contribute to their longevity, or did their longevity contribute to their enhanced detoxification (given their longer lifetime exposure and accumulation of chemicals)?[7359]

The microbiomes of centenarians and semi-supercentenarians are better able to metabolize plant fats than animal fats, but maybe that's just due to their eating more plant-based diets.[7360] The Bama County longevity region centenarians who had such an abundance of fiber feeders were eating more than 70 percent more fiber (38 g versus only 22 g per 2,000 calories) compared to those aged eighty through ninety-nine living in the same region.[7361] The only way to know if their longer lives eating more healthfully just led to a better microbiome or if their better microbiome actually contributed to their living longer is to put it to the test.

FECAL TRANSPLANT EXPERIMENTS

Longevity researchers have good reason to suspect a causal, rather than bystander, role for age-related microbiome changes, given fecal transplant studies I detail in see.nf/transplant, showing that the lives of old animals can be extended by receiving gut bugs from younger animals.[7362] Centenarian stool has anti-aging effects when fed to mice. Researchers fed mice fecal matter from a 70-year-old individual that contained *Bilophila wadsworthia*,[7363] a pro-inflammatory bacteria enriched by a diet high in animal products,[7364] versus feces from a 101-year-old containing more fiber feeders. Mice transplanted with the centenarian microbiome ended up displaying a range of youthful physiological indicators, including less age pigment in their brains. This raises the possibility that we will one day be

using centenarian fecal matter to promote healthy aging.[7365] Why bathe in the blood of virgins when you can dine on the dung of the venerable?

DYSBIOSIS

An unhealthy imbalance of gut bacteria can result from a deficiency of fiber or an excess of antibiotic exposure, salt, protein, and certain food additives.

PLUGGING LEAKS WITH FIBER

One of the mechanisms by which intestinal dysbiosis may accelerate aging is a leaky gut. Watch see.nf/leaky for details, but basically, across animal species, intestinal barrier integrity has been shown to decline with age.[7366] This can lead to tiny bits of undigested food, microbes, and toxins slipping through our gut lining and entering uninvited into our bloodstream, triggering chronic systemic inflammation.[7367] Thankfully, there's something we can do about it.

To avoid gut dysbiosis, inflammation, and leakiness, plants should be preferred. The reason vegetarians tend to have a better intestinal microbiome balance, a high bacterial biodiversity, and enhanced integrity of the intestinal barrier,[7368] and also produce markedly less uremic toxins in the gut,[7369] is likely that fiber is the primary food for a healthy gut microbiome.[7370] Cause and effect was established in a randomized, double-blind, crossover study of pasta with or without added fiber.[7371]

Other ways to heal a leaky gut, detailed in see.nf/sealthegut, is to stop alcohol consumption,[7372] avoid NSAIDs, like aspirin, ibuprofen, and naproxen,[7373] which can cause gastrointestinal lining damage within five minutes,[7374] and (from see.nf/leaky) get the amount of daily zinc found in about a cup of cooked lentils.[7375]

DYSBIOSIS INFLAMMATION IMMUNOSUPPRESSION

The most important role a healthy microbiome has for preserving health as we age is thought to be the prevention of systemic inflammation.[7376] Inflammaging is a strong risk factor not only for premature death.[7377] Those with higher-than-average levels of inflammatory markers in their blood for their age are more likely to be hospitalized,[7378] frail,[7379] and less

independent,[7380] and suffer from a variety of diseases, including common infections.[7381]

In Japan, for example, more than 40 percent of all centenarian deaths are due to pneumonia and other infectious diseases.[7382] In one of the largest studies, involving nearly 36,000 British centenarians, pneumonia was the leading identifiable cause of death.[7383] Inflammaging has not only been shown to increase susceptibility to coming down with the leading cause of bacterial pneumonia[7384] but older adults with more inflammation also tend to suffer increased severity[7385] and decreased survival.[7386]

As we age, our immune system macrophages (from the Greek for "big eaters") start to lose their ability to engulf and destroy bacteria.[7387] The same happens in regular mice. But mice raised microbe-free don't suffer from the leaking gut, subsequent inflammation, and loss of macrophage function. To connect the dots between the inflammation and loss of function, researchers found that the macrophage impairment could be induced in microbe-free mice by infusing them with an inflammatory mediator, which, when dripped on macrophages in a petri dish, could directly interfere with their ability to kill pneumonia bacteria.[7388] Because our immune system is also responsible for cancer defense, immune dysfunction caused by the inflammation resulting from dysbiosis may also help explain why cancer incidence increases so steeply as we age (and why microbe-free mice have fewer tumors and live longer).[7389]

AVOIDING DIETARY ANTIBIOTICS

Other than getting enough fiber, what else can we do to prevent dysbiosis in the first place? There are a number of factors that contribute to microbiome imbalance. For example, on any given day, an average of about two and a half doses of antibiotics are consumed for every one hundred people in Western countries.[7390] The havoc this can play on our microbiome may explain why antibiotic use predicts an increased risk of cancer, though confounding factors, such as smoking, that are associated with both, could also potentially explain this link.[7391]

Up to three-quarters of antibiotic use is of questionable therapeutic value.[7392] Avoiding unnecessary use of antibiotics and using targeted, narrow-spectrum agents whenever possible can help protect our gut

flora,[7393] but most people may not realize they're consuming antibiotic residues every day in the meat, dairy, and eggs they eat. As much as 80 percent of the antibiotics used in the United States doesn't go to treat sick people but rather is fed to farm animals[7394] in part as a crutch to compensate for the squalid conditions that now characterize much of modern agribusiness.[7395] But do enough antibiotics make it onto our plates to make a difference?

Infections with multidrug-resistant bacteria are on target to become the world's leading cause of disease and death by the year 2050, poised to surpass even cancer and heart disease. Excessive antibiotic use can result in our guts becoming colonized with these superbugs,[7396] so researchers set out to calculate how many animal products one would need to eat to achieve antibiotic concentrations in our colon to give resistant bugs an advantage. Single servings of beef, chicken, or pork were found to contain enough tetracycline, ciprofloxacin, tilmicosin, tylosin, sarafloxacin, and erythromycin to favor the growth of resistant bacteria. One and a half servings of fish (150 g) exceeded minimum selective concentrations of ciprofloxacin and erythromycin. Two cups of milk could tip the scales for tetracycline, ciprofloxacin, tilmicosin, tylosin, and lincomycin. And, legal levels of erythromycin and oxytetracycline in two eggs could also exceed safe levels.[7397]

Most resistant bacteria have mobile genetic elements like plasmids, little circles of DNA that carry the resistance genes that they can pass on to other bacteria, including those in our own gut.[7398] In an intestinal model, the transfer of an antibiotic-resistance plasmid from an *E. coli* bacterium originating from a chicken into human gut bugs occurred within two hours. This explains why the antibiotic-resistance gene loads in those eating strictly plant-based diets are significantly lower than in omnivores or ovo-lacto vegetarians. A higher incidence of resistance genes to even vancomycin was found in consumers of eggs, poultry, and fish.[7399] Vancomycin is one of our antibiotics of last resort, used to treat serious life-threatening strep and staph infections, including MRSA.

We need to stop squandering lifesaving miracle drugs just to speed the growth of farm animals reared in unhygienic conditions, and we also need to stop the reckless overuse in medicine. But, sometimes, you have to take antibiotics. To reduce the collateral damage to your friendly flora, a series

of mouse studies suggest that you can make your microbiome more resilient by eating healthfully—for example, by consuming more fiber and less sugar.[7400] Prebiotics protect mice from colonization by the bad bug *Clostridium difficile* during antibiotic treatment,[7401] and higher-fiber, lower-fat diets can even protect mice from dying from sepsis after surgery due to antibiotic microbiome disruption.[7402]

FOOD ADDITIVES TO AVOID

The ultraprocessed foods that make up the majority of our diet[7403] aren't just deficient in fiber but include additives that have been shown to muck with our microbes. Even something as simple as salt can affect our microbiome. Approximately doubling sodium intake by adding a teaspoon of salt to people's diets not only increases their blood pressure and boosts pro-inflammatory cells[7404] implicated in autoimmune disease[7405] but it rapidly depletes the gut of the good bacteria *Lactobacillus*. Nine out of ten study subjects who started out with *Lactobacillus* in their gut had it completely wiped out by the added salt within just two weeks.[7406]

Check out see.nf/notsosweet to learn about the adverse microbiome effects of artificial sweeteners. The good news is that after stopping them, the original balance of gut bacteria may be restored within weeks.[7407] It's more difficult to avoid the ingestion of emulsifiers, the most widely used food additives.[7408] Details in see.nf/emulsifiers, but the bottom line is that out of twenty different commonly used emulsifiers, most appeared to have detrimental effects, including carboxymethylcellulose and polysorbate 80, but two emulsifiers seemed to be okay: soy lecithin and mono- and diglycerides.[7409]

PROTEIN PUTREFACTION

Have you heard the takeoff of the industry slogan "Beef: It's What's for Dinner"? "Beef: It's What's Rotting in Your Colon." I saw this on a shirt once when I was with some friends and was such a party pooper—no pun intended—that I explained to everyone that meat is fully digested in the small intestine and never makes it down into the colon. (It's no fun hanging out with biology geeks.) But I was wrong! (About meat in the colon, not about being the occasional science-based buzzkill.)

On a typical Western diet, it's been estimated that up to 12 g of protein can escape digestion, and, when it reaches the colon, it can be turned into toxic substances like ammonia.[7410] This degradation of undigested protein in the colon is called putrefaction. So, a little meat *can* actually end up putrefying in our colon. The problem is that some of the by-products of this putrefaction process can be toxic.[7411]

As I explain in see.nf/sulfide, animal proteins tend to have more sulfur-containing amino acids like methionine, which can be turned into hydrogen sulfide in our colon. This may help explain[7412] why those who eat meat appear to be at higher risk of both inflammatory bowel disease[7413] (see.nf/hsibd) and colon cancer[7414] (see.nf/hscancer). Sulfur preservatives (sulfites and sulfur dioxide) in nonorganic wine and dried fruit may also be an issue,[7415] but the sulfur-containing compounds in cabbage-family vegetables don't seem to be a problem.[7416]

Silent, but Deadly

There's a reason hydrogen sulfide is called "rotten egg gas." It's thought to be responsible for the "malodorous rectal flatus" associated with a low-carb diet.[7417] One of the strongest predictors of fecal odor when comparing fresh stool samples was found to be whether or not someone eats meat.[7418] To shrink the stink, the *Harvard Health Letter* offers the recommendation to cut back on meat and eggs.[7419] Randomize people to different quantities of meat, and a clear correlation with fecal sulfide concentrations can be found.[7420] Compared to those eating plant-based diets, individuals who regularly eat meat were found to generate up to fifteen times as much.[7421]

HOW TO REDUCE TMAO EXPOSURE

Prebiotics, like fiber and resistant starch, can feed our probiotic good bacteria, like *Lactobacillus* and *Bifidobacteria*, to make beneficial postbiotics, like butyrate and acetate. However, feeding the wrong foods

can foster the growth of bad bacteria that create toxic postbiotics, like TMAO.

Short for *trimethylamine oxide*, TMAO is considered the "smoking gun" of microbiome-disease interactions.[7422] It was identified when researchers compared the blood of patients who had had a stroke or heart attack against the blood of those who hadn't.[7423] (View the full story in see.nf/tmaodiscovery.) Whether young or old, male or female, smoker or nonsmoker, with high blood pressure or low blood pressure, high cholesterol or low, having high levels of TMAO is associated with a significantly higher risk of having a heart attack or stroke, or dying prematurely in general.[7424]

In mice, TMAO promotes atherosclerosis by promoting the accumulation of cholesterol and inflammatory cells within artery walls.[7425] Two other mechanisms for the role of TMAO in cardiovascular disease have been directly demonstrated in human interventional trials. One of the reasons high TMAO levels appear to increase the odds of stroke by 68 percent[7426] and quadruple the odds of dying from it[7427] is that it effectively makes our blood-clotting platelets stickier, the opposite effect of aspirin.[7428] This results in a prothrombotic (clot-promoting) state, whereas the reason TMAO impairs artery function appears to be due to oxidative stress, as an IV infusion of vitamin C can restore TMAO-impaired function in middle-aged and older adults.[7429]

We used to think the toxic effects of TMAO were limited to cardiovascular disease,[7430] but, more recently, it has been associated with everything from psoriatic arthritis[7431] to polycystic ovary syndrome (PCOS),[7432] including eight of our ten leading causes of death: cancer (ovarian,[7433] colorectal,[7434] and breast[7435]), COPD,[7436] dementia,[7437] diabetes,[7438] pneumonia,[7439] and kidney failure.[7440] See details in see.nf/tmaorisk. Based on twenty studies following more than 30,000 people for an average of about five years, a systematic review and meta-analysis found that higher TMAO was associated with a nearly 50 percent increase in all-cause mortality risk.[7441]

Where does TMAO originate? From bad bacteria in our gut when we eat a lot of choline, which is concentrated in eggs and lecithin supplements, or carnitine, which is found in abundance in meat and some energy drinks. Within hours of eating eggs[7442] or meat,[7443] TMAO levels get bumped up—

unless antibiotics had recently been taken, wiping out our gut flora. (It can take weeks for bad bacteria to grow back.) Instead of taking drugs, why not prevent the growth of these bad bacteria by not feeding them to begin with? Researchers found that even after a vegan ate steak, virtually no TMAO was produced, presumably because the growth of steak-eating bacteria had not been fostered on a meat-free diet.[7444]

Remarkably, even if you give plant-based eaters the equivalent of an 18-oz steak[7445,7446] every day for two months, only about half of them start ramping up production, showing how far their gut flora had changed.[7447] But it's not all or nothing. As I explore in see.nf/swap, even just exchanging two servings a day of regular meat for plant-based meat can lower TMAO levels within a matter of weeks.

Even plant foods that are relatively rich in choline don't seem to cause the same problem. For example, pistachios[7448] and brussels sprouts[7449] can even make TMAO levels go down. I explore the mixed effects of different plant foods and the pros and cons of carnitine supplements in aging in my video see.nf/tmaoupdate. In short, the best strategy to reduce TMAO exposure is probably to prevent the bloom of bad bacteria in the first place. As one endocrinology journal editorial put it, maybe TMAO should stand for "Time to Minimize intake of Animal prOducts."[7450]

PROBIOTICS

It's been said that the only thing that stops a bad microbiome is a good microbiome.[7451] The question is how to establish that healthy gut flora. There is a multibillion-dollar industry pushing probiotic supplements,[7452] but despite thousands of clinical trials, we, like our microbiome, are left largely in the dark. When researchers analyzed the first 150 results that Google pulled up on probiotics, commercial sites were the most common, which provided, on average, the least reliable information. Most of the claimed benefits were found to be supported by little or no scientific evidence.[7453]

SAFETY AND EFFICACY OF PROBIOTIC SUPPLEMENTS

As I explore in see.nf/probiotics, a recent systematic review of randomized controlled trials of probiotic supplements for healthy older adults found that

there was insufficient evidence for the improvement of health outcomes,[7454] and an analysis of hundreds of trials found harms reporting was often missing, insufficient, or inadequate, which undermines our confidence in the safety of these supplements.[7455] For example, there are concerns about antibiotic resistance.

Probiotics are often intentionally selected to be antibiotic-resistant so they can be coadministered with antibiotics to reduce diarrhea rates,[7456] but they may transfer that resistance to pathogens in the gut.[7457] The irony is that probiotics can actually interfere with microbiome recovery after taking antibiotics rather than facilitate it, so just as it may be wise to bank your own blood before an elective procedure should you need a transfusion, those saving their own stool before the course of antibiotics were able restore their microbiomes back to normal within a matter of days.[7458]

MISLABELING AND CONTAMINATION OF PROBIOTIC SUPPLEMENTS

Even if a particular probiotic is proven to be beneficial, there's no guarantee that what's listed on the supplement label is present in the product. No probiotic formulation has been approved by the FDA, so they are sold under the lax regulatory rubric of the dietary supplement industry.[7459] There are products on the market containing microorganisms like *Bacillus licheniformis* not known to even inhabit the human digestive tract.[7460] (It's a soil microbe used to degrade chicken feathers for use in animal feed.[7461]) What about just choosing a probiotic generally considered safe and effective, like *Bifidobacteria*? Good luck. A survey of sixteen commercial *Bifidobacteria* supplements found that only one matched the contents claimed on its label. Even within the same brand, the contents sometimes changed from lot to lot or even sometimes from pill to pill within the same bottle.[7462]

An analysis of commercial probiotics in the United States found that many major brands, including GNC, Walgreens, Procter & Gamble, NaturesPlus, Nature's Bounty, and New Chapter Organics, failed to live up to their label content claims. Most were also contaminated with microorganisms not listed on the label, including, in the case of a GNC product, mold.[7463] Most foods making probiotic claims were also inaccurate.[7464] For example, as few as two in twenty-five "probiotic" dairy

products tested, like yogurt, matched their labeling.[7465] Unfortunately, no improvement in the quality of probiotic products has been found.[7466] A review titled "The Unregulated Probiotic Market" explained the simple reason why: With such poor regulation, there's just no incentive for producers to accurately represent their products.[7467]

The probiotic data are said to be so tainted by personal and commercial biases and so inapplicable due to insufficient regulation that they "make objective interpretation close to impossible."[7468] Even if you could get the right dose of the right strain of the right probiotic, they don't appear to actually colonize our gut.[7469] Presumably, if the conditions within your gut were amenable to the growth of good bugs, they would be there already. Without a change in diet to change the gut ecosystem, probiotics don't take root, so you'd have to keep taking them forever.[7470] Stool transplants and probiotics may only be temporary fixes if we keep using the wrong fuel. If we don't change our diets, it may be a waste of money to go shopping for vegan poop on the black market. (Brown market?) On the other hand, by eating foods rich in *pre*biotics, in other words, increasing "whole plant food consumption,"[7471] we may select for *and* foster the growth of our own good bacteria.

What About Fermented Foods?

If commercial probiotics are unreliable, how about the ones that occur naturally in fermented foods? I talked about the potential benefits of souring milk to eliminate some of the galactose, branched-chain amino acids, or microRNAs (see here). Beyond the aging implications, fermented dairy would be less distressing to those who are lactose-intolerant (which includes the majority of humanity).[7472] Although no significant differences were noted for abdominal pain or diarrhea after the consumption of milk versus kefir, a fermented milk product, the kefir caused fewer farts—seven over the subsequent eight hours versus thirteen after the milk.[7473]

A randomized, double-blind, placebo-controlled trial of kefir found no benefit for preventing antibiotic-associated diarrhea compared to a heat-killed matching placebo with no live microbes.[7474] Similarly, a randomized controlled trial found no benefit of live versus dead (pasteurized) sauerkraut for irritable bowel syndrome.[7475] In Japan and Korea, pickled vegetable consumption is associated with higher risk of stomach cancer (whereas consumption of fresh vegetables is linked to lower risk).[7476] This is suspected to be due to the salt added to fermenting vegetables to keep unwanted microbes from growing.[7477] However, in Japan, pickled vegetable consumption is associated with lower all-cause mortality, though no more than fresh vegetables.[7478]

Bacillus subtilis, the bacterium used to make a fermented slimy soy food called natto, was found to extend the lifespan of *C. elegans*.[7479] In people, greater natto consumption is associated with living longer, but not necessarily when adjusting for other dietary and lifestyle traits, suggesting that it may be more of a marker of a traditional Japanese eating pattern rather than the natto itself.[7480]

PREBIOTICS AND POSTBIOTICS

If you look at the most frequently cited articles in the scientific nutrition literature, the original glycemic index paper comes in at number ten, cited more than a thousand times.[7481] But, in the top five, cited more than two thousand times, is "Dietary Modulation of the Human Colonic Microbiota: Introducing the Concept of Prebiotics." As I've discussed, prebiotics are the food components that feed and nourish the good bacteria in the gut, like fiber and resistant starch.[7482] For every 1 g of fiber we eat, we can get an increase of nearly 2 g of stool because we are boosting bacterial growth.[7483] Though probiotic pills have been positioned as the next big source of Big Pharma billions,[7484] why take a pill when you can grow your own at home? A meta-analysis of more than five dozen randomized controlled trials of

prebiotics found that they boosted the abundance of common probiotics, such as *Bifidobacteria* and *Lactobacillus*.[7485]

*Pre*biotics don't just boost growth of preexisting *pro*biotics. They are used by our friendly flora to create *post*biotics, those by-products of microbiome metabolism that can be beneficial. Our good bugs eat prebiotics like fiber and make short-chain fatty acids (SCFAs) that are then absorbed into our bloodstream from our colon, circulate throughout our body, and even make their way to our brain.[7486] These far-reaching fiber-sourced SCFAs may have wide-ranging effects on everything from inflammation and immune function[7487] to mental health.[7488]

Remember from here how just one high-fiber meal can improve lung function in asthmatics within a matter of hours? SCFA postbiotics may explain why higher fiber intake is associated with a lower risk of developing osteoarthritis[7489] and worsening knee pain over time.[7490] To give you an idea how protective fiber-rich foods can be, those randomized to eat more whole plant foods during radiation therapy for cancer not only experienced reduced toxicity during the treatments but suffered fewer long-term side effects a full year later.[7491]

Hormones are defined as signaling messengers produced in one organ that circulate throughout the bloodstream and have a regulatory effect on another organ. So, SCFAs could be considered to be hormones—it's just that the organ producing them is the community of bacteria in our gut. But just like our thyroid gland can't make its hormones unless we eat iodine, our microbiome can't make SCFAs unless we eat fiber.

PREBIOTICS FOR FRAILTY

The anti-inflammatory effects alone can help explain why those who eat more fiber tend to live longer and healthier lives. A systematic review and meta-analysis based on more than a hundred million person-years of data found that, compared with those who consumed the least fiber, those who consumed the most had about a 15 to 30 percent decrease in the risk of dying prematurely from all causes put together, including the risk of getting and dying from heart disease, stroke, and cancer.[7492] Fiber intake is also associated with significantly greater likelihood of "successful aging," which

is defined as the absence of disability, cognitive impairment, depression, respiratory symptoms, or chronic disease.[7493]

Prebiotics[7494] and postbiotics[7495] can be shown to extend the lives of model animals, but interventional trials in humans are largely limited to risk factors. For example, a meta-analysis of more than fifty randomized controlled trials showed that prebiotics like fiber can significantly improve blood sugar, blood pressure, weight, and cholesterol control.[7496] However, as I note in see.nf/frailtyprebiotics, there was a randomized, double-blind, placebo-controlled trial of prebiotics for frailty, showing significant improvements in both exhaustion and muscle strength.[7497]

When we eat fiber-rich foods, we get a double benefit: the formation of short-chain fatty acids and the selective cultivation of the bugs that make them. The contents of the colons of people eating more plant-based have nearly three times the capacity to form short-chain fatty acids, ounce for ounce.[7498] We get not only more raw materials for SCFA production when we eat healthfully but also improved microbial machinery to create even more of them. In contrast, short-chain fatty acid production can be slashed by up to 75 percent on a low-carb diet.[7499]

PROMOTING *PREVOTELLA*

In my Microbiome-Friendly chapter in *How Not to Diet*, I detail how all of humanity basically clusters in one of two *enterotypes*, those who eat healthier diets and grow mostly *Prevotella* species and those who eat westernized diets and grow mostly *Bacteroides*.[7500] If that sounds curious—thousands of bacteria species but only two enterotypes—think of our guts as ecosystems.[7501] On our planet, there are millions of different species of animals, but they aren't distributed randomly. There are jungle species in the jungle and desert species in the desert. Each ecosystem has its own collection of unique selective pressures, like temperature, humidity, or rainfall. It seems that there are two types of colon ecosystems, so we can be divvied up into groups whose guts grow a lot of *Prevotella*-type bacteria and those whose guts are better homes for *Bacteroides* species.

As fiber-feeders, *Prevotella* churn out more short-chain fatty acids,[7502] helping to explain why African Americans (who typically have a *Bacteroides* enterotype) have fifty times more colon cancer than native

Africans (who typically harbor *Prevotella*).[7503] Within days, though, by switching between plant- and animal-based diets, you can flip your gut flora from one to the other.[7504]

Prevotella also tend to be anti-inflammatory, which could explain why lower levels of that bacteria are also something you see in autoimmune conditions, such as Hashimoto's thyroiditis, multiple sclerosis, and type 1 diabetes.[7505] That may be one reason why autoimmune disorders were rare or virtually unknown among those in rural sub-Saharan Africa eating diets composed nearly entirely of plant foods.[7506] Most studies reported that vegetarians harbor higher numbers of *Prevotella*,[7507] but when researchers put them on a diet of meat, eggs, and dairy, their levels were driven down within as few as four days.[7508]

Plant-based diets have been recommended for maintaining beneficial gut microbiota for healthy aging.[7509] Vegetarians tend to harbor a greater abundance of potential probiotic (good) bacteria, whereas omnivores teem with more potential pathobiont (bad) bacteria.[7510] Plant protein intake is associated with more *Bifidobacteria* and *Lactobacillus*, greater short-chain fatty acid production, decreased inflammation, and an improved gut barrier, whereas animal protein intake fosters the growth of bacteria like *Bilophila* and leads to a drop in short-chain fatty acid production and a rise in toxic metabolites like TMAO.[7511]

A comparison of the stool samples of vegans, vegetarians, and omnivores found a continuum of inflammatory markers, with a significant increase from the most to the least plant-based[7512]—inflammation that can be doused by switching to a completely plant-based diet.[7513] This may have more to do with protective effects of plants, though, than any adverse effects of animal products.[7514] An in-depth study of the microbiomes and habitual diets of more than a thousand people found that the dietary factor that most shaped gut flora was the quantity and diversity of healthy plant foods. The microbiomes of those eating fiber-depleted processed foods, such as soda and refined grain products, clustered with those eating more animal foods.[7515] So a junk-food vegan may not be doing their good bugs many favors.

It needn't be all or nothing. People following a Mediterranean-type diet brimming with beans, fruits, and vegetables, while avoiding meat (including fish), eggs, or dairy on a day-to-day basis, had short-chain fatty

acid levels that were comparable to vegans, despite not being totally plant-based all the time.[7516]

WITH EVERY FIBER OF YOUR BEAN

The benefits of short-chain fatty acids rely on us eating fiber *and* having fiber-feeding bugs, just like the detrimental effects from TMAO need us to not only eat eggs, dairy, or meat but also carry the egg-, dairy-, or meat-munching bugs. Remember the steak-scarfing vegan? Their gut didn't harbor the bad bugs that make TMAO, and it could take months of eating steaks to ramp up production. Similarly, it may take months for those eating less healthy diets to realize the full potential of increased fiber consumption as their microbiome of fiber-eating organisms grows.[7517]

As I detail in see.nf/cultivate, the benefits of eating more fiber plateaus when our available fiber-feeders are maxed out, but the sky's the limit for those who have habitually been cultivating the growth of fiber-feeders like *Prevotella*.[7518] The U.S. federal recommendation for fiber intake is at least 14 g per 1,000 calories, which comes out to about 25 g a day for women and 38 g a day for men.[7519] Even though that's a far cry from the 100 g our body was designed to get (based on the diets of isolated modern-day hunter-gatherer tribes[7520] and analyzing coprolites, human fossilized feces[7521]), fewer than 3 percent of Americans even reach the minimal minimum recommendation.

We know that fiber is only found in plants by definition,[7522] with typically little found in processed foods and none at all in any animal foods. Since fruits and vegetables are mostly water, the fiber-rich superstars of the plant kingdom are the whole grains and legumes.[7523] A cup of fruit may only have about 3 g of dietary fiber and a cup of vegetables 5 g, but a cup of beans or a cup of intact whole grains, like barley groats, may have 15 g.

50-FOOD CHALLENGE

The Yanomami tribe in the Amazon jungle have the richest microbiomes ever recorded. They had had no prior contact with the modern world,[7524] which makes me wonder how that conversation went: *We come in peace. Can we have your poop?*

Today's low-fiber diet is thought to be a key culprit in microbiome depletion.[7525] In its profound and potentially catastrophic upheaval of the microbiome ecosystem, the loss of dietary fiber in the modern diet has been compared to the Chicxulub impactor, the meteor that killed off the dinosaurs.[7526] Why can't we just take a fiber supplement? There are literally thousands of types of fiber in plant foods, and each may support different communities of bacteria in our gut.[7527] Unlike whole foods, like brown rice or whole-grain barley, fiber supplements don't seem to work to improve the richness of the microbiome.[7528] What's more, a combination of brown rice and barley synergistically works better than either alone.[7529] That's the reasoning behind recommendations that people take a "50-food challenge," eating at least fifty different plant foods a week to achieve a diet diverse enough to feed a vast spectrum of bacteria.[7530]

No wonder fiber supplements are a poor substitute. Some, like psyllium (sold as Metamucil), don't appear to be utilized by our microbiome at all.[7531] The hubris reminds me of probiotic supplements. There are thousands of different species of bacteria in our guts[7532] that all potentially interact with one another, yet we're surprised a half dozen out of thousands stuffed into a pill don't have more of an impact? No microbe is an island.[7533] Major starch munchers like *Bifidobacteria* produce acetate, which feeds some of the major butyrate producers, and lactate, which acidifies the gut. This further stimulates the growth of butyrate producers, as well as suppressing the growth of bad bugs,[7534] in the same way sauerkraut does. The best way to support this symphony of interaction is to eat plants—not pills or powders.

RESISTANT STARCH

Fiber isn't the only prebiotic. For example, about 30 percent of the caloric content of human breast milk is made of "indigestible" oligosaccharides.[7535] Though we may not be able to digest them, guess who can? *Bifidobacterium infantis*, good bacteria in the guts of infants. That's how important the human-bacteria relationship is. We were designed to be a symbiotic species.

Inulin, concentrated in such vegetables as onion and garlic, can have a "huge" bifidogenic effect.[7536] Ironically, some people with irritable bowel syndrome actively avoid inulin because it is a type of FODMAP, or

fermentable oligo-, di-, and monosaccharides and polyols. Individuals following FODMAP-restricted diets tend to end up with depleted levels of *Bifidobacteria*, so it's been theorized that such eating patterns could actually impair long-term gut health.[7537]

There is "resistant starch"—starches resistant to digestion in our small intestines so they make their way to our colon, where they can act as prebiotics to feed our good bacteria, just as fiber does. I mentioned the trick of cooling cooked starches here, but the best source of resistant starch are legumes.[7538] Two daily servings of cooked chickpeas can reduce the colonization of pathogenic and putrefactive gut bacteria within three weeks. Study participants had about a 50 percent reduction in the presence of a highly ammonia-producing bug.[7539] Perhaps this explains why a single serving of legumes a day is associated with about a 20 percent lower risk of colorectal cancer.[7540] In rats, feeding them black beans cuts down by 75 percent the incidence of colon cancer caused by a carcinogen.[7541]

As with fiber, you need to eat the prebiotics *and* have prebiotic-eating bugs to benefit. Those carrying starch scarfers like *Ruminococcus* can ferment nearly all the resistant starch they eat, whereas those who don't are only able to take advantage of 20 to 30 percent.[7542] How do you foster the growth of more of these good bugs? Eat more foods containing resistant starch! Within just ten days of being randomized to a diet high in resistant starch, the abundance of starch eaters like *Ruminococcus* can be quadrupled.[7543]

SURVIVING INTACT

The preferred prebiotic of *Bifidobacteria* is starch, so how can we ferry more starch to our colon?[7544] Wrap it in fiber. That is, within intact grains and legumes. I allude to this here and do a deep dive in my Wall Off Your Calories chapter in *How Not to Diet*. When we chew and our stomach churns, anything we eat gets reduced down to smaller than two millimeters or so, about one-sixteenth of an inch, before entering our intestines.[7545] That may sound tiny, but a two-millimeter piece of wheat may contain about 10,000 plant cells filled with starch and only approximately 3,800 of them would be ruptured open on their surface,[7546] leaving 62 percent of the starch

in that particle of grain protected inside indigestible plant cell walls, which leads to ample leftovers to feed our microbiome.[7547]

Compare that to even whole *milled* grains. Ground flour particles can be a hundred times smaller—even smaller than the cells themselves—so nearly every one may be ruptured open, spilling their contents early and leaving our gut flora in the lurch.[7548] That's why we should try to de-flour our diets. Whole grains are good, but intact whole grains (groats) are better. It's the same reason why eating nuts can alter our microbiome for the better, boosting the growth of good bugs that produce short-chain fatty acids, but there appears to be no prebiotic influence when we eat the same amount of nut butter.[7549]

Remember acarbose from here, the drug that effectively turns regular starch into resistant starch? The average and maximum lifespan extension in mice from acarbose may be from the release of a hormone called GLP-1[7550] from specialized *L cells* that line our colons.[7551] That's the same hormone mimicked by the expensive new class of injectable weight-loss drugs like Wegovy.[7552] This same effect can be obtained in a drug-free manner with prebiotics. Researchers have achieved this in a petri dish[7553] or in a person, by infusing their rectum with an SCFA enema[7554] or just having them eat fiber[7555] or, even better, fiber-rich foods.[7556]

POLYPHENOL PREBIOTICS

Another major class of prebiotics are the polyphenols concentrated in fruits and vegetables.[7557] Those who discount the power of polyphenols often refer to studies showing their low bioavailability. Up to 85 percent of the polyphenol pigments that make blueberries blue do not get absorbed and end up in our colons, for example,[7558] but more advanced detection methods have recently shown that the majority of polyphenols may be absorbed after all.[7559] And our colon may be exactly where some of the magic happens.

When blueberry polyphenols[7560] are mixed with a culture of fecal bacteria, beneficial bugs like *Bifidobacteria* and *Lactobacillus* grow within a matter of hours.[7561] If you randomize people to a cup or so of wild blueberries,[7562] they get a significant bump in *Bifidobacteria* in their stools.[7563] How can we know that the polyphenols caused it and not the fiber? Well, apples also boost *Bifidobacteria*,[7564] but the isolated apple fiber

pectin on its own does not.[7565] Bananas and berries have a similar fiber content, but bananas have fewer polyphenols. Eating bananas does not significantly boost *Bifidobacteria*,[7566] which is more evidence that polyphenols may be playing a special role.

An interventional trial in which older individuals were randomized to swap out some low-polyphenol snacks for foods like berries and dark chocolate experienced a significant increase in good (butyrate-producing) bacteria and a bolstering of the gut barrier.[7567] However, polyphenol-rich beverages probably provide the best proof. Tea leaves and coffee beans have a lot of polyphenols that end up in the brew, whereas the fiber is completely left behind. Both green tea[7568] and coffee[7569] are bifidogenic. Three cups of coffee a day can raise *Bifidobacteria* levels in the gut significantly within three weeks.[7570]

Isn't tea antimicrobial? It's used in mouthwash to kill plaque bacteria,[7571] in acne creams to kill pimple bugs,[7572] and in foot baths to help control athlete's foot fungus.[7573] That indeed may be one of the ways it helps increase the proportion of good bugs like *Bifidobacteria*—by inhibiting the growth of the bad,[7574] though polyphenols from green, black, and oolong tea also boost *Bifidobacteria* and short-chain fatty acid production.[7575]

In a gut simulator, ginger extracts also promote *Bifidobacteria* growth in fecal samples. Fresh ginger extracts have been shown to ameliorate antibiotic-associated diarrhea in rats and accelerate microbiome recovery, but clinical studies are still lacking.[7576]

Microbiome Manipulation for Dementia

In see.nf/gutbrain, I profile a remarkable case report titled "Rapid Improvement in Alzheimer's Disease Symptoms Following Fecal Microbiota Transplantation"[7577] and review the inconsistent results of dozens of randomized controlled trials of prebiotics, probiotics, and fermented foods for cognition.[7578] Unfortunately, some of the most promising findings are plagued by concerns of data integrity,[7579] including oligomannate,[7580] a prebiotic conditionally

approved in China in 2019 to treat mild to moderate Alzheimer's disease.[7581]

POLYPHENOL POSTBIOTICS

Just as the benefits of fiber result from both the prebiotic fueling of good bacteria and the resulting postbiotic metabolites (short-chain fatty acids), polyphenols can act as prebiotics and also result in beneficial postbiotics. For example, there is an immediate bump of blueberry pigments in our blood within an hour of consumption, but a day later, new blueberry-derived compounds continue to appear in our bloodstream as our bacteria churn out new goodies from them.[7582] In this way, berry polyphenols can be the gift that keeps on giving.

As I detail in see.nf/urolithins, one class of postbiotics important to aging are urolithins, which are created in our large intestine by our friendly flora from ellagic acid, which is formed in our small intestine when we eat ellagitannins,[7583] the most common form of tannin,[7584] characteristically astringent-tasting natural compounds found in many of our ancestral foods, including berries, nuts, acorns, and tree leaves.[7585] Since tannins aren't bioavailable, they have been neglected in the field of nutrition or even considered as "antinutrients," a view that has "changed dramatically" once it was recognized that they could be metabolized by the microbiome into urolithins, now thought responsible for some of the benefits of berries, nuts, and pomegranates.[7586]

In *C. elegans*, urolithins extend lifespan by inducing mitophagy, mitochondria autophagy, the prevention of the accumulation of dysfunctional mitochondria with age.[7587] A decline in mitophagy has been linked to low muscle mass and poor physical function (slower walking speed) in the elderly.[7588] Urolithins have been found to counter age-related muscle function decline by improving the exercise capacity of older rodents[7589] and, in people, induced a molecular signature of improved mitochondrial health and biogenesis in muscle biopsies, similar to what one might see after an aerobic exercise regimen.[7590] This then translates into improved muscle endurance even in the absence of any exercise training.[7591] Like any postbiotic, though, it depends on having the requisite microbial

machinery. Studies show that some people are poor urolithin producers and some people's microbiomes can't make it at all.[7592]

Give people a pomegranate extract, and producers of urolithins experienced a significant reduction in LDL cholesterol, but the nonproducers did not. After a few weeks of supplementation, though, there were a few conversions—nonproducers turned into producers.[7593] This may explain why vegetarians tend to have a higher abundance of urolithin-producing microbes, their greater intake of plants.[7594] However, some plants have more than others. Among berries and nuts, the highest levels of ellagitannins are found in boysenberries, marionberries, yellow raspberries, pomegranates, and walnuts.[7595]

CALORIC RESTRICTION

Three meals a day (plus snacks!) is an evolutionarily novel behavior. In see.nf/fasting, I review how the story of life on Earth is a story of starvation.[7596] If our physiology is so well tuned to periodic scarcity, maybe it would be beneficial to cut back? Beyond just freeing up all the resources that would normally be used for nutrient digestion and storage, during fasting, our cells switch over to a protective mode[7597] that results in a reduction of free radical damage and inflammation.[7598] It's the hormesis concept of that-which-doesn't-kill-us-makes-us-stronger.[7599] This was perhaps most starkly demonstrated in a set of cringe-worthy experiments in which mice were blasted with Hiroshima-level gamma radiation sufficient to kill 50 percent within two weeks. But, of the mice that had been intermittently fasted for six weeks before the radiation blast, not a single one died.[7600]

A TIME TO FAST

Benjamin Franklin said, "To lengthen thy life, lessen thy meals."[7601] Might this hormetic bolstering of defenses result in a longer life? Using caloric restriction to slow aging became a topic of interest during the Great Depression in the 1930s when, contrary to expectations, average lifespan appeared to increase.[7602] The same was noted earlier during World War I in

Denmark, when blockaded food supplies were accompanied by a 34 percent reduction in death rates, and later in Norway during World War II, when a 20 percent drop in calories was accompanied by a 30 percent drop in death rates.[7603] The quality of the diets changed as well, though, complicating the picture, with the switch to eating feed crops like barley rather than the livestock to which they were being fed.[7604]

In the lab, caloric restriction without malnutrition is one of the most powerful non-pharmacological interventions for extending healthspan and lifespan across a multitude of species,[7605] considered perhaps "the most important discovery in the biology of aging to date."[7606] Simply reducing food intake can double or triple the lifespans of yeast, fruit flies, and worms, and prolong the average and maximum lifespans of rats and mice by up to 50 percent.[7607] The experiments can be as simple as feeding some flies to some spiders (cutely named *bowl and doily spiders*): One fly a week and they live an average of eighty-one days, three flies a week and they only live sixty-four days, and at five flies a week, only forty-two days.[7608]

The animals in some of these experiments live not just longer lives but healthier lives. The apparent slowing of the aging process conserved up through primates is accompanied by resistance to a range of age-related diseases, preventing or delaying autoimmune diseases, cancer, cardiovascular disease, glaucoma, kidney disease, and neurodegeneration.[7609] In Part I, I covered many of the theoretical underpinnings to the longevity benefits of caloric restriction, from boosting AMPK to "cleaning out the cupboards" autophagy—clearing out misfolded proteins, damaged cell structures, and senescent cells.[7610] As one review on the mechanisms by which intermittent fasting benefits cardiometabolic disease was subtitled, "The Janitor Is the Undercover Boss."[7611]

THE CANDLE THAT BURNS TWICE AS BRIGHT BURNS HALF AS LONG

Another potential mechanism may be the slowing of our metabolism. Because of our millions of years of evolution hard-wiring us to survive scarcity,[7612] when we start losing weight, in addition to unconsciously starting to move less as a behavioral adaptation to conserve energy,[7613] there are metabolic adaptations as well.[7614] Every pound of weight loss may

reduce our resting metabolic rates by seven calories a day.[7615] Though a bane for dieters (see.nf/biggestloser), a slower metabolism may actually be a good thing.

Caloric restriction can increase the lifespans of animals,[7616] and the metabolic slowdown may be the mechanism.[7617] That may be why the tortoise lives ten times longer than the hare.[7618] (Harriet, a tortoise evidently collected from the Galápagos by Charles Darwin in the 1830s, lived until 2006.[7619]) Slow and steady may indeed win the race.

One of the ways our body lowers our resting metabolic rate is by creating cleaner-burning, more efficient mitochondria, the power plants that fuel our cells.[7620] It's like our body passes its own fuel-efficiency standards. These new mitochondria appear to create the same energy with less oxygen and produce less free-radical "exhaust." After all, our body is afraid that famine is afoot, so it tries to conserve as much energy as it can.

The largest caloric-restriction trial to date found both metabolic slowing and a reduction in free radical–induced oxidative stress, both of which may slow the rate of aging.[7621] The metabolic slowing from eating nitrate-rich vegetables (see here) may be why eating leafy greens has been found to be among the six most powerful things we can do to potentially live longer.[7622] Whether restricting calories will translate into greater human longevity is an unanswered question. Caloric restriction has been said to extend the lifespan of "every species studied,"[7623] but this isn't even true of all strains within a single species.[7624]

STRAIN FOR EFFECT

If rodent results could be replicated in humans, what kind of life extension might people expect? Well, a 50 percent lifespan increase would extend the current U.S. life expectancy from 77 years[7625] to around 115, but that's based on experiments that restricted food intakes between 40 and 60 percent, starting immediately after weaning.[7626] See a full chart in see.nf/extrapolate, but even cutting down one's intake from 2,500 calories a day to 1,750 calories, a 30 percent drop, for a few decades starting in one's forties could potentially add a few years to your life. Same for reducing caloric intake just to 2,125 starting in one's thirties. Again, though, this is assuming we can extrapolate from rodents to humans.[7627]

A study of more than forty strains of mice found that caloric restriction *shortened* the lifespans of three times as many strains as it extended. Cutting food intake by 40 percent, one of the most common experimental regimens, extended the lifespans of five strains of mice, shortened it in fifteen, and had no significant effect on the majority. In one strain, the longevity of female mice was increased while that of male mice was decreased.[7628] If we can't even extrapolate the effects of caloric restriction from one strain of mouse to another, how can we extrapolate from mice to men or women? I explore other problems with generalizing results to humans in see.nf/extrapolate.

CALORIE RESTRICTION OR JUST OBESITY RESTRICTION?

One important critique of the entire field is that even the most successful studies more likely illustrate the life-shortening effects of obesity rather than the life-extending effects of caloric restriction.[7629] The control group animals in most caloric restriction experiments are allowed to eat ad libitum, meaning as much as they want.[7630] So maybe any benefits researchers find are less about restricting and more about just not overeating.

As anyone with pets knows, if you allow them to eat as much as they want, they can get fat.[7631] Middle-aged Labrador retrievers given unlimited food access in their youth end up with more than twenty pounds of body fat and only live about eleven years.[7632] If you pair litter puppies and restrict one to 75 percent of what their sibling eats ad libitum during that period, they put on less than ten pounds of fat and live an average of thirteen years. Nine out of twenty-four of the diet-restricted dogs (37.5 percent) survived past the time all their unrestricted siblings had died. Is that evidence that caloric restriction is good, or just evidence that obesity is bad?

Ironically, this aspect of the experiments may make them more generalizable to the human populace. Nearly three-quarters (73.6 percent) of the U.S. adult population is overweight or obese.[7633] So, using ad libitum controls may be the appropriate comparator. Those who are very obese (BMI $\geq$ 35) throughout their adult lives lose at least seven years of life and nineteen years of healthy life.[7634] Obviously, caloric restriction would be good for them, but most of the restriction experiments don't offer insight

into whether someone who is already at a healthy weight would benefit from restricting further. Control group considerations play heavily into the interpretation of conflicting results found in a famous pair of long-term caloric restriction monkey experiments.

MONKEYING AROUND WITH DIETARY RESTRICTION

There have been four investigations of caloric restriction and lifespan in nonhuman primates.[7635], [7636], [7637], [7638] The particulars are worth exploring, as I do in detail in see.nf/primatecr, but bottom line, if I had to sum up what we've learned from the primate data in one sentence, it would be: If you're overweight or living off junk food, eating less is a good idea.

CRONIE CATABOLISM

What about human data? Lifelong randomized controlled trials aren't going to happen,[7639] but there have been shorter-term ones, studies of those who calorically restrict voluntarily, as well as a variety of creative approaches to answer the question: *Does eating less help you live more?* For example, do those suffering from anorexia live longer? Far from it. Anorexia nervosa is one of the deadliest mental disorders. Anorexics die at a rate about ten times that of the general population,[7640] suffering from a range of electrolyte abnormalities, anemia, osteoporotic bone fractures, and cardiac arrhythmias.[7641] Researchers found that developing chronic anorexia from age fifteen would be expected to shave twenty-five years off a woman's lifespan.[7642]

Anorexia is an example of extreme caloric restriction. As many as nearly one-third of those diagnosed with the disease who seek treatment have a BMI under 15,[7643] about half the weight of the average American woman.[7644] Unlike laboratory protocols that dictate caloric restriction without malnutrition, those with anorexia can suffer from starvation-related nutrient deficiencies so severe that they can go blind.[7645] Their contracted lives may therefore not bear direct relevance to the question at hand, not to mention that one in five anorexia victims die by suicide.[7646]

The only long-term human study of extreme caloric restriction was the (in)famous Minnesota Starvation Experiment that used conscientious

objectors as guinea pigs during World War II. Unlike caloric restriction experiments designed to meet recommended daily allowances of essential nutrients, the Minnesota Starvation Experiment was deficient on purpose. The malnourished study subjects suffered from chronic weakness, painful leg swelling, and severe emotional distress. Interestingly, though, half the study participants went on to celebrate their eightieth birthdays, living at least eight years longer than expected for men in their generation,[7647] though other factors peculiar to a pacifist cohort could have played a role.

Speaking of unusual groups, self-styled CRONies (for *calorie restriction with optimal nutrition*) are active members of the Calorie Restriction Society, started by caloric restriction researcher and practitioner Roy Walford. He attempted to popularize the practice in the 1980s with his book *The 120 Year Diet*. Sadly, Walford himself died well short of the promised 120 at age 79 (of ALS).[7648] I review all the research on CRONies in see.nf/cronies. All in all, long-term practitioners of calorie restriction appear to be in excellent health, but they're a rather unique, self-selected bunch of individuals.[7649] As always, you don't really know until you put it to the test. Enter CALERIE, the Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy, the first large, long-term, clinical trial to test the effects of caloric restriction.[7650]

THE CALERIE TRIAL

Although the standard caloric restriction diet used in rodent studies is 40 percent less than the quantity consumed by ad libitum controls, even a 10 percent reduction can extend the lifespan of rats.[7651] Caloric restriction that modest would be amenable to a randomized controlled trial.

In the CALERIE trial, hundreds of nonobese men and women were randomized to two years of caloric restriction. (Details in see.nf/calerie.) As I mentioned, the study participants in the Minnesota Starvation Experiment suffered both physically and psychologically.[7652] However, the subjects started out lean and had their caloric intakes cut in half. The CALERIE study ended up being four times less restrictive, at only about 12 percent below baseline caloric intake, and enrolled normal-weight individuals, which in the United States these days means overweight on average. As such, the CALERIE subjects experienced nothing but positive quality-of-

life benefits, with significant improvements in mood, general health, sex drive, and sleep.[7653] They also wiped out more than half of their visceral abdominal fat,[7654] which translated into significant improvements in blood pressure, insulin sensitivity, triglycerides, and cholesterol levels.[7655] During the final year, they were eating only about 300 fewer calories than they had been at baseline,[7656] so they got all those benefits after cutting only about a snack-sized bag of chips' worth of calories from their daily diets.

What happened at the end of the trial, though? In both the Minnesota Starvation Experiment[7657] and experiments on U.S. Army Rangers,[7658] as soon as subjects were released from restriction, they tended to rapidly regain the weight—and sometimes more. The leaner they started out, the more their bodies seemed to drive them to overeat to pack back on extra body fat. In contrast, after the completion of the CALERIE study, even though their metabolisms were slowed by about a hundred calories a day,[7659] they retained about 50 percent of the weight loss two years after the trial ended.[7660] They must have acquired new eating attitudes and behaviors that allowed them to keep their weight down and did so without any signs of increased susceptibility to eating disorders.[7661] Indeed, after extended caloric restriction, cravings for sugary and fatty foods can go down.[7662]

The slowed metabolism, presented as "a reduction in the rate of living," would be expected to contribute to longevity[7663] and may explain part of the reduction in whole body oxidative stress within the first year of caloric restriction.[7664] However, even just culturing cells in the blood of those practicing caloric restriction makes them significantly more resistant to free radical damage, perhaps due to a doubling of antioxidant enzyme activity within cells bathed in calorically restricted blood.[7665] Furthermore, two different biomarker algorithms used to calculate "biological age" found that the caloric restriction intervention appeared to slow the rate of aging, and this appeared to be independent of the degree of weight loss. By one estimate, the ad libitum control group appeared to be aging at an average rate of 0.7 "years" per year, whereas the caloric restriction group averaged only 0.1. Based on that algorithm (the Klemera-Doubal Method), the caloric restriction group hardly appeared to be aging much at all.[7666]

The multitude of physiological, psychological, and aging benefits attributed to this sustained, moderate (11.9 percent) caloric restriction must be interpreted with the proviso that the composition of the diet changed

along with the quantity. Much of the caloric restriction was achieved through a reduction in fat intake.[7667] The type of fat was not specified, but given that the leading sources of fat in the American diet have typically been meat and dairy, followed by desserts like donuts, cookies, and cake, this may have been accompanied by an improvement in diet quality that could account for some of the measured effects.[7668] That caveat aside, the CALERIE trial does suggest that even "normal weight" individuals should eat less to improve their health and longevity.[7669]

Thinking Outside the Icebox

Studies following more than five million men and women found that abdominal obesity was associated with an increased likelihood of developing cognitive impairment and dementia in men and women older than sixty-five.[7670] Caloric restriction has been deemed one of the most effective dietary interventions to improve the cognitive performance of rodents.[7671] What about in people? There don't appear to be any human caloric restriction trials for dementia,[7672] but there have been about a dozen randomized controlled trials on cognitive effects on those who are cognitively intact or mildly impaired.[7673]

Although hardly any of the individual studies were able to show significant improvements, when all the studies were compiled together, there did appear to be cognitive benefit to cutting down calories. Most of the thousand or so study subjects were obese, so the benefit may have derived more from the weight loss than the caloric restriction per se.[7674] It doesn't take much, though. When overweight, borderline obese elderly men and women (BMI of 29.9) were advised to reduce their calories by 30 percent for three months, they only achieved about a 12 percent reduction in caloric intake, losing about five pounds, but nonetheless experienced a significant improvement in verbal memory performance.[7675]

A 12 percent reduction is what the CALERIE intervention group participants averaged. At the end of the two years, they had better working (short-term) memory than those randomized to the control group. Interestingly, the cognitive improvement was related mostly to lower protein intake.[7676] This was directly tested in a study titled "Dietary Effects on Cognition and Pilots' Flight Performance." Commercial airline pilots were randomly rotated through four-day high-carbohydrate, high-protein, high-fat, or control diets, then had their flying performance evaluated using a full-motion flight simulator. Compared to being on any of the other three diets, when the pilots were on the high-protein diet, their flight performance suffered.[7677]

More extreme fasting appears to have rather equivocal effects on cognition in the short term.[7678] Those randomized to eat nothing for a day subjectively feel greater "mental fatigue" than those given about 500 calories of food throughout the day, but they perform just as well on objective tests of cognitive performance.[7679] Given the potential for psychological influence, there was actually a randomized, double-blind, placebo-controlled trial of forty-eight hours of caloric deprivation. How can you blind someone to whether they eat or not? They were fed indistinguishable gels, either nearly calorie-free or providing thousands of calories a day. Surprisingly, two days of near-total caloric deprivation didn't affect the cognitive performance, activity, sleep, or mood of healthy young adults. This makes sense from an evolutionary point of view. Remaining sharp during a downturn in food availability would presumably offer a survival advantage.[7680]

POTENTIAL DOWNSIDES OF CALORIC RESTRICTION

Caloric restriction has been heralded as a fountain of youth.[7681] The near-universal benefits seen in the CALERIE trial support the potential health

and longevity benefits of mild caloric restriction without the downsides seen with more extreme restriction: loss of libido, strength, and bone mass; menstrual irregularities; infertility; cold sensitivity; slower wound healing; blood pressure dropping too low; and psychological conditions such as depression, emotional deadening, and irritability[7682] (not to mention walking around starving all the time).

Two of the most potentially serious pitfalls—impaired wound healing and recovery from infection—could possibly be restored sufficiently by temporarily resuming a full diet in the event of injury or illness. Full wound healing capacity was reestablished in calorically restricted rats[7683] and mice[7684] within days or weeks of full feeding, but the refeeding was done *before* the wounds were inflicted. This could be useful in the case of scheduled surgery but may have limited relevance to spontaneous injury.

One might presume that immune suppression could result from steroid stress hormones released in an underfed state, but, although total fasting can dramatically increase cortisol levels—as much as doubling them within five days[7685]—less severe caloric restriction does not.[7686] Though many indicators of immune function improve during caloric restriction,[7687] this doesn't necessarily translate into improved survival from infection.[7688] Despite an apparent rejuvenation in immune system parameters, when actually put to the test, feeding rodents 20 to 40 percent less than ad libitum intake has been found to have detrimental impacts in fighting bacterial,[7689] viral,[7690] fungal,[7691] and parasitic[7692] infections. Refeeding calorie-restricted mice two weeks before influenza infection improved survival back toward the level of normal-fed mice.[7693] For those without crystal balls, the researchers suggest unrestricting caloric intake before, or perhaps throughout, the flu season.[7694]

One of the most consistent benefits of caloric restriction is improvement in blood pressure in as short as one or two weeks.[7695] Unfortunately, this can work a little too well and cause orthostatic intolerance,[7696] manifesting as light-headedness or dizziness upon standing, which, in severe cases, can cause fainting. Staying hydrated can help.[7697]

What about loss of muscle mass? Unintuitively, caloric restriction appears to actually delay age-related muscle loss in rats and monkeys. Details in see.nf/restrictionpitfalls, but in the CALERIE trial, participants generally got stronger. There was also a small increase in aerobic capacity

in the restricted group compared to control.[7698] Increased protein intakes are commonly suggested to preserve more lean mass, but most studies fail to show a beneficial effect on preserving muscle strength or function, whether young or old, active or sedentary,[7699] and high-protein intake during weight loss has been found to have "profound" negative metabolic effects, undermining the benefits of weight loss on insulin sensitivity. Lose twenty pounds, and you can dramatically improve your body's ability to handle blood sugars, compared to a control group who maintained their weight. Lose the exact same amount of weight but while on a high-protein diet (getting about an extra 30 g a day), and, from a blood sugar control standpoint, it's like you never lost any weight at all.[7700]

Though you can always bulk back up afterward, the best way to preserve muscle mass during weight loss is exercise. Resistance training even just three times a week can prevent more than 90 percent of lean body mass loss during caloric restriction.[7701] The same may be true of bone loss. Lose weight through caloric restriction alone, and you experience a decline in bone mineral density in fracture-risk sites like the hip and spine. However, in the same study, those randomized to lose weight with exercise didn't suffer any bone loss.[7702] It's hard to argue with calls for increased physical activity, but even without an exercise regimen, the "very small" drop in bone mineral density in the CALERIE study might only increase the ten-year risk of osteoporotic fracture by about 0.2 percent.[7703] A high-resolution MRI study of the bones of CRONies found a reduction in bone quantity but not bone quality. The honeycomb-like microarchitectural structure within the bone appeared to be preserved despite the reduction in bone mass.[7704]

Chipping Away at Pollutants?

Body fat may play a protective role by sequestering toxic pollutants, such as PCBs and DDT, which come spilling out when we lose weight.[7705] That's one of the reasons health authorities recommend that women don't try to slim down during breastfeeding.[7706] I cover the ways in which we can protect our vital organs in see.nf/fastingdetox. Eating

Pringles made with the fake fat olestra doesn't seem to help,[7707] but fiber can bind to these pollutants and potentially flush them out of the body.[7708] See see.nf/eatlow for ways to prevent the buildup of industrial toxins in the first place.

MORE FOOD, LESS CALORIES

The bottom line is that the benefits of mild caloric restriction revealed by the CALERIE trial—improved blood pressure, cholesterol, mood, libido, and sleep—would seem to far outweigh any potential risks. The fact that a reduction in calories seemed to have such wide-ranging positive effects led commentators in the American Medical Association's internal medicine journal to write: "The findings of this well-designed study suggest that intake of excess calories is not only a burden to our physical homeostasis but also on our psychological well-being."[7709] This is all the more remarkable given how little they were actually restricting.

By the end of the twenty-four months of the CALERIE trial, the caloric restriction group was eating just one hundred fewer calories a day than the ad libitum control group, a slip in compliance from the two hundred or so fewer calories a day at the end of the first year.[7710] A common refrain from commentators is that all of this benefit can be yours by skipping your daily latte or cutting your muffin du jour in half,[7711] but by switching to healthier foods, you can achieve the same caloric reduction while eating *more* food, not less.

The reason obesity rates among vegans may run as low as 2 to 3 percent[7712] is that those eating more plant-based eat as many as 464 fewer calories a day while eating the same amount of food[7713]—or even more.[7714] That's the beauty of foods with low calorie density: more food, less weight. For an in-depth discussion of caloric density, please see my book *How Not to Diet*.

The founding director of Harvard's center on aging research, David Sinclair, wrote: "After twenty-five years of researching aging and having read thousands of scientific papers, if there is one piece of advice I can offer, one surefire way to stay healthy longer, one thing you can do to maximize your lifespan right now, it's this: eat less."[7715] Eating fewer calories, however, doesn't necessarily mean you need to cut portions. For

example, part of Okinawans' longevity may be because they were only eating about 1,800 calories a day. However, because whole plant foods are so calorically dilute, they were actually eating a greater quantity of food.[7716]

INTERMITTENT FASTING

Rather than cutting calories day in and day out, what if, instead, you just ate as much as you wanted every other day? Or for only a few hours a day? Or what if you fasted two days a week or five days a month? These are all examples of intermittent fasting regimens, and they may even be the way we were built to eat. For millennia, our ancestors often may have consumed only one large meal a day or went several days at a time without food.[7717]

Might intermittent fasting stress our body in a good way, like exercise, through hormesis? Mark Twain thought so: "A little starvation can really do more for the average sick man than can the best medicines and the best doctors. I do not mean a restricted diet; I mean *total abstention from food for one or two days*."[7718] But Twain also said, "Many a small thing has been made large by the right kind of advertising."[7719] Is the craze over intermittent fasting just hype?

I cover all the important studies on alternate-day fasting in see.nf/altdayfasting and 5:2 fasting (eating five days a week) in see.nf/52fmd. The bottom line: There do not appear to be any advantages over chronic daily restriction.[7720] And, as I discuss in see.nf/altdaysafety, the largest and longest trial of alternate-day fasting disturbingly found a significant increase in LDL cholesterol.[7721] One study of postmenopausal women also found that intermittent caloric restriction led to twice the loss of lean body mass compared to weight loss from chronic restriction.[7722] I also caution diabetics[7723] and those on medications,[7724] though concerns about mood, cognition, and eating disorders have been eased. Symptoms of irritability and inability to concentrate on fasting days may wane over time.[7725] And, of eleven interventional studies, although four showed an increase in binge eating, two showed no change and the other five showed decreases in bingeing.[7726]

INTERMITTENT FASTING AND LONGEVITY

Most intermittent fasting studies focus on weight loss. What about life extension? Mormon teachings call for a once-monthly fast when adherents are expected to skip two consecutive meals (thereby fasting about twenty-four hours). Could this play a role in Utah routinely having among the lowest rates of death due to heart disease[7727] and help explain why men active in the Mormon church have tended to live about seven years longer than the U.S. average?[7728]

In a study of a cardiac patient population with a preponderance of Mormons, routine fasters were found to have lower rates of diabetes and severe heart disease.[7729] Does this translate into living longer? About two thousand patients in a medical center in Salt Lake City were followed for four years after cardiac catheterization. About four hundred were routine fasters, adhering to the monthly practice for an average of forty-two consecutive years, about two-thirds of their lives. Did they do better than their nonfasting colleagues? Yes, they had a 46 percent lower risk of dying in the subsequent years of follow-up.[7730]

The obvious confounding would be other tenets of religious observation. Those following Mormon teachings on fasting to the letter might be more likely to follow other doctrines of the church, and indeed routine fasters were significantly less likely to smoke and significantly more likely to be teetotalers. However, both of these factors were taken into account, and the survival benefit remained.[7731] What they didn't control for, though, is diet composition. In addition to monthly fasting, the Mormon church recommends consumption of whole grains, fruits, and vegetables,[7732] with meat only to be eaten "sparingly."[7733] Hence, it's not clear how much of the survival advantage among the fasters was due to the quality of their diets rather than the periodic dips in quantity. The only way to prove cause and effect is to put intermittent fasting to the test, which it was, remarkably, in the 1950s.

Inspired by the data being published on life extension with caloric restriction on lab rats, researchers split 120 residents of a senior home in Madrid into two groups. Sixty residents continued to eat their regular diets, and the other sixty were put on an alternate-day modified fast for three years. Details on the study and its outcomes are in see.nf/fastinglongevity,

but basically, it's held up as evidence that caloric restriction may improve one's healthspan and potentially even one's lifespan, given that there were approximately twice as many deaths and hospitalization days in the control group.[7734] But, as I explain in the video, serious caveats are in order.[7735]

FASTING-MIMICKING DIET

Instead of 5:2, what about 25:5, spending five days a month on a "fasting-mimicking diet"? Longevity researcher Valter Longo designed a five-day meal plan to try to simulate the metabolic effects of fasting by being low in proteins, sugars, and calories with zero animal protein or animal fat. By making it plant-based, he was hoping to lower the level of the cancer-promoting growth hormone IGF-1, related to animal protein consumption, which he accomplished, along with a drop in markers of inflammation, after three cycles of his five-days-a-month program.[7736] Check out see.nf/52fmd for the pros and cons.

Dr. Longo created a company to commercially market his meal plan but says, to his credit, that he donates the profits to his nonprofit research foundation.[7737] The whole diet ("ProLon") appears to be mostly a few dehydrated soup mixes of vegetables, mushrooms, and tomatoes, herbal teas like hibiscus and chamomile, kale chips, nut-based energy bars, an algae-based DHA supplement, and a multivitamin dusted with vegetable powder.[7738] I figure, why spend fifty dollars a day on a few processed snacks when you could instead just eat a few hundred calories a day of real vegetables?

TIME-RESTRICTED EATING AND LONGEVITY

What about fasting a little bit every day? The reason many blood tests are taken after an overnight fast is that meals can tip our systems out of balance, bumping up certain biomarkers for disease, such as blood sugars, insulin, cholesterol, and triglycerides, yet fewer than one in ten Americans may even make it twelve hours a day without eating.[7739] Might it be beneficial to give our body a bigger break?

Time-restricted eating is defined as fasting for periods of at least twelve hours but less than twenty-four.[7740] In see.nf/tre, I present evidence that

early time-restricted eating, a narrow eating window shifted toward the morning, carried a variety of metabolic benefits. For example, as I profile in see.nf/earlytre, those randomized to stick to a six-hour eating window ending before 3:00 p.m. experienced a drop in blood pressures, oxidative stress, and insulin resistance even when all the study subjects were maintained at the same weight. The average drop in blood pressures was extraordinary, from 123 over 82 down to 112 over 72 in just five weeks, comparable to the effectiveness of potent blood pressure drugs.[7741]

As I note in see.nf/earlytre, studies suggest that prolonged nightly fasting with reduced evening food intake may decrease cancer risk and recurrence.[7742] It may even play a role in the health of perhaps the longest-living population in the world, the Seventh-day Adventists in California. Slim, vegetarian, nut-eating, exercising, nonsmoking Adventists live about a decade longer than the general population.[7743] Their greater life expectancy has been ascribed to these healthy lifestyle behaviors, but there's one lesser-known component that may be playing a role. Historically, eating two large meals a day, breakfast and lunch, with a prolonged overnight fast was a part of Adventist teachings. Today, only about one in ten Adventists surveyed was eating just two daily meals, but most (63 percent) reported breakfast or lunch was their largest meal of the day.

A study of older Italians found that those who had a food window that was narrower than ten hours a day had 72 percent lower odds of suffering from cognitive impairment. However, this was limited to those practicing early time-restricted feeding (i.e., not skipping breakfast). In general, shifting food intake toward the morning—eating breakfast like a king, lunch like a prince, and dinner like a pauper or skipped entirely—has beneficial cardiometabolic effects, whereas the same eating window pushed toward the evening (skipping breakfast) can have null or negative effects.[7744]

DON'T TRY THIS AT HOME

What about periodic longer fasts? Proponents speak of fasting as a cleansing process, but some of what they are purging from their body are essential vitamins and minerals.[7745] In see.nf/fastingsafety, I cover the very real risks of prolonged fasts. Contrary to the popular notion that the heart

muscle is specially spared during fasting, the heart appears to experience similar muscle wasting.[7746] Breaking the fast appears to be the most dangerous part.[7747] After World War II, as many as one in five starved Japanese prisoners of war tragically died following liberation.[7748] Now known as "refeeding syndrome," multiorgan system failure can result from resuming a regular diet too quickly.[7749]

Medically supervised fasting has gotten much safer now that there are proper refeeding protocols, we know what warning signs to look for, and we know who shouldn't be fasting in the first place,[7750] such as those with advanced liver or kidney failure, porphyria, uncontrolled hyperthyroidism, and pregnant and breastfeeding women.[7751] Fasting for longer than twenty-four hours and particularly for three or more days should only be done under the supervision of a physician and preferably in a live-in clinic. This is not just legalistic mumbo jumbo. For example, your kidneys normally dive into sodium conservation mode during fasting, but should that response break down, you could rapidly develop an electrolyte abnormality that may only manifest with nonspecific symptoms, like fatigue or dizziness, which could be easily dismissed until it's too late.[7752]

Fasting for Cancer Treatment

Short-term fasting before and immediately after cancer treatment can minimize side effects while, at the same time, may actually make cancer cells more susceptible.[7753] I review the preclinical studies in see.nf/fastingcancer, including experiments showing how fasting can mean the difference between 100 percent of animals dying versus 100 percent surviving.[7754]

In see.nf/fastingchemo, I run through the clinical trials. Water-only fasting for a total of seventy-two hours before and after chemo appeared to reduce the toxicity of treatment[7755] without detectable harm.[7756] Fasting-mimicking diets have also been tested.

In the DIRECT trial (DIetary REstriction as an Adjunct to Neoadjuvant ChemoTherapy), more than one hundred

breast cancer patients were randomized to the same sort of plant-based, low-calorie, low-protein, and low-carbohydrate fasting-mimicking diet (FMD) of mostly soup, teas, and broth for three days before, and the day of, each chemotherapy cycle. Unfortunately, there was no difference in quality of life or chemo side effects between those randomized to the FMD or those in the regular diet control group. However, a per-protocol analysis did find benefits, meaning that if you took compliance into account and only counted those who actually followed the instructions and stuck to the FMD, they did significantly better across a range of emotional and physical function scores. Isn't that what we care about—what happens when you actually do it? The problem with per-protocol analyses is that we lose the bias-busting power of randomization. For example, maybe people who felt better in the first place were more likely to stick to the program.[7757]

Quality of life aside, did the FMD make the chemo work any better? Fasting-mimicking diets appear to help control cancer in mice, and a series of promising human case reports have been published,[7758] but what happened in the DIRECT trial where it was actually put to the test? There was no significant difference in the most important measure: complete response rate, the disappearance of all signs of cancer from the body. (That occurred in about 11 percent of cases in the FMD group versus 13 percent in the control group.) There was, however, three times the rate of radiological evidence of tumor shrinkage on MRI or ultrasound in the FMD group,[7759] though the impact of this on long-term outcomes is uncertain.[7760] In the per-protocol analysis, there was also an improvement in pathological response (the disappearance of cancer cells in surgical specimens), though, as with any per-protocol analysis, this carries the potential for selection bias.[7761] The lack of more robust evidence of benefit has been blamed on the lack of compliance with the FMD regimen, which was attributed

mainly to the dislike of certain prepackaged components. A suggestion was made that future trials consider incorporating fresh foods.[7762]

LOWERING IGF-1 WITH DIETARY RESTRICTION

Is there anything we can tweak in our diet to get similar benefits without having to fast? As I elaborate in see.nf/fmdcancer, one of the ways fasting works is by reducing the levels of the cancer-promoting growth hormone insulin-like growth factor 1[7763] (see the IGF-1 chapter). Reduced levels of IGF-1 appear to mediate the differential protection of normal versus cancer cells in response to fasting because restoration of IGF-1 can be sufficient to reverse the protective effects.[7764] Add chemo to various types of cancer in a petri dish, and half or more of the cancer cells can be wiped out.[7765] Under starvation conditions, the same dose of chemo can wipe out about twice as many cancer cells in a petri dish, but this effect vanishes when IGF-1 is added back to the mix.

The downregulation of IGF-1 through fasting is conceptualized as a way of "turning anti-ageing genes against cancer."[7766] If you remember, the lowering of IGF-1 levels, genetically or otherwise, can lead to a significantly longer lifespan. But fasting isn't the only way to drop IGF-1. Yes, a few days of fasting can cut levels in half,[7767] but that's largely because you're cutting your protein intake. Protein intake is considered a key determinant of circulating IGF-1 levels in humans, suggesting that some of the anticancer and anti-aging benefits of eating less food could be captured by just eating less protein.[7768]

In rodents, caloric restriction alone can reduce IGF-1, but in people, just cutting down on food in general isn't enough.[7769] For example, in the CALERIE trial, two years of caloric restriction didn't lower IGF-1 compared to the control group. This isn't surprising, since there was no concomitant drop in protein intake.[7770] Even severe caloric restriction doesn't decrease IGF-1 levels unless protein intake is also reduced.[7771]

CRONies practicing about a 30 percent caloric restriction for an average of six years had IGF-1 levels similar to those eating a full standard American diet. Again, no surprise, as the CRONies were eating 1.7 g per kg of protein a day, twice the recommended dietary allowance (RDA) of 0.8

g/kg. In contrast, a group of vegans eating right around the RDA for protein had about 25 percent lower IGF-1 levels in their blood. This was assumed to be due to the protein difference, since interventional trials show increasing protein intake increases IGF-1,[7772] but how can we be sure it's not some other factor? By putting it to the test. And indeed, when CRONies eating 1.7 g/kg of protein dropped their intake to 1 g/kg or less, within three weeks their IGF-1 dropped by 25 percent, on par with the vegans.[7773]

PROTEIN RESTRICTION

Reducing protein intake would seem to be a more feasible lifelong strategy than serious long-term caloric restriction,[7774] but the relative contribution of protein restriction to the overall longevity benefits of caloric restriction is controversial. In insects, the life extension from restricting overall food intake appears to be wholly a protein reduction phenomenon,[7775] but in mammals, the data appear to be mixed. There is a body of evidence that suggests that protein restriction alone accounts for approximately half of the life-extending effects of caloric restriction—a 20 percent average increase in maximum lifespan of rodents compared to about 40 percent with caloric restriction.[7776] At the same time, there are rodent studies showing lifespan extension with dietary restriction that appears independent of protein intake—nearly identical longevity from cutting food intake by 40 percent whether or not protein intake is held steady.[7777] More recently, the pendulum has swung in the other direction, suggesting that all the lifespan benefits of caloric restriction derive from the drop in protein intake.[7778] In this chapter, I'll explore how can we account for these discrepancies and what implications this has for human longevity.

FGF21

In the year 2000, a new human hormone was discovered. It was the twenty-first documented fibroblast growth factor, so it was named FGF21.[7779] Since its discovery, it has emerged as a key agent for promotion of metabolic and artery health, leanness, and longevity.[7780] Inject FGF21 into fat monkeys, and they lose body weight without reducing food intake, and not just a little

—a 27 percent drop in body fat eating the same amount.[7781] In mice, it increases their lifespan by 30 to 40 percent, comparable to lifelong caloric restriction, but achieved without decreasing food intake.[7782] FGF21 appears to act through multiple aging pathways, boosting AMPK and sirtuin activity,[7783] while inhibiting IGF-1 and mTOR signaling. The thought that FGF21 could potentially be used as a hormone therapy to extend lifespan got Big Pharma salivating,[7784] raising the question, "Can aging be 'drugged'?"[7785]

The idea that one drug could treat obesity, diabetes, and hypertension, all the while slowing aging, might have seemed impossible but suddenly became a tantalizing prospect.[7786] The reason you can't just give people straight FGF21 is that it gets rapidly broken down in the body, so you'd have to get injections every hour or two around the clock.[7787] So, drug companies started to patent a variety of longer-acting FGF21 look-alikes.[7788] And indeed, give people some PF-05231023, and they can lose about ten pounds in twenty-five days, along with dramatic drops in triglycerides and cholesterol.[7789] But then the side effects of these newfangled drugs start cropping up.[7790] What about packaging the FGF21 gene into a virus, then injecting the virus and having it stitch extra FGF21 genes into your DNA?[7791] Or you can just lace up your running shoes.[7792]

EXERCISE AND FASTING TO BOOST FGF21

Exercise boosts FGF21 levels, which may in fact be one of the reasons it's so good for us.[7793] Circulating FGF21 rises immediately after a bout of exercise, peaking an hour afterward and returning to baseline within three hours.[7794] Which works better, though? Aerobic exercise (eight weeks of running training) or resistance exercise (eight weeks of lifting weights)? The answer is both, but the resistance exercise edged out the running, a 42 percent increase in FGF21 versus a 25 percent increase, respectively.[7795]

What can we do with diet? Rather than gene editing or injections, wouldn't it be easier to just stimulate our own endogenous, natural production through diet?[7796] One way is through no diet at all.[7797] FGF21 is known both as the "pro-longevity hormone" and the "starvation hormone."[7798] Fasting induces FGF21, but not just a day or two without food.[7799] Unlike mice, which show an increase after only six hours of

fasting, humans don't get a notable surge in FGF21 until after a week. Fasting can quadruple FGF21, but that takes ten days of fasting, which is the very poster child of an unsustainable eating pattern.[7800]

HOW TO BOOST FGF21 WITH DIET

How can we get the benefits of fasting without the starvation? Might a ketogenic diet be able to mimic the fast?[7801] In rodents, keto diets raise FGF21 levels,[7802] but in people, they don't work.[7803] In fact, FGF21 levels may drop by 40 percent after one[7804] to three[7805] months on a ketogenic diet. High-fat diets may even interfere with the boost you get from exercise, as demonstrated in a twelve-week study of high-intensity interval training.[7806] Thankfully, the starvation hormone, characterized as a "systemic enhancer of longevity," can be raised by less drastic measures than a prolonged fast:[7807] by eating more carbs and less protein.[7808]

Even without reducing protein intake, FGF21 levels shoot up when people are fed lots of starchy foods.[7809] The healthiest sources would likely be legumes and intact whole grains.[7810] FGF21 is bumped up by butyrate, the short-chain fatty acid our good gut flora make from fiber,[7811] as well as the starch-blocking drug acarbose (at least in mice).[7812] This suggests slow-digesting starches, such as pasta, beans, and intact grains, could have a similar "pro-longevity" effect.[7813]

Circulating FGF21 levels are also "rapidly and robustly" induced by dietary protein restriction. Researchers saw a more than 150 percent increase in FGF21 within four weeks, even in the context of overeating calories.[7814] And the "protein restriction" was just restricting protein intake from the typical excess that most Americans get down close to the recommended amount.

The recommended dietary allowance for protein is around 50 g a day (46 g for women, 56 g for men).[7815] The researchers took men who were averaging twice that—112 g, which is about the average of what many American men get[7816]—and randomized them down to 64 g of protein a day. So, the "protein-restricted" group was still getting more than enough protein. Do that, and you can essentially double FGF21 levels in the blood within about six weeks.[7817] That may help explain why, despite them getting significantly more calories,[7818] they lost more body fat.[7819] How can you eat

hundreds more calories a day and still lose two more pounds of straight body fat? By just bringing your protein levels down to recommended levels. Who hasn't fantasized about a diet that allows ingestion of excess calories that are burned off effortlessly by ramping up fat burning?[7820] The researchers concluded that "even a quite modest PR [protein restriction] regimen may have significant clinical benefits."[7821]

A similar study found that even less protein restriction, taking men down to 73 g a day, resulted in a sixfold increase in FGF21 within a single week, accompanied by a significant increase in insulin sensitivity. The researchers concluded that "dietary protein dilution" promotes metabolic health in humans.[7822] Switching men and women from a high-protein diet of 138 g per day down to a more than adequate 67 g[7823] also multiplied FGF21 levels in the blood sixfold, but within just four days.[7824]

FGF21 may help explain the mounting evidence suggesting that a lower protein intake is associated with increased health and survival.[7825] Interestingly, both studies were feeding people about 9 percent of calories from protein, which is what the Okinawans were getting when they were among the longest-living populations in the world.[7826] However, not all proteins are the same.

ANIMAL PROTEIN VS. PLANT PROTEIN

Some proteins may be more important to restrict than others. FGF21 is considered to be the most important mediator of the metabolic health benefits of restricting the amino acid methionine.[7827] As we know, amino acids are the building blocks of proteins. There are about twenty different kinds of them,[7828] similar to the number of letters in the alphabet. Just as different sentences can be made from different combinations of letters, different proteins are made from stringing together different sequences of the various amino acids. Since methionine is one such amino acid, found predominantly in animal proteins,[7829] we could potentially boost FGF21 levels by lowering methionine intake even without changing overall protein consumption just by switching from animal to plant sources. Legumes (beans, split peas, chickpeas, and lentils) deliver as much as five to ten times less methionine than meat.[7830] (See the chart here.)

FGF21 has been proposed as an explanation for the protection from cancer, autoimmune diseases, obesity, and diabetes afforded by vegan diets.[7831] Maybe that's one of the reasons plant-based interventions have yielded such extraordinary results. Take Dr. Esselstyn's work, for example, suggesting that heart disease, our number one killer, can largely be halted or reversed, and risk for heart attack almost eliminated, with the help of a whole food, low-fat, plant-based diet. This benefit cannot be attributed solely to cholesterol reduction, as we now have powerful drugs that can force cholesterol levels as low as healthy eating can, but the pills appear to have far less effect. So, maybe it's not just the fat and cholesterol but the quantity and quality of protein playing a role.[7832]

Harvard School of Public Health researchers proposed the "protein package" explanation for why plant protein sources are preferable to animal protein sources.[7833] Food is, after all, a package deal, so why get your protein prepackaged with saturated fat and cholesterol when you can get it with fiber and phytonutrients instead? But FGF21 presents a reason why the plant protein itself may be healthier. The theory was first proposed in 2015,[7834] but the first testing of vegan FGF21 levels wasn't published until 2019.[7835]

FGF21 levels were found to be markedly higher in those eating plant-based.[7836] To prove cause and effect, omnivores were switched to a vegetarian diet and the FGF21 levels in their blood shot up by more than 200 percent after just four days free of meat. The bottom line? A major review out of NIH's National Institute on Aging and the USC Longevity Institute published on the clinical applications of fasting concluded that "various fasting approaches are likely to have limited efficacy, particularly on aging and conditions other than obesity, unless combined with high-nourishment diets such as the moderate calorie intake and mostly plant-based Mediterranean or Okinawa low-protein diets.…" The researchers specified that by "low protein" they meant 0.8 g of protein per kg of body weight, which is, rather, the recommended daily intake.[7837]

HOW TO LOWER IGF-1 WITH DIET

In mice, protein restriction not only increases lifespan but reduces frailty and improves physical performance later in life. FGF21 is suspected to

mediate these benefits because all the anti-aging effects of protein restriction disappear in mice engineered to be unable to express FGF21.[7838] In people, other aging pathways may be involved. Diets with excess protein may be associated with increased oxidative stress[7839] and inflammation, as well as lower levels of NAD^+, which is critical for sirtuin function.[7840] Reducing protein intake can also reduce blood levels of IGF-1.

Low IGF-1 levels predict survival in people with exceptional longevity.[7841] Remember from here how age-related pathologies like cancer were practically absent in those born with lifelong low IGF-1?[7842] IGF-1 appears to mediate the benefits of fasting for cancer,[7843] and its reduction with fasting is what causes the differential protection of normal cells and cancer cells, improving chemo's ability to kill cancer but spare normal cells. We know this because restoration of IGF-1 was sufficient to reverse fasting's protective effects.[7844] Starved cancer cells are more vulnerable to chemo in vitro, but this effect vanishes if the diminished IGF-1 is added back to the petri dish.[7845]

A few days of fasting can cut IGF-1 levels in half,[7846] but that's largely because you're cutting your protein intake.[7847] A key determinant of circulating IGF-1 levels in humans is protein, particularly animal protein. Women[7848] and men[7849] eating strictly plant-based diets have significantly lower IGF-1 levels compared to those eating typical diets, including those who are comparatively slim (long-distance endurance runners).[7850] It's not because they're eating fewer calories, because, when it comes to lower IGF-1 levels, those eating plant-based also beat out CRONies, the members of the Calorie Restriction Society intentionally eating even fewer calories in an attempt to live longer whom I mentioned earlier.

In mice, caloric restriction alone lowers IGF-1,[7851] but people require protein reduction. The IGF-1 levels of practitioners of serious, long-term caloric restriction remain elevated. As I noted before, the reason we suspect it's the protein is, if you take such practitioners and have them cut their protein intake from 1.67 g/kg down to 0.95 g/kg a day, IGF-1 levels drop more than 20 percent within three weeks. IGF-1 is presented as the reason reduced protein intake may represent an important component of anti-aging and anticancer diets.[7852]

Potential Downside of IGF-1 Lowering

For at least twenty years, whole food, plant-based diets have been advocated for slowing the human aging process by way of lowering IGF-1.[7853] IGF-1 also appears causally linked to cancer,[7854] heart disease, diabetes,[7855] and osteoarthritis, so it may help account for a panoply of plant-based perks.[7856] Those born with lower lifetime IGF-1 also have enhanced cognitive performance.[7857] However, as I detail in see.nf/igf1bp, there may be a downside of IGF-1 lowering among those with high blood pressure.[7858] So, those cutting down on animal protein should be particularly mindful of their blood pressure by reducing processed foods and added salt, while ensuring an ample supply of potassium-rich foods, such as beans, sweet potatoes, and dark green leafy vegetables.[7859]

PROTEIN RESTRICTION

Evidence that protein restriction extends lifespan[7860] actually predates the evidence from studies using caloric restriction.[7861] Data on the relative importance of protein versus caloric restriction are mixed,[7862] but a comprehensive comparative meta-analysis of dietary restriction of more than a hundred studies across dozens of species found that when it comes to life extension, protein reduction was more important.[7863] Sometimes it's hard to tease out, though. For example, when studies find that mice restricted to 70 percent of what they'd normally eat live longer, this may be chalked up to caloric restriction, even though protein was cut by the same amount. On the other hand, "protein restriction" studies in which mice are given all-they-can-eat low-protein chow may fail to show benefits because the mice eat more food to compensate, so they don't end up cutting their protein after all.[7864]

The most impressive study to date tried to control for these factors by randomizing nearly a thousand mice to one of twenty-five different diets systematically differing in protein, carbohydrate, fat, and calorie content.

They found that the diets with the lowest protein-to-carbohydrate ratios yielded the longest maximum lifespans independent of calories.[7865] Markers of late-life health, including improved blood pressure, cholesterol, mitochondrial function, insulin sensitivity,[7866] and immune function were also best on the low-protein diets and worst on the high-protein or high-fat diets.[7867] Low-protein, high-carbohydrate diets are able to generate the metabolic[7868] and immunity[7869] benefits of up to a 40 percent caloric restriction without restricting calories at all. As the protein levels dropped, average lifespan increased from about 95 weeks to 125 weeks, an approximate 30 percent increase in lifespan even at the same caloric intake.[7870]

The restriction of protein, not calories, was found to be driving the survival effect.[7871] In fact, researchers discovered that only restricting calories appeared to *shorten* lifespans.[7872] How can we square that with past studies with the same mouse strain that found the opposite?[7873] The new twenty-five-diets mega-study used a novel method for restricting calories. The researchers designed all the diets ad libitum. How can you restrict calories if the animals can eat all they want? The calorie-restriction diet was bulked up with indigestible cellulose (basically sawdust) such that even when the mice gorged themselves, they would still be left with a 30 percent calorie deficit.[7874] Yet, despite the caloric restriction, they lived shorter, not longer, lives.[7875]

How do we explain same calories, different effects? Maybe the customary caloric restriction effect is really more of an intermittent fasting effect.[7876] Unlike the cellulose dilution diet where the mice can eat anytime they want, if you just underfeed mice by giving them a fraction of what they'd normally eat, then once they finish their daily ration, they are effectively fasting until the next day. Might the conventional benefits instead be due to hunger signal pathways in the brain you might get from dietary restriction but perhaps not from dietary dilution?[7877] Or maybe traditional caloric restriction cuts protein, too, and that's the real driver of longevity.[7878]

One potential caveat that arose from these series of experiments involves the "protein leverage" effect. On low-protein diets, the mice tended to overeat to try to compensate, so they were in effect eating more calories and still living longer.[7879] Obesity was prevented by feeding them

high-fiber diets,[7880] but you can imagine how you wouldn't be doing your body any favors if your idea of a low-protein diet is one filled with ultraprocessed junk like SnackWell's cookies. Indeed, low-protein longevity is undercut in mice fed diets high in refined carbs.[7881] In humans, any negative effects of protein leverage[7882] may be countered by eating whole plant-based foods.[7883]

ANIMAL PROTEIN VS. PLANT PROTEIN

The optimum ratio of protein to carbohydrates across species for lifespan appears to be about one to ten,[7884] which is remarkably similar to the Okinawan ratio.[7885] The traditional Okinawan diet was 9 percent protein and 85 percent carbohydrates (mostly from sweet potatoes, if you recall).[7886] Before they westernized their diets, they had among the highest numbers of centenarians in the world, with 80 percent lower rates of common cancers[7887] and five times lower mortality rates from a variety of age-related diseases in general.[7888] Some have suggested this was due to their relative caloric restriction, consuming about 20 percent fewer net calories than Americans,[7889] but they were also consuming about 50 percent less protein.[7890]

In animal studies, the shortest lifespans were among those fed high-protein diets.[7891] This is consistent with a meta-analysis of prospective human cohort studies showing that higher total protein intake is associated with higher all-cause mortality rates.[7892] But that's because most protein eaten in the Western world comes from animal sources.[7893] The higher the animal protein intake, the higher the mortality rates, whereas the higher the plant protein intake, the lower the mortality rates.[7894]

There is some evidence that those over age sixty-five could benefit from slightly higher protein intakes[7895]—for example, 1.0 g per kg of body weight instead of 0.8 g/kg,[7896] which is still less than what most older Americans get.[7897] However, longevity experts suggest that this should be from plant-based sources to prevent excess IGF-1 activation.[7898] As I mentioned, the NIH-AARP study, based on more than six million person-years of observation, found that swapping just 3 percent of calories from animal protein to plant protein was associated with 10 percent decreased overall mortality in both men and women.[7899] Not all such studies showed this

effect,[7900] but a meta-analysis of thirty-two such prospective cohort studies following people for up to thirty-two years found that, overall, as little as a 3 percent increase in plant protein was associated with significantly lower risk of dying from all causes put together.[7901]

Significant improvements in healthspan appear to be achievable by even just a 1 percent animal-to-plant swap. A study of unhealthy aging used a "deficit accumulation index," tracking more than fifty different functional impairments, measures of self-reported health and vitality, mental health indicators, chronic diseases, and needs of health services. Those who increased their plant protein by even 1 percent at the expense of animal protein (a swap of only about 5 g a day) accumulated significantly fewer deficits over a period of eight years.[7902] In the Women's Health Initiative, which followed 100,000 older women for eighteen years, a 5 percent animal-to-plant protein swap was associated with about a 20 percent drop in the risk of dying from perhaps the biggest deficit of all, dementia.[7903] One study even found that swapping out a single serving *a week* of unhealthy protein sources, like eggs, for a healthy source like nuts or whole grains, would hypothetically extend your lifespan.[7904] A 2022 meta-analysis on plant versus animal protein substitutions concluded their findings suggested "introducing plant protein-rich sources to replace animal proteins to prevent aging-related diseases, and promote longevity and healthy aging."[7905]

Even more distinct than the caloric or protein restriction in the Okinawan Japanese was the skew toward plant sources. Animal products constituted less than 1 percent of their traditional diet, the equivalent of one serving of fish a week, other meats once a month, one egg about every two months, and practically no dairy.[7906] As we've discussed, the only formally studied population with a longer life expectancy didn't eat a 99 percent meat-free diet, but rather 100 percent meat-free, the California Adventist vegetarians,[7907] even though they were eating 30 percent over the RDA for protein.[7908] As a review on the impact of protein intake on longevity concluded, the protein source may be more important than the overall level of protein intake,[7909] though, at high enough protein intake, IGF-1 levels may not drop even with a switch to mostly plant-based sources.[7910]

What about randomizing people to a switch from animal to plant sources of protein and also a drop in overall protein intake? Sixteen weeks later, the lower-protein plant-based group lost about ten pounds of straight body fat,

including hundreds of cubic centimeters of visceral fat, the dangerous deep belly fat, and experienced a significant decrease in insulin resistance.[7911] In *Ageing Research Reviews*, this study was characterized as suggesting that a decrease in animal protein "may be pivotal in improving metabolic health and aging," but given the concordant drop in animal fat as well, it's hard to tease out the primary driver of metabolic improvements.[7912]

Cancer Restriction via Protein Restriction

T. Colin Campbell and colleagues showed nearly a half century ago that rats on a 5 percent casein (milk protein) diet developed 75 percent fewer precancerous lesions in response to a carcinogen compared to rats fed a 20 percent casein diet.[7913] Protein reduction can extend the lifespans of mice by about 30 percent,[7914] but cancer accounts for more than 90 percent of deaths of common inbred strains of laboratory mice. Given the outsized impact of protein reduction on cancer, we wouldn't expect the same life extension in people, who die more often from heart disease.[7915]

Human cancers show a similar response when transplanted into mice fed different diets. Human breast and prostate tumors show a 56 to 70 percent reduction in cancer growth rates in mice switched from 21 percent of calories from protein down to 7 percent. Even at the higher protein intake, just switching from animal protein to plant protein can decrease tumor weights by 37 percent, though, at the low protein intake, source didn't seem to matter.[7916]

The decrease in tumor size from protein reduction was presumed to be due to a drop in cancer growth fueled by IGF-1,[7917] but low-protein diets were also found to stimulate the targeted killing of cancer cells by the immune system, increasing tumor infiltration by lymphocytes[7918] and enhancing the "tumoricidal capacity" of macrophages.[7919] Low-protein diets can also cause shrinkage of tumors in

immune-deficient mice, suggesting it's a combination of factors.[7920] Even just limiting a single amino acid, methionine, can also slow the growth of cancerous tumors.[7921]

METHIONINE RESTRICTION

Just as many of the benefits of dietary restriction can be replicated simply by restricting protein,[7922] most of the benefits of protein restriction may be due to the reduction of just a few of the amino acids that make up proteins, for example, methionine.[7923] Methionine is the only amino acid that strongly correlates with maximum lifespan across mammals, such that the more methionine in body tissues, the shorter the animal lives. ($r = -0.96$ for the stat nerds out there.) The hearts of guinea pigs have about 40 percent more methionine than the hearts of rabbits, which can live about 40 percent longer.[7924] Mice have threefold higher methionine levels than naked mole rats,[7925] which can live seven times longer.[7926] To prove cause and effect, you'd have to show that lowering methionine levels actually prolongs lifespan, and indeed methionine restriction does just that.

Simply restricting that one amino acid can increase the maximum lifespan of rats by up to 44 percent,[7927] more than one tends to see with caloric restriction.[7928] Methionine restriction also prolongs the maximum lifespan of mice, as well as improving stress resistance,[7929] decreasing visceral fat,[7930] and slowing aging of the eyes and immune system.[7931] The exact mechanisms by which reducing dietary methionine leads to slower aging are not known,[7932] but methionine restriction boosts FGF21,[7933] induces autophagy,[7934] and reduces inflammation[7935] and IGF-1.[7936] The IGF-1 pathway may be critical, as mice with growth hormone signaling defects don't respond to methionine restriction,[7937] but there are other possibilities.

In studies in which animals are fed excess amounts of different amino acids, methionine has consistently been found to be the single most toxic one.[7938] This may be because methionine has a pro-oxidant effect.[7939] Supplementing rodent diets with extra methionine results in a spike in oxidative stress markers in their blood[7940] and a depletion of tissue antioxidants.[7941] Conversely, reducing methionine intake profoundly reduces mitochondrial free radical generation and oxidative damage to

mitochondrial DNA,[7942] consistent with the mitochondrial theory of aging (see here), the only amino acid ever shown to do so. Even restricting every other amino acid except for methionine fails to reproduce this effect.[7943]

Of all the amino acids, methionine is also one of the most vulnerable to oxidation.[7944] When it becomes oxidized while incorporated into a protein, that may lead to the loss of protein function.[7945] Thankfully, there's an enzyme—*methionine sulfoxide reductase*—that repairs this damage to protect cells against methionine-related oxidative damage.[7946] Genetically engineering animals to overexpress just this methionine detox enzyme alone was shown to markedly extend longevity.[7947]

Mild restriction of protein synthesis has been shown to rejuvenate senescent cells, enabling "zombie" cells to start growing again. This was demonstrated in vitro using a drug called cycloheximide, which blocks a final translation step of protein formation. The researchers conclude, "It is desirable to find a substitute for cycloheximide … to exert a holistic health promoting effect, to reduce excess or unnecessary protein synthesis.…"[7948] This same effect may be had by methionine restriction, because methionine acts as the starting code for the translation of most proteins.[7949] Indeed, reducing the methionine concentration in a cell culture medium can result in a 60[7950] to 75 percent[7951] increase in the replicative lifespan of human cells (the Hayflick limit, the number of times a cell can double before becoming senescent—see here). Methionine-restricted cells are also significantly better at robustly resisting various stressors, including heat, radiation, carcinogens, and free radicals.[7952]

HOW TO LOWER METHIONINE INTAKE

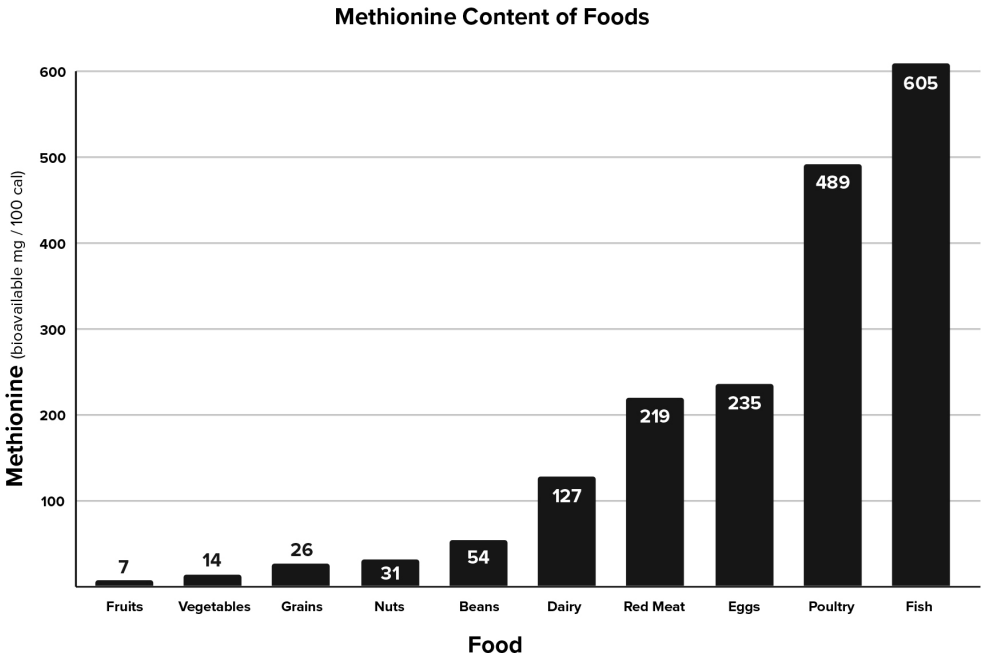
Pharmaceutical companies are fighting to be the first to come out with a drug that decreases methionine levels[7953]—methionine-munching enzymes to give to patients with advanced cancer, for example.[7954] But, since methionine is sourced mainly from food, a better strategy may be to lower methionine levels by lowering methionine intake.[7955] There are three ways to accomplish this. The first is caloric restriction—by decreasing your intake of food in general, you reduce your intake of methionine. The purported pro-longevity benefits of alternate-day fasting,[7956] for instance, have been ascribed to the periodic depletion of the "pro-aging amino-acid

methionine."[7957] Second, since methionine is in protein, instead of reducing food intake across the board, you could just cut down on protein. Simply reducing protein intake from present excessive levels down to the recommended intake is expected to offer a large potential for health benefit.[7958] Third, even keeping portions and protein consumption the same, methionine restriction could be accomplished by switching from animal to plant protein sources, which tend to be relatively low in methionine. To achieve methionine restriction, a review on the impact of dietary protein intake on health and longevity concluded that individuals may need to "eat less animal-based food."[7959]

Termed the Hoffman effect, one of the universal hallmarks of cancer is "methionine addiction."[7960] The methionine dependency of cancer cells has led to attempts to feed cancer patients a methionine-free "amino acid–modified medical food powder." Made mostly out of corn syrup, oil, and all the other amino acids, it is meant to crowd out methionine sources in the daily diet.[7961] The problem is that it's considered "not palatable," so few people stick with it.[7962] Failed compliance with these oily corn syrup concoctions has led researchers to conclude it is "necessary to develop palatable foods in which methionine has been selectively removed." We already have them. They're called fruits and vegetables.

WHERE IS METHIONINE FOUND?

Plant-based diets may "make methionine restriction feasible as a life extension strategy."[7963] Here's a graph comparing bioavailable methionine levels in common representative plant and animal foods:[7964,7965,7966]



As you can see, fish and poultry tend to have the highest levels of methionine. I used canned tuna as the representative fish, but a hundred calories of fish such as haddock, halibut, or roughy can deliver even worse levels, up to 709 mg. The lowest seafood levels are found in oysters, with levels as low as 92. For poultry, I graphed grilled chicken breast, though roasted chicken breast can reach 587.

Dairy, red meat, and eggs have less. I used hard-boiled eggs, but a whites-only omelet could top the charts at 714. I used ground beef as the representative red meat, but pork and lamb can go as high as 509 and 564, respectively (though blood sausage dips as low as 49). I used milk for dairy in the graph, though a dairy product like butter has nearly none, since it's almost all fat. In contrast, high-protein dairy foods like low-fat cottage cheese can go as high as 482.

The lowest methionine foods tend to be fruits, nuts, veggies, grains, and beans. I used canned chickpeas, but all the other beans have similar amounts, even the "methionine-rich" legume,[7967] the kidney bean, at 65. Only when plant protein is concentrated into a food like tofu can you get up around 114. For grains, I used whole-wheat bread, but teff, the most methionine-rich grain, has 99, followed by quinoa with 64. For nuts, I used mixed nuts. Most nuts are similar, with the exception of Brazil nuts at 136. Hemp seeds are also high (135). For vegetables, I used carrots. Spinach is

surprisingly high at 184, but it's so low-calorie that you'd have to eat about fifteen cups to get a hundred calories. Kale is lower, at 66 for fourteen cups. I used bananas for fruit, but even oranges, the common fruit highest in methionine, average only 34.

ACHIEVABLE METHIONINE RESTRICTION

The bottom line: A review on methionine restriction for life extension concluded, "In humans, methionine restriction may be achieved using a predominately vegan diet."[7968] Even at the same protein intake, vegetarians may consume as much as 36 percent less methionine.[7969] Given the methionine concentration of eggs and dairy, though, only vegans end up with significantly lower methionine levels in their bloodstream.[7970]

Although it may take an 80 percent reduction in methionine intake to maximize metabolic benefits in mice, a 40 percent methionine restriction was found sufficient to decrease mitochondrial free radical generation and oxidative damage to mitochondrial DNA.[7971,7972] On average, vegans consume 47 percent less methionine than meat eaters.[7973] Perhaps this helps explain some of the health benefits attributed to plant-based diets.[7974] For example, short-term methionine deprivation can slim 60 percent of the fat mass off obese mice within two weeks, despite increased caloric intake and decreased physical activity[7975] (by apparently activating a "futile cycle" of simultaneous fat formation and consumption[7976]).

So, maybe methionine reduction helps explain why vegans are forty pounds lighter on average than those who eat conventional diets.[7977] Even vegans at the same weight as typical omnivores appear to have less than half the risk of diabetes,[7978] consistent with a 2022 analysis that followed about 15,000 U.S. adults for seventeen years and found that those who ate the most methionine had more than twice the risk of dying from diabetes.[7979]

On average, American women effectively consume twice as much methionine as they need and American men three times as much.[7980] Given the cardiometabolic risk associated with higher intake, public health researchers suggest that the optimum intake may be down around the recommended intake.[7981] So, just as I'm not advocating for a low-protein diet but rather a diet with the recommended amount, one need not eat a low-methionine diet but rather just one without *excess* methionine. Given what

we now know, simply decreasing intake to recommended levels "has a great potential to lower tissue oxidative stress and to increase healthy life span in humans…."[7982]

Cysteine and Glycine

Much of the methionine we eat is converted into another amino acid within the body, called *cysteine*.[7983] Given that the provision of extra cysteine to methionine-restricted animals reverses some of the benefit, cysteine might be responsible for some of methionine's dirty work.[7984] While cysteine may be a partner in crime, the amino acid *glycine* is used by the body to aid in clearance of methionine from the system.[7985] I go into detail on both in see.nf/cysteineglycine. The bottom line is that you get more glycine in your bloodstream the same way you get less methionine and cysteine: by eating more plant-based.[7986,7987]

BRANCHED-CHAIN AMINO ACIDS

The effects of protein restriction can't be completely replicated with methionine restriction alone, since the dietary restriction of all amino acids except methionine continues to have a range of beneficial effects, such as a reduction in free radical production and oxidative DNA damage.[7988] Also to blame may be the three branched-chain amino acids (BCAA)—isoleucine, leucine, and valine.

In the twenty-five-diets mega-study, health and longevity consequences negatively correlated with BCAA levels in the blood, such that the lowest amounts were associated with the longest, healthiest lives.[7989] Interventional studies show that high-BCAA diets shorten mouse lifespans,[7990] whereas BCAA restriction increases the lifespan and delays age-related frailty in fruit flies[7991] and mice.[7992] The researchers suggest "limiting dietary levels of BCAAs may be a key to a long and healthy life."[7993]

This makes sense since BCAAs are potent activators of the engine-of-aging enzyme mTOR,[7994] which I explored in Part I. Reducing mTOR

signaling is considered "critical for improved health and lifespan,"[7995] as mTOR suppression is a "robust molecular transducer of diet-induced antiaging signals."[7996] Lower BCAA intake may help explain not only Okinawan longevity but why a disease like acne was rare or even nonexistent,[7997] as pimples are considered a visual manifestation of elevated mTOR activity.[7998] Insight into potential cognitive effects comes from maple syrup urine disease.

The irreversible breakdown of branched-chain amino acids is tightly regulated within the body.[7999] Babies born with a rare congenital defect in detoxifying BCAAs develop sweet-smelling urine and can go on to suffer encephalopathy, brain swelling, and death. The disease clearly shows that large excesses of BCAAs are hazardous to the brain, raising the question of whether milder elevations might also be neurotoxic.[8000] In a mouse model of Alzheimer's disease, high-BCAA diets made cognitive performance worse, whereas low-BCAA diets made it better.[8001] This is consistent with a Mendelian randomization analysis that found that people born with a genetic predisposition to higher isoleucine levels were significantly more likely to develop Alzheimer's disease,[8002] but a meta-analysis of eight cohort studies found that higher levels of BCAAs (including isoleucine) were associated with a *lower* risk of dementia.[8003]

The BCAA literature seems surprisingly rife with this kind of contradictory evidence, with studies suggesting that BCAAs have harmful, harmless, or helpful effects on aging and age-related conditions.[8004] For example, there was an observational study that found that higher BCAA intakes were associated with a significantly lower all-cause mortality.[8005] With "such levels of complexity," concluded a recent review on BCAAs and aging, "there is unlikely to be any unifying conclusion about overall benefits or harms of BCAAs in older people."[8006] However, at least when it comes to metabolic effects, we have human interventional trials to prove harms or benefits one way or another.

BCAAs AND INSULIN RESISTANCE

Insulin resistance is the cause of prediabetes and type 2 diabetes.[8007] Even in nondiabetics, insulin resistance[8008] and the elevated blood sugars that can result[8009] are associated with premature death, based on meta-analyses of

prospective cohort studies. (For a backgrounder on what insulin resistance is and what it does, see my Low Insulin Index chapter in *How Not to Diet*.) Insulin resistance, the inability of our body to sufficiently respond to the blood sugar–lowering hormone insulin, can be caused by the intake of saturated fat (see.nf/insulin), as well as the intake of branched-chain amino acids.[8010] It turns out a BCAA breakdown product appears to stimulate fat uptake and accumulation inside the muscle cells,[8011] which interferes with insulin signaling.[8012]

Reducing BCAA intake in obese mice reduced insulin resistance, caused dramatic fat loss even without a reduction of calories, and restored metabolic health,[8013] whereas a high-BCAA diet induces mouse obesity.[8014] In people, an "overwhelming" number of studies[8015] have consistently shown that blood and urine levels of branched-chain amino acids are tied to insulin resistance. In fact, increased BCAA in the blood, dubbed the "BCAA signature," is a hallmark of obesity and diabetes.[8016] This doesn't necessarily mean that decreasing intake of BCAAs will help, though, since there are other factors that influence levels in the blood.[8017]

Yes, BCAAs can cause insulin resistance,[8018] but insulin resistance also seems to cause an increase in BCAA levels[8019] due to a reduction in BCAA breakdown, potentially leading to a positive feedback loop that can spiral out of control.[8020] The epidemiology is contradictory, though.[8021] The microbiome has even been thrown into the mix by a study of twin pairs showing that a fecal transplant from a heavier twin increases blood BCAA levels in mice more than a fecal transplant from the thinner twin.[8022] The proof is in the pudding, though. Just like you can make someone insulin-resistant by infusing fat into their bloodstreams,[8023] you can do the same by infusing BCAAs.[8024] Just as a single dose of butter can cause insulin resistance within hours, so can downing a protein drink of straight whey and water.[8025,8026]

This may help explain the results of the study I detailed in the FGF21 section above (see here), in which protein intakes were dropped from typical American diet levels down to recommended levels. Not only did FGF21 double within about six weeks compared to the control group, but the drop in BCAA levels in the participants' blood was accompanied by a significant drop in blood sugars and pounds of fat loss despite averaging hundreds more calories a day.[8027] Given the restoration of metabolic health

demonstrated by decreasing consumption of branched-chain amino acids, leaders in the field have suggested the invention of pharmaceuticals to block BCAA absorption to "promote metabolic health and treat diabetes and obesity without reducing caloric intake."[8028] Or, we can just try to not eat so many branched-chain amino acids in the first place.

BCAA Supplements

Branched-chain amino acid supplements are a multimillion-dollar business, marketed for the widely believed claim that BCAAs can boost muscle mass by stimulating muscle protein synthesis,[8029] a belief based on rat studies going back more than forty years.[8030] Yet, the only two human studies showed that BCAAs actually cause a *reduction* in muscle protein synthesis.[8031,8032] I review the somewhat mixed research on BCAA supplementation in older adults in see.nf/bcaas, but basically, we're left with the bottom line of a recent review in a journal of exercise metabolism: "In conclusion, the proposed benefits of BCAA used in the marketing of supplements appear to be at odds with the overall state of the current literature, which does not support the efficacy of supplementation on muscle strength and hypertrophy [size]."[8033]

HOW TO LOWER BCAA INTAKE

Since BCAAs are mostly found in meat, including chicken and fish, dairy products, and eggs,[8034] this may explain why animal protein intake intensifies insulin resistance[8035] and is associated with higher diabetes risk,[8036] whereas plant foods tend to have the opposite effect. Substituting in even just 5 percent of plant protein for animal protein may decrease diabetes risk by more than 20 percent.[8037] Although fasting blood levels of BCAAs taken in the morning don't necessarily correlate with dietary intake,[8038] meals high in animal protein can quadruple levels in the bloodstream, which can remain elevated for seven to eight hours.[8039]

A crossover clinical trial found that those randomized to replace just two servings of meat for lentils, chickpeas, split peas, or beans a few days a week can significantly improve fasting blood sugars and insulin levels, beyond just the improvements you'd expect, like lower cholesterol and triglycerides.[8040] Based on more than a dozen randomized controlled trials, even just swapping a third or so of protein from animal to plant sources can significantly improve blood sugar control.[8041]

Like methionine, branched-chain amino acid intake is lower among vegetarians compared to omnivores, but only vegans achieve significantly lower fasting levels in their blood, consuming 30 percent less compared to only about 15 percent less among vegetarians.[8042] Randomizing people to a strictly plant-based diet for a month can significantly drop fasting levels of all three BCAAs, which correlated with anti-inflammatory effects of the switch.[8043]

BCAAs may explain why those randomized to a plant-based diet eliminate significantly more of the deeper, more dangerous fat, even when taking in the same number of calories.[8044] Those eating plant-based also had lower levels of fat stuck inside individual muscle fibers themselves, which may help explain why vegans in particular are often found to have the lowest odds of diabetes.[8045,8046] It's not only because they're slimmer. Even if you match subjects pound for pound, significantly less fat has been found inside the muscle cells of vegans compared to omnivores, as measured in one of their calf muscles.[8047] It is therefore no wonder why those eating plant-based diets average significantly lower insulin levels and have less insulin resistance, even compared to nonvegetarians at the same body weight.[8048,8049]

Those who eat meat have up to 50 percent higher insulin levels in their bloodstreams.[8050,8051] Compared to a control group who made no dietary changes, people randomized to a plant-based diet experienced a significant drop in insulin resistance, fasting blood sugars, and insulin levels.[8052] But add some egg whites to a plant-based diet, and you can cause a "dramatic"[8053] rise in insulin output—by as much as 60 percent within just four days.[8054] Add tuna to mashed potatoes, and the insulin reaction is about 50 percent higher than eating the mashed potatoes alone.[8055] Adding broccoli instead, however, results in the insulin response being cut by about 40 percent within the first thirty minutes after consumption.[8056] This didn't

appear to be a fiber effect, either, since giving the equivalent amount of isolated broccoli fiber provided no significant benefit. The differential effect of plant versus animal protein has been attributed to their contrasting amino acid profiles.[8057]

The reason branched-chain amino acids are suspected is, if you give some vegans straight BCAA supplements, you can make them as insulin-resistant as omnivores, in effect proving that BCAAs can have a direct negative impact on insulin sensitivity.[8058] Conversely, take some omnivores and put them through even just a "48-hour vegan diet challenge," and you can produce significant improvements in metabolic health.[8059] After two days on a healthy plant-based diet, not only did cholesterol and triglycerides drop but so did insulin and insulin resistance, presumed to be due in part to the "strong modulatory effect" on circulating BCAA levels. This has been suggested to explain some of the lifespan benefits of plant-based diets,[8060] but because the benefits appeared so rapidly, the researchers suggested metabolic benefits could be gotten from an "intermittent vegan diet" or even the "flexitarian approach" of alternating between animal and plant protein choices.[8061]

Turning It Up to Eleven

Note that protein restriction is the only intervention in the chart here that blocks every one of the eleven aging pathways, yet the prevailing dogma in our society is to eat more protein.[8062] A survey of U.S. adults suggests that about 65 percent are trying to do just that.[8063] Although high-protein diets can help with compliance in weight-loss interventions,[8064] they do not align with the protein reduction recommended in anti-aging diets.[8065] The best available balance of evidence supports the advice of longevity experts like Drs. Valter Longo[8066] and Luigi Fontana to advise cutting down on protein to live longer: "Eating more protein than what is needed … will not increase muscle mass but will accelerate aging and increase the risk of developing many chronic diseases."[8067]

NAD+

Our understanding of *nicotinamide adenine dinucleotide* (NAD^+) arose from humble beginnings as a factor noted to enhance yeast fermentation in a 1906 paper unassumingly titled "The Alcoholic Ferment of Yeast-Juice."[8068] Little did the authors know that waves of NAD-related discoveries would go on to yield, thus far, a total of four Nobel Prizes.[8069] NAD^+ is now known as an essential molecule for all living organisms,[8070] required for the function of about five hundred enzymatic reactions,[8071] including, notably, the extraction of metabolic energy from food.[8072] The twenty-first century has produced yet another scientific renaissance for NAD^+ with the realization that it was critical for the activity of sirtuins,[8073] those "guardians of mammalian healthspan"[8074] I detail in Part I.

NAD^+ is one of the most abundant molecules in our body. Once considered relatively stable, it is now known to be in a constant state of synthesis, recycling, and breakdown.[8075] Our pool of NAD^+ is turned over as often as several times a day.[8076] To maintain cellular vitality in the face of this turnover, an adequate supply of NAD^+ precursors and sufficiently high NAD^+-synthesizing enzyme activity is critical.[8077] The importance of NAD^+ is exemplified by the devastating consequences of a deficiency of its precursors like niacin (vitamin B_3).[8078] The deficiency syndrome, called *pellagra*, is characterized by the four Ds: dermatitis, dementia, diarrhea, and, eventually, death.[8079]

Thankfully, since life as we know it can't exist without it,[8080] NAD^+ and its precursors are found in everything we eat—plant, animal, or fungi.[8081] The niacin in corn is tightly bound up but can be released by presoaking in alkaline limewater. Sadly, when maize was exported from Latin America to become a dietary staple elsewhere without the requisite knowledge about traditional processing techniques, an epidemic of pellagra ensued.[8082] An estimated 100,000 Americans died from pellagra in the first few decades of the twentieth century before bread started to be fortified with niacin in 1938.[8083]

DO NAD+ LEVELS DECLINE WITH AGE?

The pitch for NAD+ boosting as an anti-aging strategy is as follows: All species, including humans, naturally experience a decline in NAD+ levels over time, and this decline is in fact one of the major reasons organisms age.[8084] By restoring youthful levels, the argument goes, these age-related disorders can be delayed or even reversed.[8085] Two leaders in the field, one from Harvard and the other from MIT, have said, respectively, that NAD+ boosters may "hold the promise of increasing the body's resilience, not just to one disease, but to many, thereby extending healthy human lifespan"[8086] and that sirtuin activation by NAD+ repletion "may be the most actionable item to emerge from aging research."[8087] Of course, both of them have been involved with multimillion-dollar dietary supplement companies.[8088,8089]

The first premise, that NAD+ levels decline with age, has been called into question. For example, a 2022 review titled "Age-Dependent Decline of NAD+—Universal Truth or Confounded Consensus?" concluded that, despite systemic claims to the contrary, the evidence supporting the premise is very limited.[8090] Indeed, the most comprehensive study to date found significant changes in NAD+ levels in only about half of tested tissues in old versus young mice.[8091] The human data, which I review in see.nf/nadecline, are similarly inconsistent.

The bottom line is that, given the conflicting findings from the remarkably few studies on the subject, it is misleading to say NAD+ universally decreases with age.[8092] Regardless, the proof is in the pudding. What about the second premise, that boosting levels late in life can improve health and longevity?

INCREASED HEALTHSPAN AND LIFESPAN IN RODENTS

The effects of NAD+ boosters on aged rodents have been described in the medical literature as "dramatic" and "remarkable."[8093] Treated mice had increased physical activity[8094] and endurance, improved vision, and strengthened bones,[8095] while delaying, preventing, or reversing muscle atrophy,[8096] hearing loss,[8097] ovarian aging,[8098] and cognitive decline.[8099] Benefits to nearly every organ system have been documented,[8100] including improved functions of the arteries,[8101] brain,[8102] heart,[8103] immune system,[8104]

kidneys,[8105] liver,[8106] and muscles. For example, a single week of a NAD^+ booster was sufficient to restore key markers of muscle health in a twenty-two-month-old mouse to levels similar to those of a six-month-old mouse.[8107] That's roughly the equivalent of reverting those of a seventy-year-old person back to age twenty.[8108]

NAD^+ boosters can also extend the lifespans of other animals, presumed to be due to the elevation of NAD^+-dependent sirtuin activity.[8109] This longevity effect was first demonstrated more than twenty years ago in yeast cells. An overexpression of the genes involved in NAD^+ synthesis extended replicative lifespans by up to 60 percent.[8110] In the microscopic worm *C. elegans*, NAD^+-boosting compounds have been shown to extend lifespans by up to 16 percent.[8111] In mice, one NAD^+ booster was able to extend lifespan by a more modest 5 percent, but this was accomplished even when supplementation was started late in life, which is unusual for longevity treatments.[8112]

No wonder people are excited about all manner of NAD^+-boosting supplements. The big question is whether any of these healthspan or lifespan effects translate to humans.[8113]

NAD^+-BOOSTING SUPPLEMENTS

There are four major NAD^+-boosting supplements on the market these days: nicotinic acid (NA), also known as niacin, nicotinamide (NAM), also known as niacinamide, nicotinamide riboside (NR), and nicotinamide mononucleotide (NMN). NAD^+ can also be given directly, as can the hydrogenated form NADH. There are also hydrogenated forms of NMN (NMNH) and NR (NRH). So, there is quite the alphabet soup: NAD, NA, NAM, NR, NMN, NADH, NMNH, and NRH. Our body can also make NAD^+ from scratch from the amino acid tryptophan. Given the critical nature of NAD^+, it is perhaps unsurprising that the body has so many different pathways utilizing a panoply of precursors.[8114]

Converting tryptophan to NAD^+ requires eight steps, whereas NA, NAM, and NR can be turned into NAD^+ in only two or three steps.[8115] NMN is a direct precursor of NAD^+, but when NMN or NR is taken orally, it appears to just turn into NA or NAM via rapid degradation in the bloodstream[8116] or active conversion in the liver or by the microbiome.[8117]

So, why take the more expensive NMN or NR if it's just going to end up as NA or NAM? Bought in bulk, NA or NAM would cost just pennies a day versus more like a dollar a day for NR or NMN. That would add up to hundreds of dollars a year for NR or NMN compared to closer to five bucks for NA or NAM. But is it worth taking any of them?

NICOTINIC ACID (NA)

The name nicotinic acid was changed to niacin in the 1940s to avoid any confusion with nicotine.[8118] Either name has to be better than the original moniker, though: vitamin PP (for *pellagra preventing*).[8119]

In the 1950s, NA became the world's first cholesterol-lowering drug.[8120] This led to about two dozen trials involving tens of thousands of individuals taking high-dose NA for up to five years,[8121] resulting in by far the most robust safety data we have on any of the NAD^+ precursors. The most striking benefit was found in the Coronary Drug Project, a trial carried out in the pre–statin drug era of the 1960s and 1970s. The fifteen-year follow-up found that those who had been randomized to years of high-dose NA ended up with a 6.2 percent drop in absolute mortality (52 percent had died in the NA group versus 58.2 percent in the placebo group).[8122] This sparked major clinical trials that, sadly, failed so spectacularly that one was even stopped prematurely.[8123, 8124]

All in all, a Cochrane meta-analysis concluded that "no evidence of benefits from niacin therapy" was found.[8125] One possible explanation for the contrasting results is that the promising early trials used immediate-release niacin, and the newer failed trials used slow-release formulations (also known as extended or sustained release).[8126] At high doses, regular niacin commonly causes an intense flushing redness and prickly heat sensation, similar to a menopausal hot flash. A slow-release version was developed to reduce the flushing reaction, catapulting it into a billion-dollar blockbuster drug,[8127] but it simply doesn't work as well to reduce cholesterol.[8128]

The major clinical trial failures led to the withdrawal of the drug in Europe[8129] and its removal from U.S. clinical guidelines for cardiovascular disease prevention.[8130] There still may be a role for niacin preparations in

the treatment of heart disease among patients who cannot tolerate statin drugs,[8131] but what about use for the general public as an NAD^+ booster?

There is a series of rare genetic defects that can lead to a condition called *mitochondrial myopathy* that's characterized by low NAD^+ levels in the blood and muscles. In 2020, researchers demonstrated that these levels could be repleted with 750 to 1,000 mg a day of NA, which led to a significant improvement in their muscle strength.[8132] This was the first and only study to show muscle NAD^+ levels and performance improving with any sort of NAD^+ booster.[8133] In a control group of individuals without the genetic defect, blood levels of NAD^+ were raised by NA, but not muscle levels, suggesting that in normal healthy muscles, NAD^+ levels are already "topped off."[8134] As you'll see, this is a recurring theme among NAD^+ boosters.

We know that large doses of NA can boost NAD^+ levels in human blood,[8135] but a corresponding increase in sirtuin activity has yet to be demonstrated.[8136] Why not give it a try? Because of the side effects unearthed in the cholesterol-lowering trials. NA raises blood sugars[8137] and may increase your risk of developing diabetes. Based on studies of tens of thousands of individuals on high-dose NA followed for years, one would expect that one in forty-three people taking NA for five years would develop diabetes who otherwise wouldn't have.[8138] It's unclear if this risk is only limited to slow-release formulations.[8139]

The safety buffer, the ratio between the tolerable upper limit and the RDA, is the lowest for NA compared to a half dozen other common vitamins.[8140] However, the upper limit is based on the flushing reaction,[8141] which, although uncomfortable, is considered harmless and tends to dissipate over time.[8142] Long-term use can have other adverse consequences, though, including stomach ulcers, vomiting, abdominal pain, diarrhea, jaundice, and other signs of liver damage (particularly with slow-release formulations).[8143] There is also a theoretical concern that excessive NA intake may contribute to the development of Parkinson's disease.[8144] Due to the unpleasant flushing and risk of more serious side effects, interest has moved toward other NAD^+ precursors.[8145]

Ever since nicotinamide (NAM) was also shown to cure pellagra,[8146] both NA and NAM have been collectively referred to as niacin or vitamin B_3, though they are distinct compounds.[8147] For example, NAM is not plagued by the same kind of hot flash reaction. (Facial flushing attributed to niacinamide in some older studies was likely due to a less purified form contaminated with residual NA.[8148])

The relative capacity of NA versus NAM to generate NAD^+ is unclear.[8149] Neither has been demonstrated to boost sirtuin activity,[8150] but both do extend the lifespan of *C. elegans*.[8151] I couldn't find any longevity trials for NA in rodents; however, NAM was put to the test and failed to prolong the lives of mice.[8152] What clinical effects might we expect in people?

I explored the proven anti-aging effects for topical nicotinamide on the skin and the remarkable ability of oral nicotinamide to help prevent skin cancer (see here). It failed to prevent type 1 diabetes, despite promising mouse data,[8153] though it may help preserve residual function in people newly diagnosed with type 1 diabetes, but apparently not enough to affect blood sugar control.[8154] What about its use as a NAD^+ booster?

In those with mitochondrial myopathy, NA had raised muscle NAD^+ levels and improved mitochondrial and muscle function, but in healthy individuals, muscle NAD^+ levels didn't budge. However, the average age of the control group individuals was fifty. What about in older adults whose muscle NAD^+ levels might potentially be lower? Four NAD^+ precursors were tested in older adults: tryptophan, NA, NAM, and NR. They all failed to improve muscle strength or function, affect mitochondrial function, and even nudge NAD^+ levels in their muscles.[8155,8156] Why not give it a try? Again, side effects.

Like NA, high-dose NAM can cause gastrointestinal disturbances and signs of liver toxicity.[8157] However, NAM may result in more issues involving methylation.[8158] The primary first step in breaking down excess NAM is to transfer a methyl group to it, forming MeNAM. MeNAM can cross the blood-brain barrier[8159] and has been shown to be toxic to nerve cells in vitro.[8160] This may explain why NAM can cause Parkinson's-like symptoms in rats[8161] and why Parkinson's patients may have higher levels of

the NAM-methylating enzyme in their brains.[8162] Excess NAM may also deplete the body's pool of methyl groups.

If you remember from the Epigenetics chapter, DNA methylation is critical for the regulation of gene expression. Epigenetic changes caused by NAM-induced methyl depletion[8163] have been blamed as the reason why rats fed megadoses of NAM suffer from fatty livers and swollen kidneys,[8164] but that was at a human-equivalent dose far exceeding what people might take.[8165] Is there any evidence that more modest NAM supplementation might affect methylation humans? Yes, even with a single dose as low as 100 mg.

Methylation also plays a key role in breaking down fight-or-flight hormones like noradrenaline and neurotransmitters like serotonin and histamine. Within hours of a single 100-mg NAM dose, blood levels of all three become elevated, suggesting that their metabolism had been impaired by the shunting of methyl groups to deal with the excess NAM.[8166] Also noted was a significant rise in homocysteine,[8167] a by-product of methylation reactions and a risk factor for cardiovascular disease and dementia.[8168] (See, for example, here.)

Another potential problem with NAM is that it's a sirtuin inhibitor.[8169] Wasn't the whole purpose of taking NAD^+ precursors to *boost* sirtuin activity? Sirtuin enzymes use up NAD^+ and spit out NAM. This allows the body to recycle the NAM back into NAD^+ for further sirtuin use. But this also means that the body can use NAM as part of a negative feedback loop. Like a thermostat in the winter that shuts down the furnace when there's too much heat, the body shuts down NAD^+ use by sirtuins when it detects too much NAM. There was no such thing as NAM pills when our body evolved. So, in the wake of a sudden wave of NAM, the body must think sirtuins are churning out too much and dials them back. Perhaps this explains why NAM failed to prolong the lifespans of mice.[8170] When the sirtuin-suppressing effects of NAM were first reported twenty years ago, the researchers cautioned that this could potentially lead to "deleterious consequences of long-term nicotinamide therapy in humans."[8171]

NR and NMN seem to be more promising NAD^+ precursors than NA or NAM, since they don't cause flushing or directly inhibit sirtuins.[8172] In mice, NR and NMN both raise liver NAD^+ levels, but only NR raises NAD^+ in the muscles.[8173] Also, NR is so far the only NAD^+ booster shown to prolong the lifespan of mice.[8174]

There have been at least ten clinical trials of NR showing that it can boost human blood levels of NAD^+ up to 168 percent. Note, though, that most of the doses used exceeded 300 mg, the daily dose approved as safe by the FDA and the European Food Safety Authority.[8175] At the approved dose, blood NAD^+ is boosted more on the order of 50 to 60 percent,[8176] but no dose was found to affect NAD^+ levels in human muscle (compared to placebo).[8177,8178,8179,8180]

The greater preponderance of human bioavailability and safety data for NR compared to NMN has led some to proclaim NR as the preferred NAD^+ precursor. And, by some, I mean employees of a chemical company that produces NR for supplements.[8181] The question after all these human NR trials is, *have any of them shown clinical benefit?* Sadly, no.[8182]

After accounting for the sheer number of variables tested, randomized, double-blind, placebo-controlled trials of NR in young, middle-aged, and older adults failed to find any significant benefit over placebo for artery function, artery stiffness, balance,[8183,8184] BAT activation (see here), blood pressure, blood sugar control,[8185,8186] body weight,[8187] cardiac energy or ejection fraction,[8188] fat burning,[8189,8190] fatty liver,[8191] exercise capacity, fatigue, insulin sensitivity,[8192,8193] metabolic flexibility,[8194] metabolic health, metabolic rate,[8195,8196] mitochondrial function[8197] or biogenesis,[8198] muscle blood flow,[8199] upper or lower body muscle strength,[8200,8201] pancreatic function or the release of metabolic hormones,[8202] treatment of Parkinson's disease symptoms,[8203] or physical performance.[8204,8205] NR company stockholders can claim that NR is anti-inflammatory,[8206] but in their own study, only three out of ten markers of inflammation were affected[8207] and a subsequent independent study at the same dose that ran for twice as long found that *zero* markers out of twelve were affected.[8208]

Remarkably, the opposite was found for many of these outcomes in rats and mice. In rodents, NR does raise NAD^+ levels in muscle, improving

mitochondrial biogenesis and function, fat burning, insulin sensitivity, metabolic health, and on down much of the list.[8209] Why does NR work in rodents but appear to almost entirely flop in people? Some have suggested inadequate dosing.[8210] The typical dose used in mouse studies was about twice that used in many human studies, but a double dose has been tried in people to no avail.[8211]

Another possibility is sirtuin inhibition by NAM, the main degradation product of NR.[8212] Based on mouse studies, NR may metabolize to NAM or NA in the gut before it even makes it into the bloodstream.[8213] Either way, unlike in mice, NR can't seem to elevate NAD^+ in human muscle, so it's no wonder that no alteration of human sirtuin activity was found in muscle biopsies.[8214] That may explain the disparate results. In fact, the key NAD^+-synthesizing enzyme in human muscle biopsies was actually suppressed by NR supplementation. This doesn't happen in mice, but it does in us. Presumably, this downregulation is an adaptive response to the unnaturally large flood of NR coming into the system.[8215]

In mice, not only may their microbiome affect NR, but the NR may affect their microbiome. Some of the benefits of NR can be transferred between mice via fecal transplants. So, at least in mice, some of the benefits of NR may be due to modulating their microbiome. The distinct differences between the gut flora of humans and rodents may offer another explanation as to why NR works in them but not us.[8216]

Unlike NAM, supplementation with NR did not increase homocysteine levels,[8217] but one study of a combination of NR plus a resveratrol analogue called pterostilbene raised LDL cholesterol[8218] high enough to potentially kill as many as one in forty long-term consumers.[8219] However, this effect is presumed to be due to the pterostilbene,[8220] as NR alone hasn't been shown to raise LDL,[8221,8222] whereas pterostilbene has.[8223]

One study did find that NR seemed to cause a small reduction in hemoglobin, hematocrit, and platelet count in people within a week of starting.[8224] This shift toward a more anemic state was suggested to account for impaired exercise performance seen in rats given NR.[8225] However, the 35 percent drop in performance did not reach statistical significance.[8226] NR did cause a significant increase in systemic oxidative stress,[8227] and another rodent study found a worsening of inflammation and deterioration of

metabolic health,[8228] but if positive effects in rodents don't translate to people, perhaps we should expect the same from negative ones.

Regulatory authorities from Australia, Canada, Europe, and the United States have all authorized NR as safe,[8229] at least up to 300 mg a day (230 mg in pregnant and lactating women).[8230] But the lack of demonstrable clinical benefit would seem to preclude NR supplementation.[8231]

NICOTINAMIDE MONONUCLEOTIDE (NMN)

Both NR and NMN have been shown to have beneficial effects in rodents, though they haven't been tested side by side.[8232] Both precursors raise blood levels of NAD^+ in people, but similarly haven't been pitted head-to-head against each other.[8233,8234] One potential advantage of NMN over NR is that it may be more stable in the bloodstream. In mouse blood at least, within an hour, most NR is converted into NAM, whereas NMN levels remain steady. You could also argue that NMN is better because it's a direct precursor of NAD^+, whereas NR has to first be converted to NMN, so we might as well just take NMN.[8235] Ironically, the exact opposite argument can also be made based on the inability of NMN to pass through cell membranes.

Structurally, NMN is just NR with a phosphate group on it. The phosphate charge prevents NMN from passing in and out of cells, so to get inside one, it first has to be converted into NR. Then, once inside, the NR can turn back into NMN and make NAD^+. So, if NMN has to be converted to NR for cell entry, the argument goes, maybe you might as well take NR in the first place.[8236] However, an NMN transporter was controversially[8237] recently identified (at least in mouse intestines), so maybe NMN is able to skip the NR step and pass directly into cells to make NAD^+ after all.[8238]

NMN boasts a long list of rodent healthspan benefits,[8239] but, unlike NR,[8240] it has yet to demonstrate an extension of mammalian lifespan.[8241] What about specifically in people? There have only been a few human NMN studies published to date. One small study of healthy middle-aged men found various single doses had no apparent effect on any of the measured variables, including retinal (eye) function, sleep quality, heart rate, blood pressure oxygenation, or body temperature.[8242] A twelve-week study of daily NMN supplementation in middle-aged men and women similarly found no significant effects on any outcome, including lean mass,

muscle mass, body fat, blood sugars, cholesterol, or insulin sensitivity. NMN did boost blood NAD^+ levels, though they peaked after the first month and then trended down for months two and three, so there may have been an adaptive drop in NAD^+ synthesis, as was suspected with NR.[8243] Like NR, NMN also fails to raise NAD^+ in muscle tissue.[8244]

One study, evocatively titled "Nicotinamide Mononucleotide Supplementation Enhances Aerobic Capacity in Amateur Runners," tested three different doses of NMN versus placebo for six weeks among young and middle-aged recreational runners. Aerobic capacity was increased at one ventilatory threshold but not the other. No overall benefit for aerobic capacity, peak power, or any of ten other measures of cardiopulmonary function was found. If you measure enough things, though, statistical outliers—both positive and negative—can pop up as flukes. For example, the researchers noted a significantly improved single-leg stance test result, but NMN had no effect on any of the other physical function tests, including grip strength, push-ups, and sit-and-reach flexibility. And, upon closer inspection, the single-leg stance balance benefit was only found in the middle-dose group compared to the high-dose group and not for any of the doses compared to placebo. (The high-dose group ended up doing slightly worse compared to baseline.[8245])

A similar issue can be found in a twelve-week study of NMN supplementation in older adults. The NMN company–funded authors concluded that NMN "improved lower limb function and reduced drowsiness in older adults," but it failed to significantly affect sixteen other measures, including other tests of lower limb function and fatigue.[8246] There are so few NMN studies that this kind of shotgun approach is understandable, casting the widest possible net for effects to be further tested, but it can't on its own be presented as convincing proof of efficacy.

All of the above NMN studies were on healthy individuals. What about testing NMN on those who are already metabolically compromised? Overweight or obese postmenopausal women with prediabetes were randomized to NMN or placebo for ten weeks. NMN didn't seem to affect body weight or composition, liver fat, blood pressure, or a dozen other metabolic variables, but it did improve muscle insulin sensitivity, though not enough to affect insulin levels or short- or long-term blood sugar control.[8247] This may be because insulin sensitivity in the liver and body fat

remained unchanged.[8248] NMN also appeared to have no effect on mitochondrial function, muscle strength, fatigability, or recovery.[8249]

In terms of safety, NMN shills[8250] speak of it as being found naturally in fruits and vegetables,[8251] but even the most concentrated sources (edamame, avocado, and broccoli) have more than a hundred times less per serving than the typical NMN supplement dose.[8252] The same could be said for NR in milk (human and otherwise).[8253] There are safety evaluations for NMN on rats[8254] and dogs,[8255] but unlike NR, supplemental doses of NMN have yet to be proven safe for human consumption.[8256] As of early 2023 as I write this, the sale of NMN as a dietary supplement remains in legal limbo.[8257]

There are rodent studies showing that NMN can have negative metabolic consequences,[8258] but the most serious concern regards nerve degeneration. The accumulation of NMN in nerve cells is toxic.[8259] Since NR is converted to NMN, this is a concern for NR supplementation as well.[8260] The type of nerve damage (axon degeneration) is a major contributor to a variety of neurodegenerative disorders,[8261] including glaucoma.[8262] Blocking an NMN-synthesizing enzyme appeared to help damaged neurons in vitro, protection that's reversed by adding back NMN,[8263] and adding an enzyme that chews up NMN was also found to be protective.[8264] However, clinical effects remain theoretical as these adverse effects have only been demonstrated in fish, mice, and petri dishes.[8265]

NMN supplements may not even have NMN in the first place. ChromaDex, which sells a rival supplement, Tru Niagen (a form of NR), claims to have tested the twenty-two NMN brands with the highest market share on Amazon.com and found that most had NMN levels below the limit of detection, so virtually none at all.[8266] Ironically, many of the apparently fake NMN products displayed a "certificate of analysis" and carried hundreds or even thousands of positive reviews.[8267] Evidently, only three out of twenty-two were found to contain as much NMN as advertised on their labels. Of course, ChromaDex isn't above being shady itself; it's been accused of making hyped false claims for Tru Niagen by both the FDA[8268] and the Better Business Bureau.[8269] In short, NR has been demonstrated to be relatively safe but not effective, and neither safety nor efficacy has been established for NMN.

OTHER NAD+-BOOSTING SUPPLEMENTS

What about tryptophan, NAD+, NADH, NMNH, and NRH? I detail them all in see.nf/othernad. In short, if anything, tryptophan *restriction* may be beneficial,[8270,8271] taking NAD+ directly largely isn't practical because of instability and poor bioavailability,[8272,8273] and, though NMNH[8274] and NRH[8275] have superior potency, this isn't necessarily a good thing as NRH can promote inflammation[8276] and oxidation,[8277] deleterious effects presumed to be shared by NMNH (since it has to be converted to NRH to enter cells).[8278]

POTENTIAL ADVERSE EFFECTS ON INFLAMMATION AND CANCER

Most of the reported side effects for NAD+ precursors like NAM, NR, and NMN are relatively rare and minor—for example, diarrhea, nausea, rashes, hot flashes, and leg cramps.[8279] Both NR and NMN raise NAM levels,[8280] so they may share in the same concerns regarding sirtuin inhibition, methyl depletion, and potential adverse effects of NAM breakdown products.[8281] I go into detail in see.nf/nadprecautions, but basically, particular caution should be used for NAD+-boosting supplements by those with cancer, a personal or strong family history of cancer,[8282] and perhaps also those with inflammatory disorders[8283] and active *Haemophilus* infections.[8284]

WHICH BOOSTER IS BEST?

There's no clear standout in NAD+-boosting supplements,[8285] as hardly any of the preclinical effects found in the lab have translated into evidence of human clinical benefit. Perhaps this failure is to be expected given the complexity of NAD+ physiology, with its juggling of multiple precursors, production pathways, recycling routes, and myriad consuming enzymes.[8286] It's just too early to say if NAD+ booster supplementation will ever live up to even a fraction of the hype.[8287] Many more, larger, and longer-term studies are necessary to establish safety and efficacy.[8288]

The problem is that because NA, NAM, NR, and NMN are all natural products, they can't be patented, so the money for well-designed clinical trials is not as available.[8289] The reason there have been comparatively more trials done on NR than NMN is that patents were originally issued for NR before it was deemed unpatentable in 2021.[8290]

Perhaps blindly overloading the system with NAD^+ precursors is not the best way to go about NAD^+ restoration.[8291] The body seems too smart to allow such a blunt incursion to affect tissue levels. Maybe these supplements are just profit-making distractions from more natural approaches.

NATURAL APPROACHES TO BOOSTING NAD^+

There are broadly three main approaches for increasing NAD^+ levels. Increasing the supply of NAD^+ precursors is just the first. The other two means are having the body make more by activating NAD^+-synthesizing enzymes and having the body use less via an inhibition of excess NAD^+ degradation.[8292]

AMPING NAMPT

The primary determinant of NAD^+ synthesis is the enzyme *NAMPT*,[8293] and its abundance tends to decrease with age in human muscle, dropping steadily by about 40 percent between the ages of twenty and eighty.[8294] In our liver, it drops by half.[8295] However, age-related diseases, such as atherosclerosis, cancer, diabetes, and rheumatoid arthritis, have been found to exacerbate NAMPT decline, raising a chicken-or-the-egg question.[8296] This is where interventional trials come in.

Similar NAMPT declines have been noted in aging rats[8297] and mice.[8298] Does boosting this enzyme help? Increasing NAMPT or its species equivalent increases the lifespans of yeast,[8299] fruit flies,[8300] and rodents.[8301] An NAMPT boost also increases aerobic capacity[8302] and exercise endurance in mice in addition to helping them live longer.[8303]

Enhanced expression of NAMPT increases the NAD^+ levels in the muscles in mice comparably to feeding them dietary NAD^+ precursors, but if you remember, NAD^+ precursors don't seem to be able to affect NAD^+ muscle levels in most people.[8304] In fact, such supplements can actually suppress NAMPT,[8305] while boosting that methylating enzyme to rid the body of the excess. In addition to methyl depletion, chronic administration of these supplements could then potentially leave people worse off should they ever stop taking them.[8306] There is, however, a way we may naturally boost our NAMPT and NAD^+ levels without any supplements: exercise.

Athletes have about twice the NAMPT expression in their musculature compared to sedentary individuals. To prove cause and effect, sedentary men and women started a stationary bike exercise protocol, and, within three weeks, NAMPT levels increased by 127 percent.[8307] Resistance training can also increase NAMPT, and this can translate into a 127 percent increase in muscle NAD^+ levels and a rise in sirtuin activity.[8308] In other words, exercise can do what NAD^+-boosting supplements can't.

PRESERVING NAD^+ BY TAMPING PARP-1 AND CD38

The third way to maintain levels of NAD^+ is to conserve it. Besides sirtuins, the major consumers of NAD^+ are *PARP-1* and *CD38*. PARP-1 is an enzyme that uses NAD^+ to repair DNA. The more oxidative DNA damage, the more single-and double-stranded DNA breaks, the more enzymes like PARP-1 need to be activated to come to the rescue.[8309] This uses up a lot of NAD^+. As DNA damage accumulates with age, the rising need for repair enzymes like PARP-1 causes a major drain on NAD^+ levels.[8310,8311] This has led to the search for PARP-1 blockers to preserve NAD^+ levels,[8312] but rather than blocking DNA repair, why not work to prevent so much damage in the first place? See the Oxidation chapter for how to do just that.

CD38 is the other major guzzler of NAD^+. It's an enzyme that uses NAD^+ to make a type of cellular messenger.[8313] Found concentrated on the surfaces of immune cells, CD38 is robustly induced in the context of inflammation.[8314] The rise of CD38 activity with age[8315] has been blamed on persistent "inflammaging" activation[8316] and may be a major culprit for falling NAD^+ levels.[8317] For example, blocking CD38 has been found to raise NAD^+ levels in older mice comparable to that of younger mice.[8318] In addition to my chapter on reducing inflammation, my video see.nf/conservingnad dives into a number of natural CD38 inhibitors found in foods.

Conclusion

In the anti-aging journal *Rejuvenation Research*, a commentary was published titled "Finally, a Regimen to Extend Human Life Expectancy."[8319] I was all ears (or rather, eyes). Was it some new exotic gene therapy or stem cell treatment? No, it was a reference to a Harvard analysis titled "Impact of Healthy Lifestyle Factors on Life Expectancies in the US Population." More than 100,000 men and women were followed for thirty-four years, and just a few basic lifestyle behaviors appeared to translate into about thirteen years of extra lifespan for the average fifty-year-old. Even from age seventy, there are still about ten extra years on the table.[8320] Extending that back, earlier than age fifty, a Canadian study found that nearly eighteen years were up for grabs based on simple, commonsense health behaviors.[8321]

That's the kind of life extension we'd expect extrapolating from some of the advances made in laboratory animal longevity,[8322] but after decades of research and hundreds of millions of dollars spent, efforts to translate those results into humans have largely been in vain.[8323] Yet, here we are with *human* data suggesting that dramatic life extension is available to all of us right here, right now. We already have that trillion-dollar pill that anti-aging biotech has been promising us. It just may have to be effectively administered in the produce aisle or the gym. As presciently written in a textbook of geriatric medicine more than sixty-five years ago, "A more promising approach toward prolonging life in the latter years seems to be the prevention of degenerative diseases by good nutrition."[8324]

Might the wide disparity in lifespan arise from a lifelong pattern of behavior? To make sure it's not too late to turn back the clock, researchers tracked what happened to men and women trying to clean up their bad habits starting in middle age. A midlife switch between the ages of forty-

five and sixty-four to even just the barest of minimums—at least five daily servings fruits and vegetables, walking about twenty minutes a day, maintaining a healthy weight, and not smoking—resulted in a substantial reduction in mortality even in the immediate future. We're talking a 40 percent lower risk of dying in the subsequent four years. The researchers conclude that their findings emphasize that "making the necessary changes to adhere to a healthy lifestyle is extremely worthwhile, and middle-age is certainly not too late to act."[8325]

And that's just the beginning. That doesn't include the dozens of other recommendations I put forth in Part I of this book, the healthiest of healthy foods and eating patterns in the Optimal Anti-Aging Regimen in Part II, the death-defying tips on circulation and immunity in Part III, or necessarily any of my Anti-Aging Eight. There is so much we can do to extend our lifespan and our healthspan. A recent remarkable study of more than half a million participants, for example, found that those who salted their food at the table (in addition to whatever salt was used in cooking) appeared to have a two-year lower life expectancy at age fifty compared to those who didn't.[8326] So, just swapping out the salt shaker for some savory salt-free seasoning could potentially add years to your life.

All this just from tiny tweaks of the bare basics without getting really serious about diet. What we eat is considered "probably the most powerful and pliable tool that we have to attain a chronic and systemic modulation of [the] ageing process…."[8327] The apparent benefits are so extreme that they've been used to cast aspersions on the whole field of nutritional epidemiology. Meta-analyses suggesting that you could add years to your life just by avoiding eggs or bacon, or by eating nuts every day or certain fruit? It just seems too good to be true.[8328] Regardless of the absolute magnitude of the effect, diet is understood to be the number one determinant of how long we live.[8329] We are what we eat.

LIFESPAN REGRESSION

Martin Luther King Jr. warned that "human progress is neither automatic nor inevitable,"[8330] and the same may be true of the human lifespan.[8331] In 1850, life expectancy in the United States was less than forty years,[8332] but it has steadily increased over the last two centuries,[8333] gaining about two

years per decade—until recently, that is. Longevity gains have faltered and then, in 2015, started to reverse.[8334] Thanks in large part to the obesity epidemic, we may now be raising the first American generation to live shorter lives than their parents.[8335] And that was before COVID-19 knocked two years off the U.S. life expectancy, a decline not experienced since 1943, the deadliest year of World War II.[8336]

As we get older, the reserve capacity of our organs is diminished,[8337] making it even more important to eat and live healthfully. We can't continue to get away with the fast-food lifestyle we may have led with teen abandon. Unfortunately, most have not gotten the memo. The American Heart Association has tracked diet and lifestyle trends in the United States for decades. In its 2012 report, it noted that most Americans were already not smoking and nearly half achieved their "ideal" goal for exercise (at least twenty minutes or so a day of moderate intensity activity). But when it came to healthy diet score, only about 1 percent scored a four or five out of its zero-to-five diet quality scale. And, "ideal" criteria just included things like drinking less than four and a half cups of soda a week.[8338]

The American Heart Association set what it called an "aggressive" goal of improving these stats by 20 percent by 2020. Did it achieve its objective of bumping up that 1 percent to 1.2 percent? By the 2022 update, we had slipped even farther, from 1 percent down to 0.2 percent.[8339] Today, only one in five hundred Americans even gets close to a modestly healthy diet.

No wonder, in terms of life expectancy, the United States ranked down around twenty-seven or twenty-eight out of the thirty-four top free-market democracies. People in Slovenia live longer than we do.[8340] That was in 2010, down from ranking twentieth in 1990. More recently, U.S. life expectancy dipped to forty-third in the world and is expected to drop to sixty-fourth by 2040,[8341] despite spending trillions on healthcare a year, more than anyone else around the globe.[8342]

The problem isn't healthcare access. The Mayo Clinic estimates that nearly 70 percent of Americans are on prescription drugs.[8343] The problem is that those trillions in healthcare spending aren't addressing the root cause. The leading risk factor for death in the United States is what we eat.[8344] It's the food. The standard American diet is just to die for. Literally. It's almost as if we're eating as though our future doesn't matter. There are actually data to back that up, from a study I profile in see.nf/usa titled "Death Row

Nutrition."[8345] The upshot was that there wasn't much difference between the final food requests of death row inmates and what Americans normally eat. If we continue to eat as though we are having our last meals, eventually, they will be.

COALITION CONSENSUS

On the flip side, the good news is how huge the opportunity is for improvement. One of the most beautiful graphs in all of public health is that of the lung cancer death curves. It took decades to finally turn the corner, but with dropping smoking rates, the rates of lung cancer deaths have come tumbling down.[8346] I look forward to the day when we see the same with diet.

Yes, approximately 80 percent of chronic disease and premature death could be prevented by not smoking, being physically active, and "adhering to a healthful dietary pattern," but what exactly is meant by a healthy diet? [8347] Unfortunately, what we hear in the media about nutrition is often inconsistent and confusing. There's a pressure within today's competitive journalism market for sensationalism. Media analysts suggest that there may even be a purposeful disincentive to present the facts in context to sell more copies.[8348] (The analysis was published before the lure of clickbait headlines, which presumably makes matters even worse.)

There's a quote from the 1940s by a leader in the field that seems all the more relevant now, more than three-quarters of a century later: "It is unfortunate that the subject of nutrition seems to have a special appeal to the credulous, the social zealot, and, in the commercial field, the unscrupulous … [a combination] calculated to strike despair in the hearts of the sober, objective scientist."[8349]

Arguably, the most important healthcare problem we face may be our poor lifestyle choices based on misinformation.[8350] It reminds me of climate change denial, how healthy dietary advice can be overshadowed by industry interests, ideologues, and a misguided media. What we've needed is an IPCC of nutrition, and I'm proud to have contributed to just such an undertaking. The True Health Initiative is a nonprofit coalition of hundreds of experts from dozens of countries agreeing to a consensus statement as to the basics of healthy living,[8351] "fighting fake facts and combating false

doubts to create a world free of preventable diseases, using the time-honored, evidence-based fundamentals of lifestyle as medicine."[8352] Spoiler alert: The healthiest diet is one that is generally comprised mostly of minimally processed plants.[8353]

AS NATURE INTENDED

Perhaps that is not surprising, since it is what we ate from about twenty million years ago when we split with our last common primate ancestor up until we started making tools about two million years ago.[8354] We know that, for the first 90 percent of our evolution, when our nutrient requirements and digestive physiology were being established, we were eating what the rest of the great apes ended up eating, a diet centered around whole plant foods. Even the most carnivorous of apes—chimpanzees—eat a diet that is more than 98 percent plant-based.[8355] You can feed natural omnivores like dogs[8356] five hundred eggs' worth of cholesterol, and they just wag their tail, whereas a fraction of that can clog the arteries of more naturally plant-based species within a matter of months.[8357] Some animals are used to eating and ridding themselves of excess cholesterol. Our body can't handle it, as evidenced by atherosclerotic heart disease being our leading cause of death.

During the Stone Age, there was little selection pressure to protect people from their expanding diet since most prehistoric people didn't live long enough to get heart attacks. When the average life expectancy is twenty-five years,[8358] the genes that get passed along are from those who can live to reproductive age by any means necessary—and that means not dying of starvation. The more calories in food, the better. Eating lots of bone marrow and brains, human or otherwise, would have a selective advantage (as would discovering a time-machine stash of Twinkies, for that matter). If we only have to live long enough to get our kids to puberty to pass along our genes, then we don't have to evolve any protections against the ravages of chronic disease.

To find a population nearly free of chronic disease in old age, we don't have to go back millions of years. As I detailed in *How Not to Die*, in the twentieth century, networks of missionary hospitals in rural Africa found coronary artery disease to be virtually absent and the same for other leading killers, like high blood pressure, stroke, diabetes, common cancers, and

more.[8359] In a sense, populations in rural China and Africa were eating the type of diet we've been eating for 90 percent of the last twenty million years, a diet almost exclusively comprised of plant foods. How do we know it was their diet and not something else? Because of the pioneering research from Pritikin, Ornish, and Esselstyn that showed that plant-based diets could help arrest or even reverse the progression of heart disease in the majority of patients when formally put to the test. Indeed, it's the only diet that ever has.[8360]

Is a healthy diet and lifestyle all you need to fight the ravages of aging? This would have been a much thinner book if it were so. As you've read in these pages, there are a plethora of pills and procedures and salves, supplements, and specific foods that can help reduce wrinkles, grow hair, shrink prostates, and enhance vision, dentition, erection, cognition, and so on. But the foundation is diet and lifestyle, which is good news, because you hold the power.

NOTES

Preface

1. Kassirer J, Angell M. Losing weight—an ill-fated New Year's resolution. *N Engl J Med.* 1998;338(1):52–4.
2. Nelson TD. Promoting healthy aging by confronting ageism. *Am Psychol*. 2016;71(4):276–82.
3. Binstock RH. Anti-aging medicine and research: a realm of conflict and profound societal implications. *J Gerontol A Biol Sci Med Sci*. 2004;59(6):B523–33.
4. Reddy SSK, Chaiban JT. The endocrinology of aging: a key to longevity "great expectations." *Endocr Pract*. 2017;23(9):1110–9.
5. Kristjuhan Ü. Real aging retardation in humans through diminishing risks to health. *Ann N Y Acad Sci*. 2007;1119:122–8.
6. Roe DA. Health foods and supplements for the elderly. Who can say no? *N Y State J Med*. 1993;93(2):109–12.
7. Perls TT. Anti-aging quackery: human growth hormone and tricks of the trade—more dangerous than ever. *J Gerontol A Biol Sci Med Sci*. 2004;59(7):682–91.
8. United States Senate, Special Committee on Aging. Senate hearing 107–190. Swindlers, hucksters and snake oil salesmen: hype and hope of marketing anti-aging products to seniors. *U.S. Government Printing Office*. September 10, 2001.
9. United States Congress House of Representatives, Select Committee on Aging. Quackery: a $10 billion scandal. *U.S. Government Printing Office.* May 31, 1984.

10. Newton JP. Anti-ageing–fact, fiction or faction? *Gerodontology*. 2011;28(3):163–4.
11. Anti-aging treatment claims: the promises vs. the science. *Consum Rep*. 2015;80(8):15–7.
12. McConnel C, Turner L. Medicine, ageing and human longevity: the economics and ethics of anti-ageing interventions. *EMBO Rep*. 2005;6(S1):S59–62.
13. Anti-aging treatment claims: the promises vs. the science. *Consum Rep*. 2015;80(8):15–7.
14. Wick G. "Anti-aging" medicine: does it exist? A critical discussion of "anti-aging health products." *Exp Gerontol*. 2002;37(8–9):1137–40.
15. Caulfield T. Blinded by science. *The Walrus*. https://thewalrus.ca/blinded-by-science/. Published September 12, 2011. Updated April 19, 2020. Accessed January 22, 2023.
16. Winslow R. The radium water worked fine until his jaw fell off. *Wall Street Journal*. August 1, 1990:A1.
17. Turner L. The US direct-to-consumer marketplace for autologous stem cell interventions. *Perspect Biol Med*. 2018;61(1):7–24.
18. Murray IR, Chahla J, Frank RM, et al. Rogue stem cell clinics. *Bone Joint J*. 2020;102-B(2):148–54.
19. Olshansky SJ, Hayflick L, Carnes BA. No truth to the fountain of youth. *Sci Am*. 2002;286(6):92–5.
20. Epstein D. Anti-aging doctors sue professors. *Inside Higher Ed*. https://www.insidehighered.com/news/2005/06/21/anti-aging-doctors-sue-professors. Published June 21, 2005. Accessed January 22, 2023.
21. MacGregor C, Petersen A, Parker C. Hyping the market for 'anti-ageing' in the news: from medical failure to success in self-transformation. *BioSocieties*. 2018;13(1):64–80.
22. The American Academy of Anti-Aging Medicine's official position statement on the truth about human aging intervention. American Academy of Anti-Aging Medicine. https://mail.anme.com.mx/modulacion/extra/official_position_statement.pdf. Published June 2002. Accessed September 26, 2022.
23. Binstock RH. The war on "anti-aging medicine." *Gerontologist*. 2003;43(1):4–14.

24. Find an anti-aging product or service. World Health Network. https://web.archive.org/web/20020402011937/http://www.worldhealth.net/cgi-local/DB_Search/db_search.cgi?setup_file=whn_productsa.setup.cgi. Accessed January 31, 2023.
25. Zs-Nagy I. Is consensus in anti-aging medical intervention an elusive expectation or a realistic goal? *Arch Gerontol Geriatr*. 2009;48(3):271–5.
26. Binstock RH. The war on "anti-aging medicine." *Gerontologist*. 2003;43(1):4–14.
27. The American Academy of Anti-Aging Medicine's official position statement on the truth about human aging intervention. American Academy of Anti-Aging Medicine. https://mail.anme.com.mx/modulacion/extra/official_position_statement.pdf. Published June 2002. Accessed September 26, 2022.
28. Walker RF. On the evolution of anti-aging medicine. *Clin Interv Aging*. 2006;1(3):201–3.
29. Rattan SIS. Anti-ageing strategies: prevention or therapy? *EMBO Rep*. 2005;6(Suppl 1):S25–9.
30. Rae MJ. All hype, no hope? Excessive pessimism in the "anti-aging medicine" special sections. *J Gerontol A Biol Sci Med Sci*. 2005;60(2):139–40.
31. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Retraction: cardiovascular disease, drug therapy, and mortality in COVID-19. *N Engl J Med*. DOI: 10.1056/nejmoa2007621. *N Engl J Med*. 2020;382(26):2582.
32. Mehra MR, Ruschitzka F, Patel AN. Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet.* 2020;395(10240):1820.
33. Miller RA. Extending life: scientific prospects and political obstacles. *Milbank Q*. 2002;80(1):155–74.
34. Berzlanovich AM, Keil W, Waldhoer T, Sim E, Fasching P, Fazeny-DBerzl B. Do centenarians die healthy? An autopsy study. *J Gerontol A Biol Sci Med Sci*. 2005;60(7):862–5.
35. Gessert CE, Elliott BA, Haller IV. Dying of old age: an examination of death certificates of Minnesota centenarians. *J Am Geriatr Soc*.

2002;50(9):1561–5.
36. Wilson DM, Cohen J, Birch S, et al. “No one dies of old age”: implications for research, practice, and policy. *J Palliat Care*. 2011;27(2):148–56.
37. Berzlanovich AM, Missliwetz J, Sim E, et al. Unexpected out-of-hospital deaths in persons aged 85 years or older: an autopsy study of 1886 patients. *Am J Med*. 2003;114(5):365–9.
38. John SM, Koelmeyer TD. The forensic pathology of nonagenarians and centenarians: do they die of old age? (The Auckland experience). *Am J Forensic Med Pathol*. 2001;22(2):150–4.
39. Blagosklonny MV. Answering the ultimate question “what is the proximal cause of aging?” *Aging (Albany NY)*. 2012;4(12):861–77.
40. Murray CJL, Barber RM, Foreman KJ, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. *Lancet*. 2015;386(10009):2145–91.
41. Writing Group Members, Roger VL, Go AS, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. 2012;125(1): e2-e220.
42. Murphy SL, Kochanek KD, Xu J, Arias E. Mortality in the United States, 2020. *NCHS Data Brief*. 2021;(427):1–8.
43. Murray CJL, Barber RM, Foreman KJ, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. *Lancet*. 2015;386(10009):2145–91.
44. Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. *Lancet*. 2018;392(10159):2052–90.
45. Kaeberlein M. The biology of aging: citizen scientists and their pets as a bridge between research on model organisms and human subjects. *Vet Pathol*. 2016;53(2):291–8.

46. Zainabadi K. A brief history of modern aging research. *Exp Gerontol*. 2018;104:35–42.
47. Milman S, Barzilai N. Dissecting the mechanisms underlying unusually successful human health span and life span. *Cold Spring Harb Perspect Med*. 2015;6(1):a025098.
48. Iyen B, Qureshi N, Weng S, et al. Sex differences in cardiovascular morbidity associated with familial hypercholesterolaemia: a retrospective cohort study of the UK Simon Broome register linked to national hospital records. *Atherosclerosis*. 2020;315:131–7.
49. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. *Circulation*. 2022;145(8):e153–639.
50. Jortveit J, Pripp AH, Langørgen J, Halvorsen S. Incidence, risk factors and outcome of young patients with myocardial infarction. *Heart*. 2020;106(18):1420–6.
51. Giem P, Beeson WL, Fraser GE. The incidence of dementia and intake of animal products: preliminary findings from the Adventist Health Study. *Neuroepidemiology*. 1993;12(1):28–36.
52. Wahl D, Cogger VC, Solon-Biet SM, et al. Nutritional strategies to optimise cognitive function in the aging brain. *Ageing Res Rev*. 2016;31:80–92.
53. Olshansky SJ, Carnes BA, Cassel C. In search of Methuselah: estimating the upper limits to human longevity. *Science*. 1990;250(4981):634–40.
54. Vaiserman A, Koliada A, Lushchak O, Castillo MJ. Repurposing drugs to fight aging: the difficult path from bench to bedside. *Med Res Rev*. 2021;41(3):1676–700.
55. Olshansky SJ, Perry D, Miller RA, Butler RN. In pursuit of the longevity dividend. *Scientist (Philadelphia, Pa)*. 2006;20(3):28–36.
56. Blagosklonny MV. Disease or not, aging is easily treatable. *Aging (Albany NY)*. 2018;10(11):3067–78.
57. De Winter G. Aging as disease. *Med Health Care Philos*. 2015;18(2):237–43.
58. Zhavoronkov A, Bhullar B. Classifying aging as a disease in the context of ICD-11. *Front Genet*. 2015;6:326.

59. Hodgson J. Consumer, drug firms vie in vitamins. *Wall Street Journal*. https://www.wsj.com/articles/SB10001424127887323401904578155050445302398. Published December 2, 2012. Accessed January 24, 2023.
60. Davis B. The link between Big Pharma and the supplement industry. Elsevier: Pharma R&D Today. https://web.archive.org/web/20220930062808/https:/pharma.elsevier.com/pharma-rd/link-big-pharma-supplement-industry/. Published July 28th, 2017. Accessed February 10, 2023.
61. Martin KI, Glaser DA. Cosmeceuticals: the new medicine of beauty. *Mo Med*. 2011;108(1):60–3.
62. Exuviance. Johnson & Johnson. https://www.jnj.com/exuviance. Accessed January 22, 2023.
63. Spencer M. Coca-Cola, Sanofi in beauty venture. *Wall Street Journal*. https://www.wsj.com/articles/SB10000872396390443854204578060662301872612. Published October 16, 2012. Accessed January 24, 2023.
64. Miller RA. Extending life: scientific prospects and political obstacles. *Milbank Q*. 2002;80(1):155–74.
65. Donner Y, Fortney K, Calimport SRG, Pfleger K, Shah M, Betts-LaCroix J. Great desire for extended life and health amongst the American public. *Front Genet*. 2016;6:353.
66. Eissenberg JC. Hungering for immortality. *Mo Med*. 2018;115(1):12–7.
67. Hall WJ. Centenarians: metaphor becomes reality. *Arch Intern Med*. 2008;168(3):262–3.
68. Faragher RGA. Should we treat aging as a disease? The consequences and dangers of miscategorisation. *Front Genet*. 2015;6:171.
69. Marengoni A, Angleman S, Melis R, et al. Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev*. 2011;10(4):430–9.
70. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care,

research, and medical education: a cross-sectional study. *Lancet*. 2012;380(9836):37–43.

71. Smith-Uffen MES, Johnson SB, Martin AJ, et al. Estimating survival in advanced cancer: a comparison of estimates made by oncologists and patients. *Support Care Cancer*. 2020;28(7):3399–407.

72. Hole B, Salem J. How long do patients with chronic disease expect to live? A systematic review of the literature. *BMJ Open*. 2016;6(12):e012248.

73. Kaeberlein M. How healthy is the healthspan concept? *GeroScience*. 2018;40(4):361–4.

74. Crimmins EM, Beltrán-Sánchez H. Mortality and morbidity trends: is there compression of morbidity? *J Gerontol B Psychol Sci Soc Sci*. 2011 Jan;66(1):75–86.

Introduction

75. de Magalhães JP. The scientific quest for lasting youth: prospects for curing aging. *Rejuvenation Res*. 2014;17(5):458–67.
76. Furrer R, Handschin C. Lifestyle vs. pharmacological interventions for healthy aging. *Aging (Albany NY)*. 2020;12(1):5–7.
77. Barja G. Updating the mitochondrial free radical theory of aging: an integrated view, key aspects, and confounding concepts. *Antioxid Redox Signal*. 2013;19(12):1420–45.
78. de Magalhães JP. The scientific quest for lasting youth: prospects for curing aging. *Rejuvenation Res*. 2014;17(5):458–67.
79. Kirkwood T. Why can't we live forever? *Sci Am*. 2010;303(3):42–9.
80. Pakkenberg B, Pelvig D, Marner L, et al. Aging and the human neocortex. *Exp Gerontol*. 2003;38(1–2):95–9.
81. Herculano-Houzel S. The human brain in numbers: a linearly scaled-up primate brain. *Front Hum Neurosci*. 2009;3:31.
82. Pakkenberg B, Pelvig D, Marner L, et al. Aging and the human neocortex. *Exp Gerontol*. 2003;38(1–2):95–9.
83. Finlay BB, Pettersson S, Melby MK, Bosch TCG. The microbiome mediates environmental effects on aging. *BioEssays*. 2019;41(10):1800257.
84. Hayflick L. "Anti-aging" is an oxymoron. *J Gerontol A Biol Sci Med Sci*. 2004;59(6):B573–8.
85. Underwood M, Bartlett HP, Hall WD. Professional and personal attitudes of researchers in ageing towards life extension. *Biogerontology*. 2009;10(1):73–81.
86. de Grey ADNJ. Like it or not, life-extension research extends beyond biogerontology. *EMBO Rep*. 2005;6(11):1000.
87. Richmond CR. Population exposure from the fuel cycle: review and future direction. University of North Texas Libraries Government Documents Department. https://digital.library.unt.edu/ark:/67531/metadc1086292/. Published January 1, 1987. Accessed November 28, 2022.

88. de Grey ADNJ. Like it or not, life-extension research extends beyond biogerontology. *EMBO Rep*. 2005;6(11):1000.
89. Thomson W. Kelvin on science: British lord tells his hopes for wireless telegraphy. *The Newark Advocate*. https://zapatopi.net/kelvin/papers/interview_aeronautics_and_wireless.html. Published April 26, 1902. Accessed October 24, 2022.
90. Ayyadevara S, Alla R, Thaden JJ, Shmookler Reis RJ. Remarkable longevity and stress resistance of nematode PI3K-null mutants. *Aging Cell*. 2008;7(1):13–22.
91. Bartke A, Wright JC, Mattison JA, Ingram DK, Miller RA, Roth GS. Extending the lifespan of long-lived mice. *Nature*. 2001;414(6862):412.
92. Richie JP, Leutzinger Y, Parthasarathy S, Malloy V, Orentreich N, Zimmerman JA. Methionine restriction increases blood glutathione and longevity in F344 rats. *FASEB J*. 1994;8(15):1302–7.
93. Miller RA. Extending life: scientific prospects and political obstacles. *Milbank Q*. 2002;80(1):155–74.
94. Campbell S. Will biotechnology stop aging? *IEEE Pulse*. 2019;10(2):3–7.
95. Faragher RGA. Should we treat aging as a disease? The consequences and dangers of miscategorisation. *Front Genet*. 2015;6:171.
96. de Grey ADNJ. Escape velocity: why the prospect of extreme human life extension matters now. *PLoS Biol*. 2004;2(6):e187.
97. Kurzweil R, Grossman T. Fantastic voyage: live long enough to live forever. The science behind radical life extension questions and answers. *Stud Health Technol Inform*. 2009;149:187–94.
98. Raghavachari N. The impact of apolipoprotein E genetic variability in health and life span. *J Gerontol A Biol Sci Med Sci*. 2020;75(10):1855–7.
99. Medvedev ZA. An attempt at a rational classification of theories of ageing. *Biol Rev Camb Philos Soc*. 1990;65(3):375–98.
100. Willcox DC, Willcox BJ, Poon LW. Centenarian studies: important contributors to our understanding of the aging process and longevity. *Curr Gerontol Geriatr Res*. 2010;2010:484529.

101. Steves CJ, Spector TD, Jackson SHD. Ageing, genes, environment and epigenetics: what twin studies tell us now, and in the future. *Age Ageing*. 2012;41(5):581–6.

102. Kirkwood T. How can we live forever? *BMJ*. 1996;313(7072):1571.
103. Milman S, Barzilai N. Dissecting the mechanisms underlying unusually successful human health span and life span. *Cold Spring Harb Perspect Med*. 2015;6(1):a025098.
104. Ruby JG, Wright KM, Rand KA, et al. Estimates of the heritability of human longevity are substantially inflated due to assortative mating. *Genetics*. 2018;210(3):1109–24.
105. Herskind AM, McGue M, Holm NV, Sørensen TIA, Harvald B, Vaupel JW. The heritability of human longevity: a population-based study of 2872 Danish twin pairs born 1870–1900. *Hum Genet*. 1996;97(3):319–23.
106. Skytthe A, Pedersen NL, Kaprio J, et al. Longevity studies in GenomEUtwin. *Twin Res*. 2003;6(5):448–54.
107. Ruby JG, Wright KM, Rand KA, et al. Estimates of the heritability of human longevity are substantially inflated due to assortative mating. *Genetics*. 2018;210(3):1109–24.
108. Lee MB, Hill CM, Bitto A, Kaeberlein M. Antiaging diets: separating fact from fiction. *Science*. 2021;374(6570):eabe7365.
109. Search results: “the hallmarks of aging.” WebofScience.com. Accessed February 15, 2023.
110. Levine M, Crimmins E. Not all smokers die young: a model for hidden heterogeneity within the human population. *PLoS ONE*. 2014;9(2):e87403.
111. Devi AS, Thokchom S, Devi AM. Children living with Progeria. *Nurs Care Open Access J*. 2017;3(4):275–8.
112. Ahmed MS, Ikram S, Bibi N, Mir A. Hutchinson-Gilford progeria syndrome: a premature aging disease. *Mol Neurobiol*. 2018;55(5):4417–27.
113. Sosnowska D, Richardson C, Sonntag WE, Csiszar A, Ungvari Z, Ridgway I. A heart that beats for 500 years: age-related changes in cardiac proteasome activity, oxidative protein damage and expression

of heat shock proteins, inflammatory factors, and mitochondrial complexes in *Arctica islandica*, the longest-living noncolonial animal. *J Gerontol A Biol Sci Med Sci*. 2014;69(12):1448–61.

114. Taormina G, Ferrante F, Vieni S, Grassi N, Russo A, Mirisola MG. Longevity: lesson from model organisms. *Genes (Basel)*. 2019;10(7):518.
115. Jónás D, Sándor S, Tátrai K, Egyed B, Kubinyi E. A preliminary study to investigate the genetic background of longevity based on whole-genome sequence data of two Methuselah dogs. *Front Genet*. 2020;11:315.
116. Kaeberlein M, Creevy KE, Promislow DEL. The Dog Aging Project: translational geroscience in companion animals. *Mamm Genome*. 2016;27(7–8):279–88.
117. Pitt JN, Kaeberlein M. Why is aging conserved and what can we do about it? *PLoS Biol*. 2015;13(4):e1002131.
118. López M. Hypothalamic AMPK: a golden target against obesity? *Eur J Endocrinol*. 2017;176(5):R235–46.
119. Steinberg GR, Macaulay SL, Febbraio MA, Kemp BE. AMP-activated protein kinase—the fat controller of the energy railroad. *Can J Physiol Pharmacol*. 2006;84(7):655–65.
120. Salminen A, Kaarniranta K. AMP-activated protein kinase (AMPK) controls the aging process via an integrated signaling network. *Ageing Res Rev*. 2012;11(2):230–41.
121. Vazirian M, Nabavi SM, Jafari S, Manayi A. Natural activators of adenosine 5’-monophosphate (AMP)-activated protein kinase (AMPK) and their pharmacological activities. *Food Chem Toxicol*. 2018;122:69–79.
122. Jiang S, Li T, Yang Z, et al. AMPK orchestrates an elaborate cascade protecting tissue from fibrosis and aging. *Ageing Res Rev*. 2017;38:18–27.
123. Burkewitz K, Weir HJM, Mair WB. AMPK as a pro-longevity target. In: Cordero MD, Viollet B, eds. *AMP-activated Protein Kinase. Experientia Supplementum.* Vol 107. Springer; 2016:227–56.
124. Ruiz R, Pérez-Villegas EM, Manuel Carrión Á. AMPK function in aging process. *Curr Drug Targets*. 2016;17(8):932–41.

125. Salminen A, Kaarniranta K, Kauppinen A. Age-related changes in AMPK activation: role for AMPK phosphatases and inhibitory phosphorylation by upstream signaling pathways. *Ageing Res Rev*. 2016;28:15–26.
126. Wang S, Kandadi MR, Ren J. Double knockout of Akt2 and AMPK predisposes cardiac aging without affecting lifespan: role of autophagy and mitophagy. *Biochim Biophys Acta Mol Basis Dis*. 2019;1865(7):1865–75.
127. Ruiz R, Pérez-Villegas EM, Manuel Carrión Á. AMPK function in aging process. *Curr Drug Targets*. 2016;17(8):932–41.
128. Mair W, Morantte I, Rodrigues APC, et al. Lifespan extension induced by AMPK and calcineurin is mediated by CRTC-1 and CREB. *Nature*. 2011;470(7334):404–8.
129. Sokolov SS, Severin FF. Manipulating cellular energetics to slow aging of tissues and organs. *Biochemistry (Mosc)*. 2020;85(6):651–9.
130. Burkewitz K, Weir HJM, Mair WB. AMPK as a pro-longevity target. In: Cordero MD, Viollet B, eds. *AMP-activated Protein Kinase. Experientia Supplementum.* Vol 107. Springer; 2016:227–56.
131. Burkewitz K, Zhang Y, Mair WB. AMPK at the nexus of energetics and aging. *Cell Metab*. 2014;20(1):10–25.
132. Musi N, Fujii N, Hirshman MF, et al. AMP-activated protein kinase (AMPK) is activated in muscle of subjects with type 2 diabetes during exercise. *Diabetes*. 2001;50(5):921–7.
133. Kola B, Grossman AB, Korbonits M. The role of AMP-activated protein kinase in obesity. *Front Horm Res*. 2008;36:198–211.
134. Narkar VA, Downes M, Yu RT, et al. AMPK and PPARdelta agonists are exercise mimetics. *Cell*. 2008;134(3):405–15.
135. Benkimoun P. Police find range of drugs after trawling bins used by Tour de France cyclists. *BMJ*. 2009;339:b4201.
136. Niederberger E, King TS, Russe OQ, Geisslinger G. Activation of AMPK and its impact on exercise capacity. *Sports Med*. 2015;45(11):1497–509.
137. Niederberger E, King TS, Russe OQ, Geisslinger G. Activation of AMPK and its impact on exercise capacity. *Sports Med*. 2015;45(11):1497–509.

138. Hawley JA, Joyner MJ, Green DJ. Mimicking exercise: what matters most and where to next? *J Physiol*. 2021;599(3):791–802.
139. López-Lluch G, Santos-Ocaña C, Sánchez-Alcázar JA, et al. Mitochondrial responsibility in ageing process: innocent, suspect or guilty. *Biogerontology*. 2015;16(5):599–620.
140. Sharma A, Smith HJ, Yao P, Mair WB. Causal roles of mitochondrial dynamics in longevity and healthy aging. *EMBO Rep*. 2019;20(12):e48395.
141. Hill S, Van Remmen H. Mitochondrial stress signaling in longevity: a new role for mitochondrial function in aging. *Redox Biol*. 2014;2:936–44.
142. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194–217.
143. Gonzalez-Freire M, de Cabo R, Bernier M, et al. Reconsidering the role of mitochondria in aging. *J Gerontol A Biol Sci Med Sci*. 2015;70(11):1334–42.
144. Sgarbi G, Matarrese P, Pinti M, et al. Mitochondria hyperfusion and elevated autophagic activity are key mechanisms for cellular bioenergetic preservation in centenarians. *Aging (Albany NY)*. 2014;6(4):296–310.
145. Sengupta P. The laboratory rat: relating its age with human's. *Int J Prev Med*. 2013;4(6):624–30.
146. Corbisier P, Remacle J. Influence of the energetic pattern of mitochondria in cell ageing. *Mech Ageing Dev*. 1993;71(1):47–58.
147. Burkewitz K, Zhang Y, Mair WB. AMPK at the nexus of energetics and aging. *Cell Metab*. 2014;20(1):10–25.
148. Ruiz R, Pérez-Villegas EM, Manuel Carrión Á. AMPK function in aging process. *Curr Drug Targets*. 2016;17(8):932–41.
149. Wu S, Zou MH. AMPK, mitochondrial function, and cardiovascular disease. *Int J Mol Sci*. 2020;21(14):4987.
150. Agency for Healthcare Research and Quality (AHRQ). Medical Expenditure Panel Survey (MEPS) 2013–2019. ClinCalc DrugStats Database version 2021.10. https://clincalc.com/DrugStats/. Accessed May 22, 2023.
151. Inzucchi SE, Fonseca V. Dethroning the king?: the future of metformin as first line therapy in type 2 diabetes. *J Diabetes*

Complications. 2019;33(6):462–4.

152. Campbell JM, Bellman SM, Stephenson MD, Lisy K. Metformin reduces all-cause mortality and diseases of ageing independent of its effect on diabetes control: a systematic review and meta-analysis. *Ageing Res Rev*. 2017;40:31–44.

153. Glucophage® / Glucophage® XR: Response to FDA Comments of 10 12 00. U.S. Food & Drug Administration: Drugs@FDA. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021202. Accessed April 25, 2021.

154. Braun B, Eze P, Stephens BR, et al. Impact of metformin on peak aerobic capacity. *Appl Physiol Nutr Metab*. 2008;33(1):61–7.

155. Walton RG, Dungan CM, Long DE, et al. Metformin blunts muscle hypertrophy in response to progressive resistance exercise training in older adults: a randomized, double-blind, placebo-controlled, multicenter trial: the MASTERS trial [published correction appears in *Aging Cell.* 2020;19(3):e13098]. *Aging Cell*. 2019;18(6):e13039.

156. Burkewitz K, Zhang Y, Mair WB. AMPK at the nexus of energetics and aging. *Cell Metab*. 2014;20(1):10–25.

157. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393–403.

158. Iannello S, Camuto M, Cavaleri A, et al. Effects of short-term metformin treatment on insulin sensitivity of blood glucose and free fatty acids. *Diabetes Obes Metab*. 2004;6(1):8–15.

159. Wen H, Gris D, Lei Y, et al. Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling. *Nat Immunol*. 2011;12(5):408–15.

160. Carta G, Murru E, Banni S, Manca C. Palmitic acid: physiological role, metabolism and nutritional implications. *Front Physiol*. 2017;8:902.

161. Fatima S, Hu X, Gong RH, et al. Palmitic acid is an intracellular signaling molecule involved in disease development. *Cell Mol Life Sci*. 2019;76(13):2547–57.

162. Kirwan AM, Lenighan YM, O'Reilly ME, McGillicuddy FC, Roche HM. Nutritional modulation of metabolic inflammation. *Biochem Soc Trans*. 2017;45(4):979–85.

163. Arguello G, Balboa E, Arrese M, Zanlungo S. Recent insights on the role of cholesterol in non-alcoholic fatty liver disease. *Biochim Biophys Acta*. 2015;1852(9):1765–78.
164. Wang XJ, Malhi H. Nonalcoholic fatty liver disease. *Ann Intern Med*. 2018;169(9):ITC65–80.
165. Hydes T, Alam U, Cuthbertson DJ. The impact of macronutrient intake on non-alcoholic fatty liver disease (NAFLD): too much fat, too much carbohydrate, or just too many calories? *Front Nutr*. 2021;8:640557.
166. Luukkonen PK, Sädevirta S, Zhou Y, et al. Saturated fat is more metabolically harmful for the human liver than unsaturated fat or simple sugars. *Diabetes Care*. 2018;41(8):1732–9.
167. Luukkonen PK, Sädevirta S, Zhou Y, et al. Saturated fat is more metabolically harmful for the human liver than unsaturated fat or simple sugars. *Diabetes Care*. 2018;41(8):1732–9.
168. Kirwan AM, Lenighan YM, O'Reilly ME, McGillicuddy FC, Roche HM. Nutritional modulation of metabolic inflammation. *Biochem Soc Trans*. 2017;45(4):979–85.
169. Parry SA, Rosqvist F, Mozes FE, et al. Intrahepatic fat and postprandial glycemia increase after consumption of a diet enriched in saturated fat compared with free sugars. *Diabetes Care*. 2020;43(5):1134–41.
170. Grahame Hardie D. Regulation of AMP-activated protein kinase by natural and synthetic activators. *Acta Pharm Sin B*. 2016;6(1):1–19.
171. Wu Y, Song P, Zhang W, et al. Activation of AMPKα2 in adipocytes is essential for nicotine-induced insulin resistance *in vivo*. *Nat Med*. 2015;21(4):373–82.
172. Martínez de Morentin PB, Whittle AJ, Fernø J, et al. Nicotine induces negative energy balance through hypothalamic AMP-activated protein kinase. *Diabetes*. 2012;61(4):807–17.
173. Ferguson SG, Shiffman S, Rohay JM, Gitchell JG, Garvey AJ. Effect of compliance with nicotine gum dosing on weight gained during a quit attempt. *Addiction*. 2011;106(3):651–6.
174. Novak CM, Gavini CK. Smokeless weight loss. *Diabetes*. 2012;61(4):776–7.

175. Hadi A, Arab A, Ghaedi E, Rafie N, Miraghajani M, Kafeshani M. Barberry *(Berberis vulgaris L.)* is a safe approach for management of lipid parameters: a systematic review and meta-analysis of randomized controlled trials. *Complement Ther Med*. 2019;43:117–24.
176. Fouladi RF. Aqueous extract of dried fruit of *Berberis vulgaris L*. in acne vulgaris, a clinical trial. *J Diet Suppl*. 2012;9(4):253–61.
177. Emamat H, Asadian S, Zahedmehr A, Ghanavati M, Nasrollahzadeh J. The effect of barberry *(Berberis vulgaris)* consumption on flow-mediated dilation and inflammatory biomarkers in patients with hypertension: a randomized controlled trial [published online ahead of print, 2020 Dec 22]. *Phytother Res*. 2020;10.1002/ptr.7000.
178. Shidfar F, Ebrahimi SS, Hosseini S, Heydari I, Shidfar S, Hajhassani G. The effects of *Berberis vulgaris* fruit extract on serum lipoproteins, apoB, apoA-I, homocysteine, glycemic control and total antioxidant capacity in type 2 diabetic patients. *Iran J Pharm Res*. 2012;11(2):643–52.
179. McCarty MF. AMPK activation—protean potential for boosting healthspan. *Age (Dordr)*. 2014;36(2):641–63.
180. Shidfar F, Ebrahimi SS, Hosseini S, Heydari I, Shidfar S, Hajhassani G. The effects of *Berberis vulgaris* fruit extract on serum lipoproteins, apoB, apoA-I, homocysteine, glycemic control and total antioxidant capacity in type 2 diabetic patients. *Iran J Pharm Res*. 2012;11(2):643–52.
181. Funk RS, Singh RK, Winefield RD, et al. Variability in potency among commercial preparations of berberine. *J Diet Suppl*. 2018;15(3):343–51.
182. Arayne MS, Sultana N, Bahadur SS. The berberis story: *Berberis vulgaris* in therapeutics. *Pak J Pharm Sci*. 2007;20(1):83–92.
183. Grahame Hardie D. Regulation of AMP-activated protein kinase by natural and synthetic activators. *Acta Pharm Sin B*. 2016;6(1):1–19.
184. Tavakoli-Rouzbehani OM, Maleki V, Shadnoush M, Taheri E, Alizadeh M. A comprehensive insight into potential roles of *Nigella sativa* on diseases by targeting AMP-activated protein kinase: a review. *Daru*. 2020;28(2):779–87.

185. Mousavi SM, Sheikhi A, Varkaneh HK, Zarezadeh M, Rahmani J, Milajerdi A. Effect of *Nigella sativa* supplementation on obesity indices: a systematic review and meta-analysis of randomized controlled trials. *Complement Ther Med*. 2018;38:48–57.
186. Sahebkar A, Beccuti G, Simental-Mendía LE, Nobili V, Bo S. *Nigella sativa* (black seed) effects on plasma lipid concentrations in humans: a systematic review and meta-analysis of randomized placebo-controlled trials. *Pharmacol Res*. 2016;106:37–50.
187. Sahebkar A, Soranna D, Liu X, et al. A systematic review and meta-analysis of randomized controlled trials investigating the effects of supplementation with *Nigella sativa* (black seed) on blood pressure. *J Hypertens*. 2016;34(11):2127–35.
188. Daryabeygi-Khotbehsara R, Golzarand M, Ghaffari MP, Djafarian K. *Nigella sativa* improves glucose homeostasis and serum lipids in type 2 diabetes: a systematic review and meta-analysis. *Complement Ther Med*. 2017;35:6–13.
189. Agricultural Research Service, United States Department of Agriculture. Sweet sunnah, whole black seeds nigella sativa. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html#/food-details/468991/nutrients. Published April 1, 2019. Accessed May 8, 2021.
190. Montazeri RS, Fatahi S, Sohouli MH, et al. The effect of nigella sativa on biomarkers of inflammation and oxidative stress: a systematic review and meta-analysis of randomized controlled trials. *J Food Biochem*. 2021;45(4):e13625.
191. He T, Xu X. The influence of Nigella sativa for asthma control: a meta-analysis. *Am J Emerg Med*. 2020;38(3):589–93.
192. Khabbazi A, Javadivala Z, Seyedsadjadi N, Malek Mahdavi A. A systematic review of the potential effects of *Nigella sativa* on rheumatoid arthritis. *Planta Med*. 2020;86(7):457–69.
193. Tajmiri S, Abbasalizad Farhangi M, Dehghan P. *Nigella Sativa* treatment and serum concentrations of thyroid hormones, transforming growth factor β (TGF-β) and interleukin 23 (IL-23) in patients with Hashimoto's thyroiditis. *Eur J Integr Med.* 2016;8(4):576–80.

194. Ardakani Movaghati MR, Yousefi M, Saghebi SA, Sadeghi Vazin M, Iraji A, Mosavat SH. Efficacy of black seed (*Nigella sativa* L.) on kidney stone dissolution: a randomized, double-blind, placebo-controlled, clinical trial. *Phytother Res*. 2019;33(5):1404–12.
195. Latiff LA, Parhizkar S, Dollah MA, Hassan ST. Alternative supplement for enhancement of reproductive health and metabolic profile among perimenopausal women: a novel role of *Nigella sativa*. *Iran J Basic Med Sci*. 2014;17(12):980–5.
196. Lingesh A, Paul D, Naidu V, Satheeshkumar N. AMPK activating and anti adipogenic potential of *Hibiscus rosa sinensis* flower in 3T3-L1 cells. *J Ethnopharmacol*. 2019;233:123–30.
197. Amos A, Khiatah B. Mechanisms of action of nutritionally rich *Hibiscus sabdariffa*'s therapeutic uses in major common chronic diseases: a literature review [published online ahead of print, 2021 Jan 28]. *J Am Coll Nutr*. 2021;1–8.
198. Soleimani AR, Akbari H, Soleimani S, Beladi Mousavi SS, Tamadon MR. Effect of sour tea (*Lipicom*) pill versus captopril on the treatment of hypertension. *J Renal Inj Prev*. 2015;4(3):73–9.
199. Nwachukwu DC, Aneke EI, Nwachukwu NZ, Azubike N, Obika LF. Does consumption of an aqueous extract of *Hibscus sabdariffa* affect renal function in subjects with mild to moderate hypertension? *J Physiol Sci*. 2017;67(1):227–34.
200. Hopkins AL, Lamm MG, Funk JL, Ritenbaugh C. *Hibiscus sabdariffa* L. in the treatment of hypertension and hyperlipidemia: a comprehensive review of animal and human studies. *Fitoterapia*. 2013;85:84–94.
201. Bule M, Albelbeisi AH, Nikfar S, Amini M, Abdollahi M. The antidiabetic and antilipidemic effects of *Hibiscus sabdariffa*: a systematic review and meta-analysis of randomized clinical trials. *Food Res Int (Ottawa).* 2020;130:108980.
202. Abubakar SM, Ukeyima MT, Spencer JPE, Lovegrove JA. Acute effects of *Hibiscus sabdariffa* calyces on postprandial blood pressure, vascular function, blood lipids, biomarkers of insulin resistance and inflammation in humans. *Nutrients*. 2019;11(2):341.
203. Chang HC, Peng CH, Yeh DM, Kao ES, Wang CJ. *Hibiscus sabdariffa* extract inhibits obesity and fat accumulation, and improves

liver steatosis in humans. *Food Funct*. 2014;5(4):734–9.
204. Wu CH, Huang CC, Hung CH, Yao FY, Wang CJ, Chang YC. Delphinidin-rich extracts of *Hibiscus sabdariffa* L. trigger mitochondria-derived autophagy and necrosis through reactive oxygen species in human breast cancer cells. *J Funct Foods.* 2016;25:279–90.
205. Salim LZA, Mohan S, Othman R, et al. Thymoquinone induces mitochondria-mediated apoptosis in acute lymphoblastic leukaemia *in vitro*. *Molecules*. 2013;18(9):11219–40.
206. Chen H, Chen T, Giudici P, Chen F. Vinegar functions on health: constituents, sources, and formation mechanisms. *Compr Rev Food Sci Food Saf*. 2016;15(6):1124–38.
207. Ali Z, Wang Z, Amir RM, et al. Potential uses of vinegar as a medicine and related in vivo mechanisms. *Int J Vitam Nutr Res*. 2018;86(3–4):1–12.
208. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer*. 2015;112(3):580–93.
209. Shield KD, Soerjomataram I, Rehm J. Alcohol use and breast cancer: a critical review. *Alcohol Clin Exp Res*. 2016;40(6):1166–81.
210. Ceddia RB. The role of AMP-activated protein kinase in regulating white adipose tissue metabolism. *Mol Cell Endocrinol*. 2013;366(2):194–203.
211. Center for Food Safety and Applied Nutrition, Office of Regulatory Affairs. CPG sec. 525.825 vinegar, definitions—adulteration with vinegar eels. United States Food and Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cpg-sec-525825-vinegar-definitions-adulteration-vinegar-eels. Published March 1995. Accessed May 8, 2021.
212. Park J, Kim J, Kim J, et al. Pomegranate vinegar beverage reduces visceral fat accumulation in association with AMPK activation in overweight women: a double-blind, randomized, and placebo-controlled trial. *J Funct Foods*. 2014;8:274–81.
213. Kondo T, Kishi M, Fushimi T, Ugajin S, Kaga T. Vinegar intake reduces body weight, body fat mass, and serum triglyceride levels in

obese Japanese subjects. *Biosci Biotechnol Biochem*. 2009;73(8):1837–43.
214. Johnston C, Quagliano S, White S. Vinegar ingestion at mealtime reduced fasting blood glucose concentrations in healthy adults at risk for type 2 diabetes. *J Funct Foods*. 2013;5(4):2007–11.
215. Mitrou P, Petsiou E, Papakonstantinou E, et al. Vinegar consumption increases insulin-stimulated glucose uptake by the forearm muscle in humans with type 2 diabetes. *J Diabetes Res*. 2015;2015:175204.
216. Hu GX, Chen GR, Xu H, Ge RS, Lin J. Activation of the AMP activated protein kinase by short-chain fatty acids is the main mechanism underlying the beneficial effect of a high fiber diet on the metabolic syndrome. *Med Hypotheses*. 2010;74(1):123–6.
217. Abid M, Memon Z, Shaheen S, Ahmed F, Shaikh MZ, Agha F. Comparison of apple cider vinegar and metformin combination with metformin alone in newly diagnosed type 2 diabetic patients: a randomized controlled trial. *Int J Med Res Health Sci.* 2020;9(2):1–7.
218. Sakakibara S, Murakami R, Takahashi M, et al. Vinegar intake enhances flow-mediated vasodilatation *via* upregulation of endothelial nitric oxide synthase activity. *Biosci Biotechnol Biochem*. 2010;74(5):1055–61.
219. Beheshti Z, Chan YH, Nia HS, et al. Influence of apple cider vinegar on blood lipids. *Life Sci J.* 2012;9(4):2431–40.
220. Chuang MH, Chiou SH, Huang CH, Yang WB, Wong CH. The lifespan-promoting effect of acetic acid and Reishi polysaccharide. *Bioorg Med Chem*. 2009;17(22):7831–40.
221. Hu FB, Stampfer MJ, Manson JE, et al. Dietary intake of alpha-linolenic acid and risk of fatal ischemic heart disease among women. *Am J Clin Nutr*. 1999;69(5):890–7.
222. Hu GX, Chen GR, Xu H, Ge RS, Lin J. Activation of the AMP activated protein kinase by short-chain fatty acids is the main mechanism underlying the beneficial effect of a high fiber diet on the metabolic syndrome. *Med Hypotheses.* 2010;74(1):123–6.
223. Koç F, Mills S, Strain C, Ross RP, Stanton C. The public health rationale for increasing dietary fibre: health benefits with a focus on gut microbiota. *Nutr Bull.* 2020;45:294–308.

224. Pritchard SE, Marciani L, Garsed KC, et al. Fasting and postprandial volumes of the undisturbed colon: normal values and changes in diarrhea-predominant irritable bowel syndrome measured using serial MRI. *Neurogastroenterol Motil*. 2014;26(1):124–30.
225. Tang R, Li L. Modulation of short-chain fatty acids as potential therapy method for type 2 diabetes mellitus. *Can J Infect Dis Med Microbiol*. 2021;2021:6632266.
226. Hu GX, Chen GR, Xu H, Ge RS, Lin J. Activation of the AMP activated protein kinase by short-chain fatty acids is the main mechanism underlying the beneficial effect of a high fiber diet on the metabolic syndrome. *Med Hypotheses*. 2010;74(1):123–6.
227. Spiller G, ed. *Topics in Dietary Fiber Research*. Plenum Press; 1978.
228. Eaton SB, Eaton SB, Konner MJ. Paleolithic nutrition revisited: a twelve-year retrospective on its nature and implications. *Eur J Clin Nutr*. 1997;51(4):207–16.
229. Usual nutrient intake from food and beverages, by gender and age: what we eat in America, NHANES 2015–2018. Agricultural Research Service, United States Department of Agriculture. ../customXml/item1.xml. Accessed December 25, 2022.
230. McRorie JW. Evidence-based approach to fiber supplements and clinically meaningful health benefits, part 1: what to look for and how to recommend an effective fiber therapy. *Nutr Today.* 2015;50(2):82–9.
231. López M. Hypothalamic AMPK: a golden target against obesity? *Eur J Endocrinol*. 2017;176(5):R235–46.
232. Morgunova GV, Klebanov AA. Age-related AMP-activated protein kinase alterations: from cellular energetics to longevity. *Cell Biochem Funct*. 2019;37(3):169–76.
233. There are many different types of autophagy, including chaperone-mediated autophagy and microautophagy. In this book, I'm referring to macroautophagy.
234. Tschachler E, Eckhart L. Autophagy: how to control your intracellular diet. *Br J Dermatol*. 2017;176(6):1417–9.
235. Levine B, Klionsky DJ. Autophagy wins the 2016 Nobel Prize in Physiology or Medicine: breakthroughs in baker's yeast fuel advances in biomedical research. *PNAS*. 2017;114(2):201–5.

236. Vijayakumar K, Cho G. Autophagy: an evolutionarily conserved process in the maintenance of stem cells and aging. *Cell Biochem Funct*. 2019;37(6):452–8.
237. Kouda K, Iki M. Beneficial effects of mild stress (hormetic effects): dietary restriction and health. *J Physiol Anthropol.* 2010;29(4):127–32.
238. Tschachler E, Eckhart L. Autophagy: how to control your intracellular diet. *Br J Dermatol*. 2017;176(6):1417–9.
239. Cuervo AM. Calorie restriction and aging: the ultimate "cleansing diet." *J Gerontol A Biol Sci Med Sci*. 2008;63(6):547–9.
240. Madeo F, Zimmermann A, Maiuri MC, Kroemer G. Essential role for autophagy in life span extension. *J Clin Invest*. 2015;125(1):85–93.
241. Pyo JO, Yoo SM, Ahn HH, et al. Overexpression of Atg5 in mice activates autophagy and extends lifespan. *Nat Commun*. 2013;4:2300.
242. Wong SQ, Kumar AV, Mills J, Lapierre LR. Autophagy in aging and longevity. *Hum Genet*. 2020;139(3):277–90.
243. Cuervo AM. Calorie restriction and aging: the ultimate "cleansing diet." *J Gerontol A Biol Sci Med Sci*. 2008;63(6):547–9.
244. Meijer AJ. Autophagy in practice: stevia and leucine. *Autophagy*. 2019;15(12):2043.
245. Meijer AJ, Lorin S, Blommaart EF, Codogno P. Regulation of autophagy by amino acids and MTOR-dependent signal transduction. *Amino Acids*. 2015;47(10):2037–63.
246. Escobar KA, Cole NH, Mermier CM, VanDusseldorp TA. Autophagy and aging: maintaining the proteome through exercise and caloric restriction. *Aging Cell*. 2019;18(1):e12876.
247. Brandt N, Gunnarsson TP, Bangsbo J, Pilegaard H. Exercise and exercise training–induced increase in autophagy markers in human skeletal muscle. *Physiol Rep*. 2018;6(7):e13651.
248. Escobar KA, Cole NH, Mermier CM, VanDusseldorp TA. Autophagy and aging: maintaining the proteome through exercise and caloric restriction. *Aging Cell*. 2019;18(1):e12876.
249. Cuervo AM. Calorie restriction and aging: the ultimate "cleansing diet." *J Gerontol A Biol Sci Med Sci*. 2008;63(6):547–9.
250. Melnik BC. Leucine signaling in the pathogenesis of type 2 diabetes and obesity. *World J Diabetes*. 2012;3(3):38.

251. Rittig N, Bach E, Thomsen HH, et al. Anabolic effects of leucine-rich whey protein, carbohydrate, and soy protein with and without β-hydroxy-β-methylbutyrate (Hmb) during fasting-induced catabolism: a human randomized crossover trial. *Clin Nutr*. 2017;36(3):697–705.
252. Tareke E, Rydberg P, Karlsson P, Eriksson S, Törnqvist M. Analysis of acrylamide, a carcinogen formed in heated foodstuffs. *J Agric Food Chem*. 2002;50:4998−5006.
253. Song D, Xu C, Holck AL, Liu R. Acrylamide inhibits autophagy, induces apoptosis and alters cellular metabolic profiles. *Ecotoxicol Environ Saf*. 2021;208:111543.
254. Huang M, Jiao J, Wang J, Chen X, Zhang Y. Associations of hemoglobin biomarker levels of acrylamide and all-cause and cardiovascular disease mortality among U.S. adults: National Health and Nutrition Examination Survey 2003–2006. *Environ Pollut*. 2018;238:852–8.
255. Naruszewicz M, Zapolska-Downar D, Kośmider A, et al. Chronic intake of potato chips in humans increases the production of reactive oxygen radicals by leukocytes and increases plasma C-reactive protein: a pilot study. *Am J Clin Nutr*. 2009;89(3):773–7.
256. Chase P, Mitchell K, Morley JE. In the steps of giants: the early geriatrics texts. *J Am Geriatr Soc*. 2000;48(1):89–94.
257. Madeo F, Zimmermann A, Maiuri MC, Kroemer G. Essential role for autophagy in life span extension. *J Clin Invest*. 2015;125(1):85–93.
258. Arnesen E, Huseby NE, Brenn T, Try K. The Tromsø Heart Study: distribution of, and determinants for, gamma-glutamyltransferase in a free-living population. *Scand J Clin Lab Invest*. 1986;46(1):63–70.
259. Ruhl CE, Everhart JE. Coffee and tea consumption are associated with a lower incidence of chronic liver disease in the United States. *Gastroenterology*. 2005;129(6):1928–36.
260. Hayat U, Siddiqui AA, Okut H, Afroz S, Tasleem S, Haris A. The effect of coffee consumption on the non-alcoholic fatty liver disease and liver fibrosis: a meta-analysis of 11 epidemiological studies. *Ann Hepatol*. 2021;20:100254.
261. Ray K. Caffeine is a potent stimulator of autophagy to reduce hepatic lipid content—a coffee for NAFLD? *Nat Rev Gastroenterol Hepatol* 2013;10:563.

262. Sinha RA, Farah BL, Singh BK, et al. Caffeine stimulates hepatic lipid metabolism by the autophagy-lysosomal pathway in mice. *Hepatology*. 2014;59(4):1366–80.
263. Czachor J, Miłek M, Galiniak S, Stępień K, Dżugan M, Mołoń M. Coffee extends yeast chronological lifespan through antioxidant properties. *Int J Mol Sci*. 2020;21(24):9510.
264. Sutphin GL, Bishop E, Yanos ME, Moller RM, Kaeberlein M. Caffeine extends life span, improves healthspan, and delays age-associated pathology in *Caenorhabditis elegans*. *Longev Healthspan*. 2012;1(1):9.
265. Pietrocola F, Malik SA, Mariño G, et al. Coffee induces autophagy in vivo. *Cell Cycle*. 2014;13(12):1987–94.
266. Takahashi K, Yanai S, Shimokado K, Ishigami A. Coffee consumption in aged mice increases energy production and decreases hepatic mTOR levels. *Nutrition*. 2017;38:1–8.
267. Saab S, Mallam D, Cox GA, Tong MJ. Impact of coffee on liver diseases: a systematic review. *Liver Int*. 2014;34(4):495–504.
268. Kanbay M, Siriopol D, Copur S, et al. Effect of coffee consumption on renal outcome: a systematic review and meta-analysis of clinical studies. *J Ren Nutr*. 2021;31(1):5–20.
269. Grosso G, Godos J, Galvano F, Giovannucci EL. Coffee, caffeine, and health outcomes: an umbrella review. *Annu Rev Nutr*. 2017;37:131–56.
270. Thomas DR, Hodges ID. Dietary research on coffee: improving adjustment for confounding. *Curr Dev Nutr*. 2020;4(nzz142).
271. Duregon E, Bernier M, de Cabo R. A glance back at the journal of gerontology—coffee, dietary interventions and life span. *J Geront A Biol Sci Med Sci*. 2020;75(11):2029–30.
272. Li Q, Liu Y, Sun X, et al. Caffeinated and decaffeinated coffee consumption and risk of all-cause mortality: a dose–response meta-analysis of cohort studies. *J Hum Nut Diet*. 2019;32(3):279–87.
273. Spiegelhalter D. Using speed of ageing and “microlives” to communicate the effects of lifetime habits and environment. *BMJ*. 2012 Dec 14;345:e8223.
274. Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses

of multiple health outcomes. *BMJ*. 2017;359:j5024.
275. Loftfield E, Cornelis MC, Caporaso N, Yu K, Sinha R, Freedman N. Association of coffee drinking with mortality by genetic variation in caffeine metabolism: findings from the UK Biobank. *JAMA Intern Med*. 2018;178(8):1086.
276. Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ*. 2017;359:j5024.
277. Gao LJ, Dai Y, Li XQ, Meng S, Zhong ZQ, Xu SJ. Chlorogenic acid enhances autophagy by upregulating lysosomal function to protect against SH-SY5Y cell injury induced by H_2O_2. *Exp Ther Med*. 2021;21(5):426.
278. Ludwig IA, Mena P, Calani L, et al. Variations in caffeine and chlorogenic acid contents of coffees: what are we drinking? *Food Funct*. 2014;5(8):1718–26.
279. Mills CE, Oruna-Concha MJ, Mottram DS, Gibson GR, Spencer JPE. The effect of processing on chlorogenic acid content of commercially available coffee. *Food Chem*. 2013;141(4):3335–40.
280. Ludwig IA, Mena P, Calani L, et al. Variations in caffeine and chlorogenic acid contents of coffees: what are we drinking? *Food Funct*. 2014;5(8):1718–26.
281. Corrêa TAF, Monteiro MP, Mendes TMN, et al. Medium light and medium roast paper-filtered coffee increased antioxidant capacity in healthy volunteers: results of a randomized trial. *Plant Foods Hum Nutr*. 2012;67(3):277–82.
282. DiBaise JK. A randomized, double-blind comparison of two different coffee-roasting processes on development of heartburn and dyspepsia in coffee-sensitive individuals. *Dig Dis Sci*. 2003;48(4):652–6.
283. Liu J, Wang Q, Zhang H, Yu D, Jin S, Ren F. Interaction of chlorogenic acid with milk proteins analyzed by spectroscopic and modeling methods. *Spectrosc Lett*. 2016;49(1):44–50.
284. Duarte GS, Farah A. Effect of simultaneous consumption of milk and coffee on chlorogenic acids' bioavailability in humans. *J Agric Food Chem*. 2011;59(14):7925–31.

285. Lorenz M, Jochmann N, von Krosigk A, et al. Addition of milk prevents vascular protective effects of tea. *Eur Heart J*. 2007;28(2):219–23.
286. Serafini M, Testa MF, Villaño D, et al. Antioxidant activity of blueberry fruit is impaired by association with milk. *Free Radic Biol Med*. 2009;46(6):769–74.
287. Serafini M, Bugianesi R, Maiani G, Valtuena S, De Santis S, Crozier A. Plasma antioxidants from chocolate. *Nature*. 2003;424(6952):1013.
288. Budryn G, Pałecz B, Rachwał-Rosiak D, et al. Effect of inclusion of hydroxycinnamic and chlorogenic acids from green coffee bean in β-cyclodextrin on their interactions with whey, egg white and soy protein isolates. *Food Chem*. 2015;168:276–87.
289. Felberg I, Farah A, Monteiro M, et al. Effect of simultaneous consumption of soymilk and coffee on the urinary excretion of isoflavones, chlorogenic acids and metabolites in healthy adults. *J Funct Foods*. 2015;19:688–99.
290. Colombo R, Papetti A. An outlook on the role of decaffeinated coffee in neurodegenerative diseases. *Crit Rev Food Sci Nutr*. 2020;60(5):760–79.
291. Tverdal A, Selmer R, Cohen JM, Thelle DS. Coffee consumption and mortality from cardiovascular diseases and total mortality: does the brewing method matter? *Eur J Prev Cardiol*. 2020;27(18):1986–93.
292. Aubin HJ, Luquiens A, Berlin I. Letter by Aubin et al regarding article, “Association of coffee consumption with total and cause-specific mortality in 3 large prospective cohorts.” *Circulation*. 2016;133(20):e659.
293. Sakaki JR, Melough MM, Provatas AA, Perkins C, Chun OK. Evaluation of estrogenic chemicals in capsule and French press coffee using ultra-performance liquid chromatography with tandem mass spectrometry. *Toxicol Rep*. 2020;7:1020–4.
294. Yang CZ, Yaniger SI, Jordan VC, Klein DJ, Bittner GD. Most plastic products release estrogenic chemicals: a potential health problem that can be solved. *Environ Health Perspect*. 2011;119(7):989–96.
295. Sakaki JR, Melough MM, Provatas AA, Perkins C, Chun OK. Evaluation of estrogenic chemicals in capsule and French press

coffee using ultra-performance liquid chromatography with tandem mass spectrometry. *Toxicol Rep*. 2020;7:1020–4.

296. Li M, Wang M, Guo W, Wang J, Sun X. The effect of caffeine on intraocular pressure: a systematic review and meta-analysis. *Graefes Arch Clin Exp Ophthalmol*. 2011;249(3):435–42.

297. Kang JH, Willett WC, Rosner BA, Hankinson SE, Pasquale LR. Caffeine consumption and the risk of primary open-angle glaucoma: a prospective cohort study. *Invest Ophthalmol Vis Sci.* 2008;49(5):1924–31.

298. Gleason JL, Richter HE, Redden DT, Goode PS, Burgio KL, Markland AD. Caffeine and urinary incontinence in US women. *Int Urogynecol J*. 2013;24(2):295–302.

299. Davis NJ, Vaughan CP, Johnson TM, et al. Caffeine intake and its association with urinary incontinence in United States men: results from National Health and Nutrition Examination Surveys 2005–2006 and 2007–2008. *J Urol*. 2013;189(6):2170–4.

300. Bonilha L, Li LM. Heavy coffee drinking and epilepsy. *Seizure.* 2004;13(4):284–5.

301. Surdea-Blaga T, Negrutiu DE, Palage M, Dumitrascu DL. Food and gastroesophageal reflux disease. *Curr Med Chem*. 2019;26(19):3497–511.

302. Lloret-Linares C, Lafuente-Lafuente C, Chassany O, et al. Does a single cup of coffee at dinner alter the sleep? A controlled cross-over randomised trial in real-life conditions. *Nutr Diet*. 2012;69(4):250–5.

303. Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ*. 2017;359:j5024.

304. Son H, Song HJ, Seo HJ, Lee H, Choi SM, Lee S. The safety and effectiveness of self-administered coffee enema: a systematic review of case reports. *Medicine*. 2020;99(36):e21998.

305. Dirks-Naylor AJ. The benefits of coffee on skeletal muscle. *Life Sci*. 2015;143:182–6.

306. Juliano LM, Griffiths RR. A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features. *Psychopharmacology* (Berl). 2004;176(1):1–29.

307. O'Keefe JH, Bhatti SK, Patil HR, DiNicolantonio JJ, Lucan SC, Lavie CJ. Effects of habitual coffee consumption on cardiometabolic disease, cardiovascular health, and all-cause mortality. *J Am Coll Cardiol*. 2013;62(12):1043–51.
308. Mendez JD. The other legacy of Antonie van Leeuwenhoek: the polyamines. *J Clin Mol Endocrinol*. 2017;02(01):e107.
309. Bachrach U. The early history of polyamine research. *Plant Physiol Biochem*. 2010;48(7):490–5.
310. Guerra GP, Rubin MA, Mello CF. Modulation of learning and memory by natural polyamines. *Pharmacol Res*. 2016;112:99–118.
311. Madeo F, Bauer MA, Carmona-Gutierrez D, Kroemer G. Spermidine: a physiological autophagy inducer acting as an anti-aging vitamin in humans? *Autophagy*. 2019;15(1):165–8.
312. Madeo F, Eisenberg T, Pietrocola F, Kroemer G. Spermidine in health and disease. *Science*. 2018;359(6374):eaan2788.
313. Hunter DC, Burritt DJ. Polyamines of plant origin: an important dietary consideration for human health. In: Rao V, ed. *Phytochemicals as Nutraceuticals: Global Approaches to Their Role in Nutrition and Health*. InTech; 2012:225–44.
314. Kaeberlein M. Spermidine surprise for a long life. *Nat Cell Biol*. 2009;11(11):1277–8.
315. Hunter DC, Burritt DJ. Polyamines of plant origin: an important dietary consideration for human health. In: Rao V, ed. *Phytochemicals as Nutraceuticals: Global Approaches to Their Role in Nutrition and Health*. InTech; 2012:225–44.
316. Minois N, Carmona-Gutierrez D, Madeo F. Polyamines in aging and disease. *Aging (Albany NY)*. 2011;3(8):716–32.
317. Soda K, Dobashi Y, Kano Y, Tsujinaka S, Konishi F. Polyamine-rich food decreases age-associated pathology and mortality in aged mice. *Exp Gerontol*. 2009;44(11):727–32.
318. Yue F, Li W, Zou J, et al. Spermidine prolongs lifespan and prevents liver fibrosis and hepatocellular carcinoma by activating map1s-mediated autophagy. *Cancer Res*. 2017;77(11):2938–51.
319. Eisenberg T, Knauer H, Schauer A, et al. Induction of autophagy by spermidine promotes longevity. *Nat Cell Biol*. 2009;11(11):1305–14.

320. Rudman D, Kutner MH, Chawla RK, Goldsmith MA, Blackston RD, Bain R. Serum and urine polyamines in normal and in short children. *J Clin Invest*. 1979;64(6):1661–8.
321. Pucciarelli S, Moreschini B, Micozzi D, et al. Spermidine and spermine are enriched in whole blood of nona/centenarians. *Rejuvenation Res*. 2012;15(6):590–5.
322. Piore A. Can blood from young people slow aging? Silicon Valley bets it will. *Newsweek*. April 7, 2021. https://www.newsweek.com/2021/04/16/can-blood-young-people-slow-aging-silicon-valley-has-bet-billions-it-will-1581447.html. Accessed December 25, 2022.
323. Viltard M, Durand S, Pérez-Lanzón M, et al. The metabolomic signature of extreme longevity: naked mole rats versus mice. *Aging (Albany NY)*. 2019;11(14):4783–800.
324. Pucciarelli S, Moreschini B, Micozzi D, et al. Spermidine and spermine are enriched in whole blood of nona/centenarians. *Rejuvenation Res*. 2012;15(6):590–5.
325. Eisenberg T, Abdellatif M, Schroeder S, et al. Cardioprotection and lifespan extension by the natural polyamine spermidine. *Nat Med*. 2016;22(12):1428–38.
326. Flurkey K, Currer JM, Harrison DE. 2007. The Mouse in Aging Research. In *The Mouse in Biomedical Research 2nd Edition*. Fox JG, et al, editors. American College Laboratory Animal Medicine (Elsevier), Burlington, MA. pp. 637–72.
327. Eisenberg T, Abdellatif M, Schroeder S, et al. Cardioprotection and lifespan extension by the natural polyamine spermidine. *Nat Med*. 2016;22(12):1428–38.
328. Filfan M, Olaru A, Udristoiu I, et al. Long-term treatment with spermidine increases health span of middle-aged Sprague-Dawley male rats. *GeroScience*. 2020;42(3):937–49.
329. Pekar T, Bruckner K, Pauschenwein-Frantsich S, et al. The positive effect of spermidine in older adults suffering from dementia: first results of a 3-month trial. *Wien Klin Wochenschr*. 2021;133:484–91.
330. Handa AK, Fatima T, Mattoo AK. Polyamines: bio-molecules with diverse functions in plant and human health and disease. *Front Chem*. 2018;6.

331. Rinaldi F, Marzani B, Pinto D, Ramot Y. A spermidine-based nutritional supplement prolongs the anagen phase of hair follicles in humans: a randomized, placebo-controlled, double-blind study. *Derm Pract Concept*. Published online October 31, 2017:17–21.
332. Metur SP, Klionsky DJ. The curious case of polyamines: spermidine drives reversal of B cell senescence. *Autophagy*. 2020;16(3):389–90.
333. Zhang H, Alsaleh G, Feltham J, et al. Polyamines control eIF5A hypusination, TFEB translation, and autophagy to reverse B cell senescence. *Mol Cell*. 2019;76(1):110–25.e9.
334. Metur SP, Klionsky DJ. The curious case of polyamines: spermidine drives reversal of B cell senescence. *Autophagy*. 2020;16(3):389–90.
335. de Cabo R, Navas P. Spermidine to the rescue for an aging heart. *Nat Med*. 2016;22(12):1389–90.
336. Eisenberg T, Abdellatif M, Schroeder S, et al. Cardioprotection and lifespan extension by the natural polyamine spermidine. *Nat Med*. 2016;22(12):1428–38.
337. Fetterman JL, Holbrook M, Flint N, et al. Restoration of autophagy in endothelial cells from patients with diabetes mellitus improves nitric oxide signaling. *Atherosclerosis*. 2016;247:207–17.
338. Eisenberg T, Abdellatif M, Schroeder S, et al. Cardioprotection and lifespan extension by the natural polyamine spermidine. *Nat Med*. 2016;22(12):1428–38.
339. Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018;108(2):371–80.
340. Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018;108(2):371–80.
341. Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018;108(2):371–80.
342. Madeo F, Bauer MA, Carmona-Gutierrez D, Kroemer G. Spermidine: a physiological autophagy inducer acting as an anti-aging vitamin in humans? *Autophagy*. 2019;15(1):165–8.
343. Pekar T, Bruckner K, Pauschenwein-Frantsich S, et al. The positive effect of spermidine in older adults suffering from dementia: first

results of a 3-month trial. *Wien Klin Wochenschr*. 2021;133:484–91.
344. Madeo F, Eisenberg T, Pietrocola F, Kroemer G. Spermidine in health and disease. *Science*. 2018;359(6374):eaan2788.
345. Madeo F, Hofer SJ, Pendl T, et al. Nutritional aspects of spermidine. *Annu Rev Nutr*. 2020;40(1):135–59.
346. Zoumas-Morse C, Rock CL, Quintana EL, Neuhouser ML, Gerner EW, Meyskens FL. Development of a polyamine database for assessing dietary intake. *J Am Diet Assoc*. 2007;107(6):1024–7.
347. Kalač P. Health effects and occurrence of dietary polyamines: a review for the period 2005–mid 2013. *Food Chem*. 2014;161:27–39.
348. Ali MA, Poortvliet E, Strömberg R, Yngve A. Polyamines: total daily intake in adolescents compared to the intake estimated from the Swedish Nutrition Recommendations Objectified (Sno). *Food Nutr Res*. 2011;55(1):5455.
349. Varghese N, Werner S, Grimm A, Eckert A. Dietary mitophagy enhancer: a strategy for healthy brain aging? *Antioxidants* (Basel). 2020;9(10).
350. Handa AK, Fatima T, Mattoo AK. Polyamines: bio-molecules with diverse functions in plant and human health and disease. *Front Chem*. 2018;6.
351. Nishimura K, Shiina R, Kashiwagi K, Igarashi K. Decrease in polyamines with aging and their ingestion from food and drink. *J Biochem*. 2006;139(1):81–90.
352. Okamoto A, Sugi E, Koizumi Y, Yanagida F, Udaka S. Polyamine content of ordinary foodstuffs and various fermented foods. *Biosci Biotechnol Biochem*. 1997;61(9):1582–4.
353. Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018;108(2):371–80.
354. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
355. Kalač P. Health effects and occurrence of dietary polyamines: a review for the period 2005–mid 2013. *Food Chem*. 2014;161:27–39.
356. Kalač P. Health effects and occurrence of dietary polyamines: a review for the period 2005–mid 2013. *Food Chem*. 2014;161:27–39.

357. Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018;108(2):371–80.
358. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
359. Nishibori N, Fujihara S, Akatuki T. Amounts of polyamines in foods in Japan and intake by Japanese. *Food Chem*. 2007;100(2):491–7.
360. Nishimura K, Shiina R, Kashiwagi K, Igarashi K. Decrease in polyamines with aging and their ingestion from food and drink. *J Biochem*. 2006;139(1):81–90.
361. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
362. Cipolla BG, Havouis R, Moulinoux JP. Polyamine contents in current foods: a basis for polyamine reduced diet and a study of its long term observance and tolerance in prostate carcinoma patients. *Amino Acids*. 2007;33(2):203–12.
363. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
364. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
365. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
366. Nishibori N, Fujihara S, Akatuki T. Amounts of polyamines in foods in Japan and intake by Japanese. *Food Chem*. 2007;100(2):491–7.
367. Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018;108(2):371–80.
368. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.

369. Cipolla BG, Havouis R, Moulinoux JP. Polyamine contents in current foods: a basis for polyamine reduced diet and a study of its long term observance and tolerance in prostate carcinoma patients. *Amino Acids*. 2007;33(2):203–12.
370. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
371. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
372. Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018;108(2):371–80.
373. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
374. Nishimura K, Shiina R, Kashiwagi K, Igarashi K. Decrease in polyamines with aging and their ingestion from food and drink. *J Biochem*. 2006;139(1):81–90.
375. Cipolla BG, Havouis R, Moulinoux JP. Polyamine contents in current foods: a basis for polyamine reduced diet and a study of its long term observance and tolerance in prostate carcinoma patients. *Amino Acids*. 2007;33(2):203–12.
376. Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018;108(2):371–80.
377. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
378. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
379. Kalač P. Health effects and occurrence of dietary polyamines: a review for the period 2005–mid 2013. *Food Chem*. 2014;161:27–39.
380. Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J*

Clin Nutr. 2018;108(2):371–80.
381. Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018;108(2):371–80.
382. Cipolla BG, Havouis R, Moulinoux JP. Polyamine contents in current foods: a basis for polyamine reduced diet and a study of its long term observance and tolerance in prostate carcinoma patients. *Amino Acids*. 2007;33(2):203–12.
383. Cipolla BG, Havouis R, Moulinoux JP. Polyamine contents in current foods: a basis for polyamine reduced diet and a study of its long term observance and tolerance in prostate carcinoma patients. *Amino Acids*. 2007;33(2):203–12.
384. Nishibori N, Fujihara S, Akatuki T. Amounts of polyamines in foods in Japan and intake by Japanese. *Food Chem*. 2007;100(2):491–7.
385. Nishimura K, Shiina R, Kashiwagi K, Igarashi K. Decrease in polyamines with aging and their ingestion from food and drink. *J Biochem*. 2006;139(1):81–90.
386. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
387. Nishimura K, Shiina R, Kashiwagi K, Igarashi K. Decrease in polyamines with aging and their ingestion from food and drink. *J Biochem*. 2006;139(1):81–90.
388. Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018;108(2):371–80.
389. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
390. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
391. Agricultural Research Service, United States Department of Agriculture. Dill weed, fresh. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html?query=dill&utf8=%E2%9C%93&affiliate=usda&commit=Search#/fo

od-details/172233/nutrients. Published April 1, 2019. Accessed April 30, 2021.
392. Kalač P. Health effects and occurrence of dietary polyamines: a review for the period 2005–mid 2013. *Food Chem*. 2014;161:27–39.
393. Agricultural Research Service, United States Department of Agriculture. Potato, baked, NFS. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html?query=potato&utf8=%E2%9C%93&affiliate=usda&commit=Search#/food-details/1102880/nutrients. Published October 30, 2020. Accessed April 30, 2021.
394. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nut Res*. 2011;55(1):5572.
395. Agricultural Research Service, United States Department of Agriculture. Garlic, raw. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html?query=garlic&utf8=%E2%9C%93&affiliate=usda&commit=Search#/food-details/1103354/nutrients. Published October 30, 2020. Accessed April 30, 2021.
396. Zoumas-Morse C, Rock CL, Quintana EL, Neuhouser ML, Gerner EW, Meyskens FL. Development of a polyamine database for assessing dietary intake. *J Am Diet Assoc*. 2007;107(6):1024–7.
397. Buyukuslu N, Hizli H, Esin K, Garipagaoglu M. A cross-sectional study: nutritional polyamines in frequently consumed foods of the Turkish population. *Foods*. 2014;3(4):541–57.
398. Nishibori N, Fujihara S, Akatuki T. Amounts of polyamines in foods in Japan and intake by Japanese. *Food Chem*. 2007;100(2):491–7.
399. Reis GCL, Dala-Paula BM, Tavano OL, Guidi LR, Godoy HT, Gloria MBA. *In vitro* digestion of spermidine and amino acids in fresh and processed *Agaricus bisporus* mushroom. *Food Res Int*. 2020;137:109616.
400. Pietrocola F, Castoldi F, Kepp O, Carmona-Gutierrez D, Madeo F, Kroemer G. Spermidine reduces cancer-related mortality in humans. *Autophagy*. 2019;15(2):362–5.
401. Nishimura K, Shiina R, Kashiwagi K, Igarashi K. Decrease in polyamines with aging and their ingestion from food and drink. *J*

Biochem. 2006;139(1):81–90.
402. Eisenberg T, Abdellatif M, Schroeder S, et al. Cardioprotection and lifespan extension by the natural polyamine spermidine. *Nat Med*. 2016;22(12):1428–38.
403. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
404. Agricultural Research Service, United States Department of Agriculture. Mangos, raw. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html#/food-details/169910/nutrients. Published April 2018. Accessed February 10, 2023.
405. Nishimura K, Shiina R, Kashiwagi K, Igarashi K. Decrease in polyamines with aging and their ingestion from food and drink. *J Biochem*. 2006;139(1):81–90.
406. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
407. Soda K, Binh P, Kawakami M. Mediterranean diet and polyamine intake: possible contribution of increased polyamine intake to inhibition of age-associated disease. *NDS*. Published online December 2010:1.
408. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
409. Okamoto A, Sugi E, Koizumi Y, Yanagida F, Udaka S. Polyamine content of ordinary foodstuffs and various fermented foods. *Biosci Biotechnol Biochem*. 1997;61(9):1582–4.
410. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
411. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
412. Cipolla BG, Havouis R, Moulinoux JP. Polyamine contents in current foods: a basis for polyamine reduced diet and a study of its long term

observance and tolerance in prostate carcinoma patients. *Amino Acids*. 2007;33(2):203–12.

413. Konakovsky V, Focke M, Hoffmann-Sommergruber K, et al. Levels of histamine and other biogenic amines in high-quality red wines. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*. 2011;28(4):408–16.

414. Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018;108(2):371–80.

415. Okamoto A, Sugi E, Koizumi Y, Yanagida F, Udaka S. Polyamine content of ordinary foodstuffs and various fermented foods. *Biosci Biotechnol Biochem*. 1997;61(9):1582–4.

416. Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018;108(2):371–80.

417. Agricultural Research Service, United States Department of Agriculture. Lettuce, raw. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html?query=lettuce&utf8=%E2%9C%93&affiliate=usda&commit=Search#/food-details/1103358/nutrients. Published October 30, 2020. Accessed April 30, 2021.

418. Fukushima T, Tanaka K, Ushijima K, Moriyama M. Retrospective study of preventive effect of maize on mortality from Parkinson's disease in Japan. *Asia Pac J Clin Nutr*. 2003;12(4):447–50.

419. McCarty MF, Lerner A. Perspective: low risk of Parkinson's disease in quasi-vegan cultures may reflect GCN2-mediated upregulation of Parkin. *Adv Nutr*. 2021;12(2):355–62.

420. Rossetto MRM, Vianello F, Saeki MJ, Lima GPP. Polyamines in conventional and organic vegetables exposed to exogenous ethylene. *Food Chem*. 2015;188:218–24.

421. Kalač P, Krausová P. A review of dietary polyamines: formation, implications for growth and health and occurrence in foods. *Food Chem*. 2005;90(1–2):219–30.

422. Kozová M, Kalač P, Pelikánová T. Contents of biologically active polyamines in chicken meat, liver, heart and skin after slaughter and

their changes during meat storage and cooking. *Food Chem*. 2009;116(2):419–25.
423. *Sources of Energy among the US Population*. Risk Factor Monitoring and Methods Branch Website. Applied Research Program. National Cancer Institute.
424. Binh PNT, Soda K, Kawakami M. Gross domestic product and dietary pattern among 49 western countries with a focus on polyamine intake. *Health*. 2010;02(11):1327–34.
425. Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018;108(2):371–80.
426. Soda K, Binh P, Kawakami M. Mediterranean diet and polyamine intake: possible contribution of increased polyamine intake to inhibition of age-associated disease. *NDS*. Published online December 2010:1.
427. Arulkumar A, Paramithiotis S, Paramasivam S. Biogenic amines in fresh fish and fishery products and emerging control. *Aquac Fish*. Published online March 16, 2021. https://www.sciencedirect.com/science/article/pii/S2468550X21000198. Accessed December 25, 2022.
428. Cipolla BG, Havouis R, Moulinoux JP. Polyamine contents in current foods: a basis for polyamine reduced diet and a study of its long term observance and tolerance in prostate carcinoma patients. *Amino Acids*. 2007;33(2):203–12.
429. Kalač P. Health effects and occurrence of dietary polyamines: a review for the period 2005–mid 2013. *Food Chem*. 2014;161:27–39.
430. Soda K, Binh P, Kawakami M. Mediterranean diet and polyamine intake: possible contribution of increased polyamine intake to inhibition of age-associated disease. *NDS*. Published online December 2010:1.
431. Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018;108(2):371–80.
432. Kalač P. Health effects and occurrence of dietary polyamines: a review for the period 2005–mid 2013. *Food Chem*. 2014;161:27–39.

433. Nishimura K, Shiina R, Kashiwagi K, Igarashi K. Decrease in polyamines with aging and their ingestion from food and drink. *J Biochem*. 2006;139(1):81–90.
434. Nishibori N, Fujihara S, Akatuki T. Amounts of polyamines in foods in Japan and intake by Japanese. *Food Chem*. 2007;100(2):491–7.
435. Cipolla BG, Havouis R, Moulinoux JP. Polyamine contents in current foods: a basis for polyamine reduced diet and a study of its long term observance and tolerance in prostate carcinoma patients. *Amino Acids*. 2007;33(2):203–12.
436. Nishibori N, Fujihara S, Akatuki T. Amounts of polyamines in foods in Japan and intake by Japanese. *Food Chem*. 2007;100(2):491–7.
437. Kalač P. Health effects and occurrence of dietary polyamines: a review for the period 2005–mid 2013. *Food Chem*. 2014;161:27–39.
438. Nishibori N, Fujihara S, Akatuki T. Amounts of polyamines in foods in Japan and intake by Japanese. *Food Chem*. 2007;100(2):491–7.
439. Atiya Ali M, Poortvliet E, Strömberg R, Yngve A. Polyamines in foods: development of a food database. *Food Nutr Res*. 2011;55(1):5572.
440. Kiechl S, Pechlaner R, Willeit P, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am J Clin Nutr*. 2018;108(2):371–80.
441. Pekar T, Bruckner K, Pauschenwein-Frantsich S, et al. The positive effect of spermidine in older adults suffering from dementia: first results of a 3-month trial. *Wien Klin Wochenschr*. 2021;133:484–91.
442. MacMillen H. Could consuming semen make you live longer? *Cosmopolitan*. https://www.cosmo.ph/relationships/could-semen-make-you-live-longer-src-intl-a1553–20161201?ref=feed_1. Published online November 17, 2016. Accessed May 19, 2021.
443. Scott E. Drinking semen might help you live longer. *Metro.co.uk.* https://metro.co.uk/2016/11/18/drinking-semen-might-actually-help-you-live-longer-6266961/. Published November 18, 2016. Accessed April 29, 2021.
444. Owen DH, Katz DF. A review of the physical and chemical properties of human semen and the formulation of a semen simulant. *J Androl*. 2005;26(4):459–69.

445. Fair WR, Clark RB, Wehner N. A correlation of seminal polyamine levels and semen analysis in the human. *Fertil Steril*. 1972;23(1):38–42.
446. Definition of testament. Merriam-Webster.com. https://www.merriam-webster.com/dictionary/testament. Accessed February 11, 2023.
447. Agricultural Research Service, United States Department of Agriculture. Wheat germ, plain. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html?query=wheat+germ&utf8=%E2%9C%93&affiliate=usda&commit=Search#/food-details/1101819/nutrients. Published October 30, 2020. Accessed April 30, 2021.
448. Liaqat H, Jeong E, Kim KJ, Kim JY. Effect of wheat germ on metabolic markers: a systematic review and meta-analysis of randomized controlled trials. *Food Sci Biotechnol*. 2020;29(6):739–49.
449. McCarty MF, Lerner A. Perspective: low risk of Parkinson's disease in quasi-vegan cultures may reflect GCN2-mediated upregulation of Parkin. *Adv Nutr*. 2021;12(2):355–62.
450. Cara L, Borel P, Armand M, et al. Plasma lipid lowering effects of wheat germ in hypercholesterolemic subjects. *Plant Foods Hum Nutr*. 1991;41(2):135–50.
451. Moreira-Rosário A, Pinheiro H, Marques C, Teixeira JA, Calhau C, Azevedo LF. Does intake of bread supplemented with wheat germ have a preventive role on cardiovascular disease risk markers in healthy volunteers? A randomised, controlled, crossover trial. *BMJ Open*. 2019;9(1):e023662.
452. Atallahi M, Amir Ali Akbari S, Mojab F, Alavi Majd H. Effects of wheat germ extract on the severity and systemic symptoms of primary dysmenorrhea: a randomized controlled clinical trial. *Iran Red Crescent Med J*. 2014;16(8).
453. Delzenne NM, Neyrinck AM, Cani PD. Gut microbiota and metabolic disorders: how prebiotic can work? *Br J Nutr*. 2013;109 Suppl 2:S81–5.
454. Milovic V. Polyamines in the gut lumen: bioavailability and biodistribution. *Eur J Gastroenterol Hepatol*. 2001;13(9):1021–5.

455. Matsumoto M, Kurihara S, Kibe R, Ashida H, Benno Y. Longevity in mice is promoted by probiotic-induced suppression of colonic senescence dependent on upregulation of gut bacterial polyamine production. *PLoS One*. 2011;6(8):e23652.
456. Noack J, Kleessen B, Proll J, Dongowski G, Blaut M. Dietary guar gum and pectin stimulate intestinal microbial polyamine synthesis in rats. *J Nutr*. 1998;128(8):1385–91.
457. Hunter DC, Burritt DJ. Polyamines of plant origin: an important dietary consideration for human health. In: Rao V, ed. *Phytochemicals as Nutraceuticals: Global Approaches to Their Role in Nutrition and Health*. InTech; 2012:225–44.
458. Mäkivuokko H, Tiihonen K, Tynkkynen S, Paulin L, Rautonen N. The effect of age and non-steroidal anti-inflammatory drugs on human intestinal microbiota composition. *Br J Nutr*. 2010;103(2):227–34.
459. Hunter DC, Burritt DJ. Polyamines of plant origin: an important dietary consideration for human health. In: Rao V, ed. *Phytochemicals as Nutraceuticals: Global Approaches to Their Role in Nutrition and Health*. InTech; 2012:225–44.
460. Matsumoto M, Aranami A, Ishige A, Watanabe K, Benno Y. LKM512 yogurt consumption improves the intestinal environment and induces the T-helper type 1 cytokine in adult patients with intractable atopic dermatitis. *Clin Exp Allergy*. 2007;37(3):358–70.
461. Matsumoto M, Kurihara S, Kibe R, Ashida H, Benno Y. Longevity in mice is promoted by probiotic-induced suppression of colonic senescence dependent on upregulation of gut bacterial polyamine production. *PLoS One*. 2011;6(8):e23652.
462. Kibe R, Kurihara S, Sakai Y, et al. Upregulation of colonic luminal polyamines produced by intestinal microbiota delays senescence in mice. *Sci Rep*. 2014;4(1):4548.
463. Matsumoto M, Kitada Y, Naito Y. Endothelial function is improved by inducing microbial polyamine production in the gut: a randomized placebo-controlled trial. *Nutrients*. 2019;11(5).
464. Matsumoto M. Prevention of atherosclerosis by the induction of microbial polyamine production in the intestinal lumen. *Biol Pharm Bull*. 2020;43(2):221–9.

465. Noack J, Kleessen B, Proll J, Dongowski G, Blaut M. Dietary guar gum and pectin stimulate intestinal microbial polyamine synthesis in rats. *J Nutr*. 1998;128(8):1385–91.
466. de Cabo R, Navas P. Spermidine to the rescue for an aging heart. *Nat Med*. 2016;22(12):1389–90.
467. Madeo F, Eisenberg T, Pietrocola F, Kroemer G. Spermidine in health and disease. *Science*. 2018;359(6374):eaan2788.
468. Pietrocola F, Castoldi F, Kepp O, Carmona-Gutierrez D, Madeo F, Kroemer G. Spermidine reduces cancer-related mortality in humans. *Autophagy*. 2019;15(2):362–5.
469. Chavez-Dominguez R, Perez-Medina M, Lopez-Gonzalez JS, Galicia-Velasco M, Aguilar-Cazares D. The double-edge sword of autophagy in cancer: from tumor suppression to pro-tumor activity. *Front Oncol*. 2020;10.
470. Madeo F, Eisenberg T, Pietrocola F, Kroemer G. Spermidine in health and disease. *Science*. 2018;359(6374):eaan2788.
471. Madeo F, Eisenberg T, Pietrocola F, Kroemer G. Spermidine in health and disease. *Science*. 2018;359(6374):eaan2788.
472. Barardo D, Thornton D, Thoppil H, et al. The DrugAge database of aging-related drugs. *Aging Cell*. 2017;16(3):594–7.
473. DrugAge: database of ageing-related drugs. https://genomics.senescence.info/drugs/stats.php. Updated February 7, 2023. Accessed February 11, 2023.
474. Janssens GE, Houtkooper RH. Identification of longevity compounds with minimized probabilities of side effects. *Biogerontology*. 2020;21(6):709–19.
475. Hunter DC, Burritt DJ. Polyamines of plant origin: an important dietary consideration for human health. In: Rao V, ed. *Phytochemicals as Nutraceuticals: Global Approaches to Their Role in Nutrition and Health*. InTech; 2012:225–44.
476. Larqué E, Sabater-Molina M, Zamora S. Biological significance of dietary polyamines. *Nutrition*. 2007;23(1):87–95.
477. Khandia R, Dadar M, Munjal A, et al. A comprehensive review of autophagy and its various roles in infectious, non-infectious, and lifestyle diseases: current knowledge and prospects for disease prevention, novel drug design, and therapy. *Cells*. 2019;8(7):674.

478. Hayflick L, Moorhead PS. 1961. The serial cultivation of human diploid cell strains. *Exp. Cell Res.* 25, 585–621.
479. Zhang H, Simon AK. Polyamines reverse immune senescence via the translational control of autophagy. *Autophagy*. 2020;16(1):181–2.
480. Luo J, Si H, Jia Z, Liu D. Dietary anti-aging polyphenols and potential mechanisms. *Antioxidants*. 2021;10(2):283.
481. Schmitt R. Senotherapy: growing old and staying young? *Pflugers Arch-Eur J Physiol*. 2017;469(9):1051–9.
482. van Deursen JM. Senolytic therapies for healthy longevity. *Science*. 2019;364(6441):636–7.
483. Baker DJ, Petersen RC. Cellular senescence in brain aging and neurodegenerative diseases: evidence and perspectives. *J Clin Invest*. 2018;128(4):1208–16.
484. Davan-Wetton CSA, Pessolano E, Perretti M, Montero-Melendez T. Senescence under appraisal: hopes and challenges revisited. *Cell Mol Life Sci*. 2021;78(7):3333–54.
485. Prašnikar E, Borišek J, Perdih A. Senescent cells as promising targets to tackle age-related diseases. *Ageing Res Rev*. 2021;66:101251.
486. Zhu Y, Tchkonia T, Pirtskhalava T, et al. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. *Aging Cell*. 2015;14(4):644–58.
487. van Deursen JM. Senolytic therapies for healthy longevity. *Science*. 2019;364(6441):636–7.
488. Mau T, Yung R. Adipose tissue inflammation in aging. *Exp Gerontol*. 2018;105:27–31.
489. Prašnikar E, Borišek J, Perdih A. Senescent cells as promising targets to tackle age-related diseases. *Ageing Res Rev*. 2021;66:101251.
490. de Keizer PLJ. The fountain of youth by targeting senescent cells? *Trends Mol Med*. 2017;23(1):6–17.
491. Prašnikar E, Borišek J, Perdih A. Senescent cells as promising targets to tackle age-related diseases. *Ageing Res Rev*. 2021;66:101251.
492. van Deursen JM. Senolytic therapies for healthy longevity. *Science*. 2019;364(6441):636–7.
493. Hofmann B. Young blood rejuvenates old bodies: a call for reflection when moving from mice to men. *Transfus Med Hemother*. 2018;45(1):67–71.

494. Ludwig FC, Elashoff RM. Mortality in syngeneic rat parabionts of different chronological age. *Trans N Y Acad Sci*. 1972;34(7):582–7.
495. Lavazza A, Garasic M. Vampires 2.0? The ethical quandaries of young blood infusion in the quest for eternal life. *Med Health Care Philos*. 2020;23(3):421–32.
496. Rebo J, Mehdipour M, Gathwala R, et al. A single heterochronic blood exchange reveals rapid inhibition of multiple tissues by old blood. *Nat Commun*. 2016;7(1):13363.
497. Mehdipour M, Skinner C, Wong N, et al. Rejuvenation of three germ layers tissues by exchanging old blood plasma with saline-albumin. *Aging (Albany NY)*. 2020;12(10):8790–819.
498. Boada M, López OL, Olazarán J, et al. A randomized, controlled clinical trial of plasma exchange with albumin replacement for Alzheimer's disease: primary results of the AMBAR Study. *Alzheimers Dement*. 2020;16(10):1412–25.
499. Biller-Andorno N. Young blood for old hands? A recent anti-ageing trial prompts ethical questions. *Swiss Med Wkly*. 2016;146(3940):w14359.
500. Xu M, Pirtskhalava T, Farr JN, et al. Senolytics improve physical function and increase lifespan in old age. *Nat Med*. 2018;24(8):1246–56.
501. Baker DJ, Childs BG, Durik M, et al. Naturally occurring *p16^{INK4a}*-positive cells shorten healthy lifespan. *Nature*. 2016;530(7589):184–9.
502. de Keizer PLJ. The fountain of youth by targeting senescent cells? *Trends Mol Med*. 2017;23(1):6–17.
503. Chen X, Yi Z, Wong GT, et al. Is exercise a senolytic medicine? A systematic review. *Aging Cell*. 2021;20(1).
504. Fontana L, Mitchell SE, Wang B, et al. The effects of graded caloric restriction: XII. Comparison of mouse to human impact on cellular senescence in the colon. *Aging Cell*. 2018;17(3):e12746.
505. Rusznyák S, Szent-Györgyi A. Vitamin P: flavonols as vitamins. *Nature*. 1936;138(3479):27.
506. Belinha I, Amorim MA, Rodrigues P, et al. Quercetin increases oxidative stress resistance and longevity in *Saccharomyces cerevisiae*. *J Agric Food Chem*. 2007;55(6):2446–51.

507. Formica JV, Regelson W. Review of the biology of quercetin and related bioflavonoids. *Food Chem Toxicol*. 1995;33(12):1061–80.
508. Kirkland JL, Tchkonia T. Senolytic drugs: from discovery to translation. *J Intern Med*. 2020;288(5):518–36.
509. Zhu Y, Tchkonia T, Pirtskhalava T, et al. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. *Aging Cell*. 2015;14(4):644–58.
510. Geng L, Liu Z, Wang S, et al. Low-dose quercetin positively regulates mouse healthspan. *Protein Cell*. 2019;10(10):770–5.
511. Yang D, Wang T, Long M, Li P. Quercetin: its main pharmacological activity and potential application in clinical medicine. *Oxid Med Cell Longev*. 2020;2020:1–13.
512. Murphy MM, Barraj LM, Herman D, Bi X, Cheatham R, Randolph RK. Phytonutrient intake by adults in the United States in relation to fruit and vegetable consumption. *J Acad Nutr Diet*. 2012;112(2):222–9.
513. Mai F, Glomb MA. Isolation of phenolic compounds from iceberg lettuce and impact on enzymatic browning. *J Agric Food Chem*. 2013;61(11):2868–74.
514. Murphy MM, Barraj LM, Herman D, Bi X, Cheatham R, Randolph RK. Phytonutrient intake by adults in the United States in relation to fruit and vegetable consumption. *J Acad Nutr Diet*. 2012;112(2):222–9.
515. Agricultural Research Service, United States Department of Agriculture. Onions, raw. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html?query=onion&utf8=%E2%9C%93&affiliate=usda&commit=Search#/food-details/170000/nutrients. Published April 1, 2019. Accessed May 11, 2021.
516. Agricultural Research Service, United States Department of Agriculture. Onions, red, raw. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html?query=onion&utf8=%E2%9C%93&affiliate=usda&commit=Search#/food-details/790577/nutrients. Published April 1, 2020. Accessed May 11, 2021.

517. Agricultural Research Service, United States Department of Agriculture. Apple, raw. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html?query=apples&utf8=%E2%9C%93&affiliate=usda&commit=Search#/food-details/1102644/nutrients. Published October 30, 2020. Accessed May 11, 2021.
518. Formica JV, Regelson W. Review of the biology of quercetin and related bioflavonoids. *Food Chem Toxicol*. 1995;33(12):1061–80.
519. Amanzadeh E, Esmaeili A, Rahgozar S, Nourbakhshnia M. Application of quercetin in neurological disorders: from nutrition to nanomedicine. *Rev Neurosci*. 2019;30(5):555–72.
520. Vida RG, Fittler A, Somogyi-Végh A, Poór M. Dietary quercetin supplements: assessment of online product informations and quantitation of quercetin in the products by high-performance liquid chromatography. *Phytother Res*. 2019;33(7):1912–20.
521. Harwood M, Danielewska-Nikiel B, Borzelleca JF, Flamm GW, Williams GM, Lines TC. A critical review of the data related to the safety of quercetin and lack of evidence of *in vivo* toxicity, including lack of genotoxic/carcinogenic properties. *Food Chem Toxicol*. 2007;45(11):2179–205.
522. Hickson LJ, Langhi Prata LGP, Bobart SA, et al. Senolytics decrease senescent cells in humans: preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease. *EBioMedicine*. 2019;47:446–56.
523. Briggs ADM, Mizdrak A, Scarborough P. A statin a day keeps the doctor away: comparative proverb assessment modelling study. *BMJ*. 2013;347:f7267.
524. Bondonno NP, Bondonno CP, Blekkenhorst LC, et al. Flavonoid-rich apple improves endothelial function in individuals at risk for cardiovascular disease: a randomized controlled clinical trial. *Mol Nutr Food Res*. 2018;62(3).
525. Huang H, Liao D, Dong Y, Pu R. Effect of quercetin supplementation on plasma lipid profiles, blood pressure, and glucose levels: a systematic review and meta-analysis. *Nutr Rev*. 2020;78(8):615–26.
526. Tabrizi R, Tamtaji OR, Mirhosseini N, et al. The effects of quercetin supplementation on lipid profiles and inflammatory markers among

patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials. *Crit Rev Food Sci Nutr*. 2020;60(11):1855–68.

527. Mohammadi-Sartang M, Mazloom Z, Sherafatmanesh S, Ghorbani M, Firoozi D. Effects of supplementation with quercetin on plasma C-reactive protein concentrations: a systematic review and meta-analysis of randomized controlled trials. *Eur J Clin Nutr*. 2017;71(9):1033–9.
528. Nakagawa T, Itoh M, Ohta K, et al. Improvement of memory recall by quercetin in rodent contextual fear conditioning and human early-stage Alzheimer's disease patients. *Neuroreport*. 2016;27(9):671–6.
529. Nishimura M, Ohkawara T, Nakagawa T, et al. A randomized, double-blind, placebo-controlled study evaluating the effects of quercetin-rich onion on cognitive function in elderly subjects. *FFHD*. 2017;7(6):353–74.
530. Kalus U, Pindur G, Jung F, et al. Influence of the onion as an essential ingredient of the Mediterranean diet on arterial blood pressure and blood fluidity. *Arzneimittelforschung*. 2000;50(9):795–801.
531. Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *Lancet*. 1993;342(8878):1007–11.
532. Briggs ADM, Mizdrak A, Scarborough P. A statin a day keeps the doctor away: comparative proverb assessment modelling study. *BMJ*. 2013;347:f7267.
533. Hwang HV, Tran DT, Rebuffatti MN, Li CS, Knowlton AA. Investigation of quercetin and hyperoside as senolytics in adult human endothelial cells. *PLoS ONE*. 2018;13(1):e0190374.
534. Khan S, Shukla S, Sinha S, Meeran SM. Epigenetic targets in cancer and aging: dietary and therapeutic interventions. *Expert Opin Ther Targets*. 2016;20(6):689–703.
535. Geng L, Liu Z, Zhang W, et al. Chemical screen identifies a geroprotective role of quercetin in premature aging. *Protein Cell*. 2019;10(6):417–35.
536. Chondrogianni N, Kapeta S, Chinou I, Vassilatou K, Papassideri I, Gonos ES. Anti-ageing and rejuvenating effects of quercetin. *Exp*

Gerontol. 2010;45(10):763–71.

537. Zhu Y, Doornebal EJ, Pirtskhalava T, et al. New agents that target senescent cells: the flavone, fisetin, and the BCL-X_L inhibitors, A1331852 and A1155463. *Aging (Albany NY)*. 2017;9(3):955–63.

538. Wyld L, Bellantuono I, Tchkonia T, et al. Senescence and cancer: a review of clinical implications of senescence and senotherapies. *Cancers (Basel)*. 2020;12(8):2134.

539. Li W, Qin L, Feng R, et al. Emerging senolytic agents derived from natural products. *Mech Ageing Dev*. 2019;181:1–6.

540. Yousefzadeh MJ, Zhu Y, McGowan SJ, et al. Fisetin is a senotherapeutic that extends health and lifespan. *EBioMedicine*. 2018;36:18–28.

541. Maher P, Akaishi T, Abe K. Flavonoid fisetin promotes ERK-dependent long-term potentiation and enhances memory. *PNAS*. 2006;103(44):16568–73.

542. Farsad-Naeimi A, Alizadeh M, Esfahani A, Darvish Aminabad E. Effect of fisetin supplementation on inflammatory factors and matrix metalloproteinase enzymes in colorectal cancer patients. *Food Funct*. 2018;9(4):2025–31.

543. Yousefzadeh MJ, Zhu Y, McGowan SJ, et al. Fisetin is a senotherapeutic that extends health and lifespan. *EBioMedicine*. 2018;36:18–28.

544. U.S. National Library of Medicine. Search results for fisetin. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/results?cond=&term=fisetin&cntry=&state=&city=&dist=. Accessed May 29, 2021.

545. Grynkiewicz G, Demchuk OM. New perspectives for fisetin. *Front Chem*. 2019;7:697.

546. Rabin BM, Joseph JA, Shukitt-Hale B. Effects of age and diet on the heavy particle-induced disruption of operant responding produced by a ground-based model for exposure to cosmic rays. *Brain Res*. 2005;1036(1–2):122–9.

547. Miller MG, Thangthaeng N, Rutledge GA, Scott TM, Shukitt-Hale B. Dietary strawberry improves cognition in a randomised, double-blind,

placebo-controlled trial in older adults. *Br J Nutr*. Published online January 20, 2021:1–11.

548. Gao Q, Qin LQ, Arafa A, Eshak ES, Dong JY. Effects of strawberry intervention on cardiovascular risk factors: a meta-analysis of randomised controlled trials. *Br J Nutr*. 2020;124(3):241–6.

549. Schell J, Scofield RH, Barrett JR, et al. Strawberries improve pain and inflammation in obese adults with radiographic evidence of knee osteoarthritis. *Nutrients*. 2017;9(9):949.

550. Ezzat-Zadeh Z, Henning SM, Yang J, et al. California strawberry consumption increased the abundance of gut microorganisms related to lean body weight, health and longevity in healthy subjects. *Nutr Res*. 2021;85:60–70.

551. Morotomi M, Nagai F, Watanabe Y. Description of *Christensenella minuta* gen. nov., sp. nov., isolated from human faeces, which forms a distinct branch in the order *Clostridiales*, and proposal of *Christensenellaceae* fam. nov. *Int J Syst Evol*. 2012;62(1):144–9.

552. Waters JL, Ley RE. The human gut bacteria *Christensenellaceae* are widespread, heritable, and associated with health. *BMC Biol*. 2019;17(1):83.

553. Wang Y, Chang J, Liu X, et al. Discovery of piperlongumine as a potential novel lead for the development of senolytic agents. *Aging (Albany NY)*. 2016;8(11):2915–26.

554. Yadav V, Krishnan A, Vohora D. A systematic review on *Piper longum* L.: bridging traditional knowledge and pharmacological evidence for future translational research. *J Ethnopharmacol*. 2020;247:112255.

555. Kumar S, Kamboj J, Suman, Sharma S. Overview for various aspects of the health benefits of *Piper Longum* Linn. fruit. *J Acupunct Meridian Stud*. 2011;4(2):134–40.

556. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194–217.

557. van Deursen JM. Senolytic therapies for healthy longevity. *Science*. 2019;364(6441):636–7.

558. López-León M, Goya RG. The emerging view of aging as a reversible epigenetic process. *Gerontology*. 2017;63(5):426–31.

559. Sallon S, Solowey E, Cohen Y, et al. Germination, genetics, and growth of an ancient date seed. *Science*. 2008;320(5882):1464.
560. Yashina S, Gubin S, Maksimovich S, Yashina A, Gakhova E, Gilichinsky D. Regeneration of whole fertile plants from 30,000-y-old fruit tissue buried in Siberian permafrost. *Proc Natl Acad Sci U S A*. 2012;109(10):4008–13.
561. Rando TA, Chang HY. Aging, rejuvenation, and epigenetic reprogramming: resetting the aging clock. *Cell*. 2012;148(1–2):46–57.
562. Rando TA, Chang HY. Aging, rejuvenation, and epigenetic reprogramming: resetting the aging clock. *Cell*. 2012;148(1–2):46–57.
563. BBC News. 1997: Dolly the sheep is cloned. On this day: 1950—2005. BBC. http://news.bbc.co.uk/onthisday/hi/dates/stories/february/22/newsid_4245000/4245877.stm. Published February 22, 2005. Accessed May 26, 2021.
564. Gurdon JB. The cloning of a frog. *Development*. 2013;140(12):2446–8.
565. Burgstaller JP, Brem G. Aging of cloned animals: a mini-review. *Gerontology*. 2017;63(5):417–25.
566. López-León M, Goya RG. The emerging view of aging as a reversible epigenetic process. *Gerontology*. 2017;63(5):426–31.
567. Song S, Johnson FB. Epigenetic mechanisms impacting aging: a focus on histone levels and telomeres. *Genes*. 2018;9(4):201.
568. Rando TA, Chang HY. Aging, rejuvenation, and epigenetic reprogramming: resetting the aging clock. *Cell*. 2012;148(1–2):46–57.
569. Burgstaller JP, Brem G. Aging of cloned animals: a mini-review. *Gerontology*. 2017;63(5):417–25.
570. Wakayama S, Kohda T, Obokata H, et al. Successful serial recloning in the mouse over multiple generations. *Cell Stem Cell*. 2013;12(3):293–7.
571. López-León M, Goya RG. The emerging view of aging as a reversible epigenetic process. *Gerontology*. 2017;63(5):426–31.

572. Waddington CH. The epigenotype. 1942. *Int J Epidemiol*. 2012;41(1):10–13.
573. Watson JD, Crick FHC. Molecular structure of nucleic acids: a structure for deoxyribose nucleic acid. *Nature*. 1953;171(4356):737–8.
574. Song S, Johnson FB. Epigenetic mechanisms impacting aging: a focus on histone levels and telomeres. *Genes*. 2018;9(4):201.
575. Salzberg SL. Open questions: how many genes do we have? *BMC Biol.* 2018;16(1):94.
576. Govindaraju D, Atzmon G, Barzilai N. Genetics, lifestyle and longevity: lessons from centenarians. *Appl Transl Genom*. 2015;4:23–32.
577. vel Szic KS, Declerck K, Vidaković M, Vanden Berghe W. From inflammaging to healthy aging by dietary lifestyle choices: is epigenetics the key to personalized nutrition? *Clin Epigenet*. 2015;7(1):33.
578. Li X, Yi C. A novel epigenetic mark derived from vitamin C. *Biochemistry*. 2020;59(1):8–9.
579. Ciccarone F, Tagliatesta S, Caiafa P, Zampieri M. DNA methylation dynamics in aging: how far are we from understanding the mechanisms? *Mech Ageing Dev*. 2018;174:3–17.
580. Mitteldorf J. How does the body know how old it is? Introducing the epigenetic clock hypothesis. In: Yashin AI, Jazwinski SM, eds. *Aging and Health—A Systems Biology Perspective*. *Interdisciplinary Topics in Gerontology*, vol 40. Karger, Basel;2015:49–62.
581. Ashapkin VV, Kutueva LI, Vanyushin BF. Epigenetic clock: just a convenient marker or an active driver of aging? In: Guest PC, ed. *Reviews on Biomarker Studies in Aging and Anti-Aging Research*. *Advances in Experimental Medicine and Biology*, vol 1178. Springer Cham; 2019:175–206.
582. Vaiserman AM. Hormesis and epigenetics: is there a link? *Ageing Res Rev*. 2011;10(4):413–21.
583. Kawahata A, Sakamoto H. Some observations on sweating of the Aino. *Jpn J Physiol*. 1951;2(2):166–9.
584. Painter RC, Osmond C, Gluckman P, Hanson M, Phillips DI, Roseboom TJ. Transgenerational effects of prenatal exposure to the

Dutch famine on neonatal adiposity and health in later life. *BJOG*. 2008;115(10):1243–9.
585. Ornish D, Magbanua MJ, Weidner G, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. *Proc Natl Acad Sci USA*. 2008;105(24):8369–74.
586. Corona M, Velarde RA, Remolina S, et al. Vitellogenin, juvenile hormone, insulin signaling, and queen honey bee longevity. *Proc Natl Acad Sci USA*. 2007;104(17):7128–33.
587. Bacalini MG, Friso S, Olivieri F, et al. Present and future of anti-ageing epigenetic diets. *Mech Ageing Dev*. 2014;136–137:101–15.
588. Kucharski R, Maleszka J, Foret S, Maleszka R. Nutritional control of reproductive status in honeybees via DNA methylation. *Science*. 2008;319(5871):1827–30.
589. Hadi A, Najafgholizadeh A, Aydenlu ES, et al. Royal jelly is an effective and relatively safe alternative approach to blood lipid modulation: a meta-analysis. *J Funct Foods*. 2018;41:202–9.
590. Ecker S, Beck S. The epigenetic clock: a molecular crystal ball for human aging? *Aging (Albany NY)*. 2019;11(2):833–5.
591. Ecker S, Beck S. The epigenetic clock: a molecular crystal ball for human aging? *Aging (Albany NY)*. 2019;11(2):833–5.
592. Fransquet PD, Wrigglesworth J, Woods RL, Ernst ME, Ryan J. The epigenetic clock as a predictor of disease and mortality risk: a systematic review and meta-analysis. *Clin Epigenet*. 2019;11(1):62.
593. Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. *Science*. 2001;291(5507):1304–51.
594. Unnikrishnan A, Freeman WM, Jackson J, Wren JD, Porter H, Richardson A. The role of DNA methylation in epigenetics of aging. *Pharmacol Ther*. 2019;195:172–85.
595. Mendelson MM. Epigenetic age acceleration: a biological doomsday clock for cardiovascular disease? *Circ Genom Precis Med*. 2018;11(3).
596. Unnikrishnan A, Freeman WM, Jackson J, Wren JD, Porter H, Richardson A. The role of DNA methylation in epigenetics of aging. *Pharmacol Ther*. 2019;195:172–85.
597. Mitteldorf J. A clinical trial using methylation age to evaluate current antiaging practices. *Rejuvenation Res*. 2019;22(3):201–9.

598. Mendelson MM. Epigenetic age acceleration: a biological doomsday clock for cardiovascular disease? *Circ Genom Precis Med*. 2018;11(3).
599. Social Security Administration. Actuarial life table. Period life table, 2017. Social Security Administration. https://www.ssa.gov/oact/STATS/table4c6.html. Accessed May 26, 2021.
600. McCrory C, Fiorito G, Hernandez B, et al. GrimAge outperforms other epigenetic clocks in the prediction of age-related clinical phenotypes and all-cause mortality. *J Gerontol A Biol Sci Med Sci*. 2021;76(5):741–9.
601. Mitteldorf J. A clinical trial using methylation age to evaluate current antiaging practices. *Rejuvenation Res*. 2019;22(3):201–9.
602. Mendelson MM. Epigenetic age acceleration: a biological doomsday clock for cardiovascular disease? *Circ Genom Precis Med*. 2018;11(3).
603. Mitteldorf J. An incipient revolution in the testing of anti-aging strategies. *Biochemistry* (Mosc). 2018;83(12):1517–23.
604. Horvath S, Pirazzini C, Bacalini MG, et al. Decreased epigenetic age of PBMCs from Italian semi-supercentenarians and their offspring. *Aging (Albany NY)*. 2015;7(12):1159–70.
605. Declerck K, Vanden Berghe W. Back to the future: epigenetic clock plasticity towards healthy aging. *Mech Ageing Dev*. 2018;174:18–29.
606. Austad SN, Bartke A. Sex differences in longevity and in responses to anti-aging interventions: a mini-review. *Gerontology*. 2015;62(1):40–6.
607. Robert L, Fulop T. Longevity and its regulation: centenarians and beyond. *Interdiscip Top Gerontol*. 2014;39:198–211.
608. Beach SRH, Dogan MV, Lei MK, et al. Methylomic aging as a window onto the influence of lifestyle: tobacco and alcohol use alter the rate of biological aging. *J Am Geriatr Soc*. 2015;63(12):2519–25.
609. Vyas CM, Hazra A, Chang SC, et al. Pilot study of DNA methylation, molecular aging markers and measures of health and well-being in aging. *Transl Psychiatry*. 2019;9(1):118.
610. Pavanello S, Campisi M, Tona F, Dal Lin C, Iliceto S. Exploring epigenetic age in response to intensive relaxing training: a pilot study

to slow down biological age. *Int J Environ Res Public Health*. 2019;16(17):3074.

611. Chaix R, Alvarez-López MJ, Fagny M, et al. Epigenetic clock analysis in long-term meditators. *Psychoneuroendocrinology*. 2017;85:210–4.

612. Maegawa S, Lu Y, Tahara T, et al. Caloric restriction delays age-related methylation drift. *Nat Commun*. 2017;8(1):539.

613. Belsky DW, Huffman KM, Pieper CF, Shalev I, Kraus WE. Change in the rate of biological aging in response to caloric restriction: CALERIE Biobank analysis. *J Gerontol A Biol Sci Med Sci*. 2018;73(1):4–10.

614. Belsky DW, Huffman KM, Pieper CF, Shalev I, Kraus WE. Change in the rate of biological aging in response to caloric restriction: CALERIE Biobank analysis. *J Gerontol A Biol Sci Med Sci*. 2018;73(1):4–10.

615. Horvath S, Erhart W, Brosch M, et al. Obesity accelerates epigenetic aging of human liver. *Proc Natl Acad Sci USA*. 2014;111(43):15538–43.

616. de Toro-Martín J, Guénard F, Tchernof A, et al. Body mass index is associated with epigenetic age acceleration in the visceral adipose tissue of subjects with severe obesity. *Clin Epigenetics*. 2019;11(1):172.

617. Horvath S, Erhart W, Brosch M, et al. Obesity accelerates epigenetic aging of human liver. *Proc Natl Acad Sci USA*. 2014;111(43):15538–43.

618. Lu AT, Quach A, Wilson JG, et al. DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging (Albany NY)*. 2019;11(2):303–27.

619. Quach A, Levine ME, Tanaka T, et al. Epigenetic clock analysis of diet, exercise, education, and lifestyle factors. *Aging (Albany NY)*. 2017;9(2):419–37.

620. Hardy TM, Tollefsbol TO. Epigenetic diet: impact on the epigenome and cancer. *Epigenomics*. 2011;3(4):503–18.

621. Levine ME, Lu AT, Quach A, et al. An epigenetic biomarker of aging for lifespan and healthspan. *Aging (Albany NY)*. 2018;10(4):573–91.

622. Dugué PA, Bassett JK, Joo JE, et al. Association of DNA methylation-based biological age with health risk factors and overall and cause-specific mortality. *Am J Epidemiol*. 2018;187(3):529–38.
623. Lind PM, Salihovic S, Lind L. High plasma organochlorine pesticide levels are related to increased biological age as calculated by DNA methylation analysis. *Environ Int*. 2018;113:109–13.
624. Mariscal-Arcas M, Lopez-Martinez C, Granada A, Olea N, Lorenzo-Tovar ML, Olea-Serrano F. Organochlorine pesticides in umbilical cord blood serum of women from Southern Spain and adherence to the Mediterranean diet. *Food Chem Toxicol*. 2010;48(5):1311–5.
625. Ward-Caviness CK, Nwanaji-Enwerem JC, Wolf K, et al. Long-term exposure to air pollution is associated with biological aging. *Oncotarget*. 2016;7(46):74510–25.
626. Ryan J, Wrigglesworth J, Loong J, Fransquet PD, Woods RL. A systematic review and meta-analysis of environmental, lifestyle, and health factors associated with DNA methylation age. *J Gerontol A Biol Sci Med Sci*. 2020;75(3):481–94.
627. Mitteldorf J. A clinical trial using methylation age to evaluate current antiaging practices. *Rejuvenation Res*. 2019;22(3):201–9.
628. Fransquet PD, Wrigglesworth J, Woods RL, Ernst ME, Ryan J. The epigenetic clock as a predictor of disease and mortality risk: a systematic review and meta-analysis. *Clin Epigenet*. 2019;11(1):62.
629. Ashapkin VV, Kutueva LI, Vanyushin BF. Epigenetic clock: just a convenient marker or an active driver of aging? In: Guest PC, ed. *Reviews on Biomarker Studies in Aging and Anti-Aging Research*. *Advances in Experimental Medicine and Biology*, vol 1178. Springer Cham; 2019:175–206.
630. Nobel Media AB 2021. Shinya Yamanaka—Facts. NobelPrize.org. https://www.nobelprize.org/prizes/medicine/2012/yamanaka/facts/. Accessed June 5, 2021.
631. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006;126(4):663–76.
632. Shieh SJ, Cheng TC. Regeneration and repair of human digits and limbs: fact and fiction. *Regeneration*. 2015;2(4):149–68.

633. Lu Y, Brommer B, Tian X, et al. Reprogramming to recover youthful epigenetic information and restore vision. *Nature*. 2020;588(7836):124–9.
634. Jacobsen SC, Brøns C, Bork-Jensen J, et al. Effects of short-term high-fat overfeeding on genome-wide DNA methylation in the skeletal muscle of healthy young men. *Diabetologia*. 2012;55(12):3341–9.
635. Perfilyev A, Dahlman I, Gillberg L, et al. Impact of polyunsaturated and saturated fat overfeeding on the DNA-methylation pattern in human adipose tissue: a randomized controlled trial. *Am J Clin Nutr*. 2017;105(4):991–1000.
636. Miles FL, Mashchak A, Filippov V, et al. DNA methylation profiles of vegans and non-vegetarians in the Adventist Health Study-2 cohort. *Nutrients*. 2020;12(12):3697.
637. Key TJ, Appleby PN, Crowe FL, Bradbury KE, Schmidt JA, Travis RC. Cancer in British vegetarians: updated analyses of 4998 incident cancers in a cohort of 32,491 meat eaters, 8612 fish eaters, 18,298 vegetarians, and 2246 vegans. *Am J Clin Nutr*. 2014;100 Suppl 1:378S-85S.
638. Tantamango-Bartley Y, Jaceldo-Siegl K, Fan J, Fraser G. Vegetarian diets and the incidence of cancer in a low-risk population. *Cancer Epidemiol Biomarkers Prev*. 2013;22(2):286–94.
639. McCord JM. Analysis of superoxide dismutase activity. *Curr Protoc Toxicol*. 2001;Chapter 7:Unit7.3.
640. Thaler R, Karlic H, Rust P, Haslberger AG. Epigenetic regulation of human buccal mucosa mitochondrial superoxide dismutase gene expression by diet. *Br J Nutr*. 2009;101(5):743–9.
641. Johnson AA, Akman K, Calimport SRG, Wuttke D, Stolzing A, de Magalhães JP. The role of DNA methylation in aging, rejuvenation, and age-related disease. *Rejuvenation Res.* 2012;15(5):483–94.
642. ElGendy K, Malcomson FC, Lara JG, Bradburn DM, Mathers JC. Effects of dietary interventions on DNA methylation in adult humans: systematic review and meta-analysis. *Br J Nutr*. 2018;120(9):961–76.
643. Miller JW. Factors associated with different forms of folate in human serum: the folate folio continues to grow. *J Nutr*. 2020;150(4):650–1.

644. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and Its Panel on Folate, Other B Vitamins, and Choline. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. National Academies Press (US); 1998.
645. ter Borg S, Verlaan S, Hemsworth J, et al. Micronutrient intakes and potential inadequacies of community-dwelling older adults: a systematic review. *Br J Nutr*. 2015;113(8):1195–206.
646. Jacob RA, Gretz DM, Taylor PC, et al. Moderate folate depletion increases plasma homocysteine and decreases lymphocyte DNA methylation in postmenopausal women. *J Nutr*. 1998;128(7):1204–12.
647. Rampersaud GC, Kauwell GP, Hutson AD, Cerda JJ, Bailey LB. Genomic DNA methylation decreases in response to moderate folate depletion in elderly women. *Am J Clin Nutr*. 2000;72(4):998–1003.
648. Amenyah SD, Hughes CF, Ward M, et al. Influence of nutrients involved in one-carbon metabolism on DNA methylation in adults—a systematic review and meta-analysis. *Nutr Rev*. 2020;78(8):647–66.
649. Rampersaud GC, Kauwell GP, Hutson AD, Cerda JJ, Bailey LB. Genomic DNA methylation decreases in response to moderate folate depletion in elderly women. *Am J Clin Nutr*. 2000;72(4):998–1003.
650. Mathers JC, Strathdee G, Relton CL. Induction of epigenetic alterations by dietary and other environmental factors. *Adv Genet*. 2010;71:3–39.
651. Eaton SB, Eaton SB. Paleolithic vs. modern diets—selected pathophysiological implications. *Eur J Nutr*. 2000;39(2):67–70.
652. Parkhurst E, Calonico E, Noh G. Medical decision support to reduce unwarranted methylene tetrahydrofolate reductase (*MTHFR*) genetic testing. *J Med Syst*. 2020;44(9):152.
653. Levin BL, Varga E. MTHFR: addressing genetic counseling dilemmas using evidence-based literature. *J Genet Couns*. 2016;25(5):901–11.
654. Porter K, Hoey L, Hughes CF, Ward M, McNulty H. Causes, consequences and public health implications of low B-vitamin status in ageing. *Nutrients*. 2016;8(11).

655. Friso S, Choi SW, Girelli D, et al. A common mutation in the 5,10-methylenetetrahydrofolate reductase gene affects genomic DNA methylation through an interaction with folate status. *Proc Natl Acad Sci USA*. 2002;99(8):5606–11.
656. Bailey LB. Folate, methyl-related nutrients, alcohol, and the MTHFR 677C→T polymorphism affect cancer risk: intake recommendations. *J Nutr*. 2003;133(11 Suppl 1):3748S-53S.
657. Levin BL, Varga E. MTHFR: addressing genetic counseling dilemmas using evidence-based literature. *J Genet Couns*. 2016;25(5):901–11.
658. Parkhurst E, Calonico E, Noh G. Medical decision support to reduce unwarranted methylene tetrahydrofolate reductase (*MTHFR*) genetic testing. *J Med Syst*. 2020;44(9):152.
659. Seitz HK, Matsuzaki S, Yokoyama A, Homann N, Väkeväinen S, Wang XD. Alcohol and cancer. *Alcohol Clin Exp Res*. 2001;25(5 Suppl ISBRA):137S-43S.
660. Bailey LB. Folate, methyl-related nutrients, alcohol, and the MTHFR 677C→T polymorphism affect cancer risk: intake recommendations. *J Nutr*. 2003;133(11 Suppl 1):3748S-53S.
661. Griswold MG, Fullman N, Hawley C, et al. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2018;392(10152):1015–35.
662. Bo Y, Zhu Y, Tao Y, et al. Association between folate and health outcomes: an umbrella review of meta-analyses. *Front Public Health*. 2020;8:550753.
663. Bo Y, Zhu Y, Tao Y, et al. Association between folate and health outcomes: an umbrella review of meta-analyses. *Front Public Health*. 2020;8:550753.
664. Crider KS, Bailey LB, Berry RJ. Folic acid food fortification—its history, effect, concerns, and future directions. *Nutrients*. 2011;3(3):370–84.
665. Bailey SW, Ayling JE. The extremely slow and variable activity of dihydrofolate reductase in human liver and its implications for high folic acid intake. *Proc Natl Acad Sci U S A*. 2009;106(36):15424–9.

666. Selhub J, Rosenberg IH. Excessive folic acid intake and relation to adverse health outcome. *Biochimie*. 2016;126:71–8.
667. Troen AM, Mitchell B, Sorensen B, et al. Unmetabolized folic acid in plasma is associated with reduced natural killer cell cytotoxicity among postmenopausal women. *J Nutr*. 2006;136(1):189–94.
668. Bo Y, Zhu Y, Tao Y, et al. Association between folate and health outcomes: an umbrella review of meta-analyses. *Front Public Health*. 2020;8:550753.
669. U.S. Preventive Services Task Force. Final recommendation statement: folic acid for the prevention of neural tube defects: preventive medication. U.S. Preventive Services Task Force. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/folic-acid-for-the-prevention-of-neural-tube-defects-preventive-medication. Published January 10, 2017. Accessed May 26, 2021.
670. Dudeja PK, Torania SA, Said HM. Evidence for the existence of a carrier-mediated folate uptake mechanism in human colonic luminal membranes. *Am J Physiol*. 1997;272(6Pt1):G1408–15.
671. Strozzi GP, Mogna L. Quantification of folic acid in human feces after administration of *Bifidobacterium* probiotic strains. *J Clin Gastroenterol*. 2008;42 Suppl 3 Pt 2:S179–84.
672. Rando TA, Chang HY. Aging, rejuvenation, and epigenetic reprogramming: resetting the aging clock. *Cell*. 2012;148(1–2):46–57.
673. Hellwig M, Henle T. Baking, ageing, diabetes: a short history of the Maillard reaction. *Angew Chem Int Ed*. 2014;53(39):10316–29.
674. Teodorowicz M, Hendriks WH, Wichers HJ, Savelkoul HFJ. Immunomodulation by processed animal feed: the role of Maillard reaction products and advanced glycation end-products (AGEs). *Front Immunol*. 2018;9:2088.
675. Sadowska-Bartosz I, Bartosz G. Effect of glycation inhibitors on aging and age-related diseases. *Mech Ageing Dev*. 2016;160:1–18.
676. Unnikrishnan R, Anjana RM, Mohan V. Drugs affecting HbA1c levels. *Indian J Endocrinol Metab*. 2012;16(4):528–31.
677. American Diabetes Association. Understanding A1C. American Diabetes Association website. https://www.diabetes.org/a1c. Accessed June 2, 2021.

678. Sadowska-Bartosz I, Bartosz G. Effect of glycation inhibitors on aging and age-related diseases. *Mech Ageing Dev*. 2016;160:1–18.
679. Verzijl N, DeGroot J, Thorpe SR, et al. Effect of collagen turnover on the accumulation of advanced glycation end products. *J Biol Chem*. 2000;275(50):39027–31.
680. Fedintsev A, Moskalev A. Stochastic non-enzymatic modification of long-lived macromolecules—a missing hallmark of aging. *Ageing Res Rev*. 2020;62:101097.
681. Green AS. mTOR, glycotoxins and the parallel universe. *Aging (Albany NY)*. 2018;10(12):3654–6.
682. Bettiga A, Fiorio F, Di Marco F, et al. The modern Western diet rich in advanced glycation end-products (AGES): an overview of its impact on obesity and early progression of renal pathology. *Nutrients*. 2019;11(8):1748.
683. Garay-Sevilla ME, Beeri MS, de la Maza MP, Rojas A, Salazar-Villanea S, Uribarri J. The potential role of dietary advanced glycation endproducts in the development of chronic non-infectious diseases: a narrative review. *Nutr Res Rev*. 2020;33(2):298–311.
684. Chen JH, Lin X, Bu C, Zhang X. Role of advanced glycation end products in mobility and considerations in possible dietary and nutritional intervention strategies. *Nutr Metab (Lond)*. 2018;15(1):72.
685. Prasad C, Davis KE, Imrhan V, Juma S, Vijayagopal P. Advanced glycation end products and risks for chronic diseases: intervening through lifestyle modification. *Am J Lifestyle Med*. 2019;13(4):384–404.
686. Semba RD, Nicklett EJ, Ferrucci L. Does accumulation of advanced glycation end products contribute to the aging phenotype? *J Gerontol A Biol Sci Med Sci*. 2010;65A(9):963–75.
687. Green AS. mTOR, glycotoxins and the parallel universe. *Aging (Albany NY)*. 2018;10(12):3654–6.
688. Sergi D, Boulestin H, Campbell FM, Williams LM. The role of dietary advanced glycation end products in metabolic dysfunction. *Mol Nutr Food Res*. 2021;65(1):1900934.
689. Sadowska-Bartosz I, Bartosz G. Effect of glycation inhibitors on aging and age-related diseases. *Mech Ageing Dev*. 2016;160:1–18.

690. Šebeková K, Brouder Šebeková K. Glycated proteins in nutrition: friend or foe? *Exp Gerontol*. 2019;117:76–90.
691. Fedintsev A, Moskalev A. Stochastic non-enzymatic modification of long-lived macromolecules—a missing hallmark of aging. *Ageing Res Rev*. 2020;62:101097.
692. Azman KF, Zakaria R. D-galactose-induced accelerated aging model: an overview. *Biogerontology*. 2019;20(6):763–82.
693. Sadowska-Bartosz I, Bartosz G. Effect of glycation inhibitors on aging and age-related diseases. *Mech Ageing Dev*. 2016;160:1–18.
694. Fedintsev A, Moskalev A. Stochastic non-enzymatic modification of long-lived macromolecules—a missing hallmark of aging. *Ageing Res Rev*. 2020;62:101097.
695. Teissier T, Boulanger É. The receptor for advanced glycation end-products (RAGE) is an important pattern recognition receptor (PRR) for inflammaging. *Biogerontology*. 2019;20(3):279–301.
696. Green AS. mTOR, glycotoxins and the parallel universe. *Aging (Albany NY)*. 2018;10(12):3654–6.
697. Teissier T, Boulanger É. The receptor for advanced glycation end-products (RAGE) is an important pattern recognition receptor (PRR) for inflammaging. *Biogerontology*. 2019;20(3):279–301.
698. Gill V, Kumar V, Singh K, Kumar A, Kim JJ. Advanced glycation end products (AGEs) may be a striking link between modern diet and health. *Biomolecules*. 2019;9(12):888.
699. Hellwig M, Henle T. Baking, ageing, diabetes: a short history of the Maillard reaction. *Angew Chem Int Ed*. 2014;53(39):10316–29.
700. Bettiga A, Fiorio F, Di Marco F, et al. The modern Western diet rich in advanced glycation end-products (AGES): an overview of its impact on obesity and early progression of renal pathology. *Nutrients*. 2019;11(8):1748.
701. Chen JH, Lin X, Bu C, Zhang X. Role of advanced glycation end products in mobility and considerations in possible dietary and nutritional intervention strategies. *Nutr Metab (Lond)*. 2018;15(1):72.
702. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc*. 2010;110(6):911–6.e12.

703. Sgarbieri VC, Amaya J, Tanaka M, Chichester CO. Response of rats to amino acid supplementation of brown egg albumin. *J Nutr*. 1973;103(12):1731–8.
704. Koschinsky T, He CJ, Mitsuhashi T, et al. Orally absorbed reactive glycation products (glycotoxins): an environmental risk factor in diabetic nephropathy. *Proc Natl Acad Sci USA*. 1997;94(12):6474–9.
705. Gill V, Kumar V, Singh K, Kumar A, Kim JJ. Advanced glycation end products (AGEs) may be a striking link between modern diet and health. *Biomolecules*. 2019;9(12):888.
706. Zhang Q, Wang Y, Fu L. Dietary advanced glycation end-products: perspectives linking food processing with health implications. *Compr Rev Food Sci Food Saf*. 2020;19(5):2559–87.
707. Koschinsky T, He CJ, Mitsuhashi T, et al. Orally absorbed reactive glycation products (glycotoxins): an environmental risk factor in diabetic nephropathy. *Proc Natl Acad Sci USA*. 1997;94(12):6474–9.
708. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc*. 2010;110(6):911–6.e12.
709. Băbţan AM, Ilea A, Boşca BA, et al. Advanced glycation end products as biomarkers in systemic diseases: premises and perspectives of salivary advanced glycation end products. *Biomark Med*. 2019;13(6):479–95.
710. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc*. 2010;110(6):911–6.e12.
711. Goldberg T, Cai W, Peppa M, et al. Advanced glycoxidation end products in commonly consumed foods. *J Am Diet Assoc*. 2004;104(8):1287–91.
712. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc*. 2010;110(6):911–6.e12.
713. Clarivate. Web of science. https://clarivate.com/webofsciencegroup/solutions/web-of-science/. Accessed June 5, 2021.
714. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J*

Am Diet Assoc. 2010;110(6):911–6.e12.
715. Bettiga A, Fiorio F, Di Marco F, et al. The modern Western diet rich in advanced glycation end-products (AGES): an overview of its impact on obesity and early progression of renal pathology. *Nutrients*. 2019;11(8):1748.
716. Cai W, Uribarri J, Zhu L, et al. Oral glycotoxins are a modifiable cause of dementia and the metabolic syndrome in mice and humans. *Proc Natl Acad Sci USA*. 2014;111(13):4940–5.
717. Hellwig M, Gensberger-Reigl S, Henle T, Pischetsrieder M. Food-derived 1,2-dicarbonyl compounds and their role in diseases. *Semin Cancer Biol*. 2018;49:1–8.
718. Gómez-Ojeda A, Jaramillo-Ortíz S, Wrobel K, et al. Comparative evaluation of three different ELISA assays and HPLC-ESI-ITMS/MS for the analysis of Nε-carboxymethyl lysine in food samples. *Food Chem*. 2018;243:11–8.
719. Zhang Q, Wang Y, Fu L. Dietary advanced glycation end-products: perspectives linking food processing with health implications. *Compr Rev Food Sci Food Saf*. 2020;19(5):2559–87.
720. Kuzan A. Toxicity of advanced glycation end products (Review). *Biomed Rep*. 2021;14(5):46.
721. Morales FJ, Somoza V, Fogliano V. Physiological relevance of dietary melanoidins. *Amino Acids*. 2012;42(4):1097–109.
722. Ottum MS, Mistry AM. Advanced glycation end-products: modifiable environmental factors profoundly mediate insulin resistance. *J Clin Biochem Nutr*. 2015;57(1):1–12.
723. Cai W, Gao Q, Zhu L, Peppa M, He C, Vlassara H. Oxidative stress-inducing carbonyl compounds from common foods: novel mediators of cellular dysfunction. *Mol Med*. 2002;8(7):337–46.
724. Nicholl ID, Bucala R. Advanced glycation endproducts and cigarette smoking. *Cell Mol Biol (Noisy-le-grand)*. 1998;44(7):1025–33.
725. Garay-Sevilla ME, Beeri MS, de la Maza MP, Rojas A, Salazar-Villanea S, Uribarri J. The potential role of dietary advanced glycation endproducts in the development of chronic non-infectious diseases: a narrative review. *Nutr Res Rev*. 2020;33(2):298–311.
726. Rungratanawanich W, Qu Y, Wang X, Essa MM, Song BJ. Advanced glycation end products (AGEs) and other adducts in aging-related

diseases and alcohol-mediated tissue injury. *Exp Mol Med*. 2021;53(2):168–88.

727. Garay-Sevilla ME, Beeri MS, de la Maza MP, Rojas A, Salazar-Villanea S, Uribarri J. The potential role of dietary advanced glycation endproducts in the development of chronic non-infectious diseases: a narrative review. *Nutr Res Rev*. 2020;33(2):298–311.
728. Goldberg T, Cai W, Peppa M, et al. Advanced glycoxidation end products in commonly consumed foods. *J Am Diet Assoc*. 2004;104(8):1287–91.
729. del Castillo MD, Iriondo-DeHond A, Iriondo-DeHond M, et al. Healthy eating recommendations: good for reducing dietary contribution to the body's advanced glycation/lipoxidation end products pool? *Nutr Res Rev*. 2021;34(1):48–63.
730. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc*. 2010;110(6):911–6.e12.
731. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc*. 2010;110(6):911–6.e12.
732. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc*. 2010;110(6):911–6.e12.
733. Rungratanawanich W, Qu Y, Wang X, Essa MM, Song BJ. Advanced glycation end products (AGEs) and other adducts in aging-related diseases and alcohol-mediated tissue injury. *Exp Mol Med*. 2021;53(2):168–88.
734. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc*. 2010;110(6):911–6.e12.
735. Davis KE, Prasad C, Vijayagopal P, Juma S, Adams-Huet B, Imrhan V. Contribution of dietary advanced glycation end products (AGE) to circulating AGE: role of dietary fat. *Br J Nutr*. 2015;114(11):1797–806.
736. Semba RD, Nicklett EJ, Ferrucci L. Does accumulation of advanced glycation end products contribute to the aging phenotype? *J Gerontol A Biol Sci Med Sci*. 2010;65A(9):963–75.

737. Senolt L, Braun M, Olejarova M, Forejtova S, Gatterova J, Pavelka K. Increased pentosidine, an advanced glycation end product, in serum and synovial fluid from patients with knee osteoarthritis and its relation with cartilage oligomeric matrix protein. *Ann Rheum Dis*. 2005;64(6):886–90.
738. Hein G, Wiegand R, Lehmann G, Stein G, Franke S. Advanced glycation end-products pentosidine and N epsilon-carboxymethyllysine are elevated in serum of patients with osteoporosis. *Rheumatology (Oxford)*. 2003;42(10):1242–6.
739. Meerwaldt R, Graaff R, Oomen PHN, et al. Simple non-invasive assessment of advanced glycation endproduct accumulation. *Diabetologia*. 2004;47(7):1324–30.
740. Mahmoudi R, Jaisson S, Badr S, et al. Post-translational modification-derived products are associated with frailty status in elderly subjects. *Clin Chem Lab Med*. 2019;57(8):1153–61.
741. Cavero-Redondo I, Soriano-Cano A, Álvarez-Bueno C, et al. Skin autofluorescence–indicated advanced glycation end products as predictors of cardiovascular and all-cause mortality in high-risk subjects: a systematic review and meta-analysis. *J Am Heart Assoc*. 2018;7(18):e009833.
742. Igase M, Ohara M, Igase K, et al. Skin autofluorescence examination as a diagnostic tool for mild cognitive impairment in healthy people. *J Alzheimers Dis*. 2017;55(4):1481–7.
743. Cai W, Uribarri J, Zhu L, et al. Oral glycotoxins are a modifiable cause of dementia and the metabolic syndrome in mice and humans. *Proc Natl Acad Sci U S A*. 2014;111(13):4940–5.
744. Giem P, Beeson WL, Fraser GE. The incidence of dementia and intake of animal products: preliminary findings from the Adventist Health Study. *Neuroepidemiology.* 1993;12(1):28–36.
745. Cao GY, Li M, Han L, et al. Dietary fat intake and cognitive function among older populations: a systematic review and meta-analysis. *J Prev Alzheimers Dis*. 2019;6(3):204–11.
746. Holloway CJ, Cochlin LE, Emmanuel Y, et al. A high-fat diet impairs cardiac high-energy phosphate metabolism and cognitive function in healthy human subjects. *Am J Clin Nutr*. 2011;93(4):748–55.

747. Cai W, He JC, Zhu L, et al. Reduced oxidant stress and extended lifespan in mice exposed to a low glycotoxin diet: association with increased AGER1 expression. *Am J Pathol*. 2007;170(6):1893–902.
748. Akhter F, Chen D, Akhter A, et al. High dietary advanced glycation end products impair mitochondrial and cognitive function. *J Alzheimers Dis*. 2020;76(1):165–78.
749. Peppa M, He C, Hattori M, McEvoy R, Zheng F, Vlassara H. Fetal or neonatal low-glycotoxin environment prevents autoimmune diabetes in NOD mice. *Diabetes*. 2003;52(6):1441–8.
750. Tsakiri EN, Iliaki KK, Höhn A, et al. Diet-derived advanced glycation end products or lipofuscin disrupts proteostasis and reduces life span in *Drosophila melanogaster*. *Free Radic Biol Med*. 2013;65:1155–63.
751. Peppa M, He C, Hattori M, McEvoy R, Zheng F, Vlassara H. Fetal or neonatal low-glycotoxin environment prevents autoimmune diabetes in NOD mice. *Diabetes*. 2003;52(6):1441–8.
752. Cai W, He JC, Zhu L, et al. Oral glycotoxins determine the effects of calorie restriction on oxidant stress, age-related diseases, and lifespan. *Am J Pathol*. 2008;173(2):327–36.
753. Negrean M, Stirban A, Stratmann B, et al. Effects of low- and high-advanced glycation endproduct meals on macro-and microvascular endothelial function and oxidative stress in patients with type 2 diabetes mellitus. *Am J Clin Nutr*. 2007;85(5):1236–43.
754. Šebeková K, Brouder Šebeková K. Glycated proteins in nutrition: friend or foe? *Exp Gerontol*. 2019;117:76–90.
755. Šebeková K, Brouder Šebeková K. Glycated proteins in nutrition: friend or foe? *Exp Gerontol*. 2019;117:76–90.
756. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care*. 2008;31(12):2281–3.
757. Gaesser GA, Rodriguez J, Patrie JT, Whisner CM, Angadi SS. Effects of glycemic index and cereal fiber on postprandial endothelial function, glycemia, and insulinemia in healthy adults. *Nutrients*. 2019;11(10):2387.
758. Pereira MA, Swain J, Goldfine AB, Rifai N, Ludwig DS. Effects of a low-glycemic load diet on resting energy expenditure and heart

disease risk factors during weight loss. *JAMA*. 2004;292(20):2482–90.

759. Jenkins DJ, Taylor RH, Goff DV, et al. Scope and specificity of acarbose in slowing carbohydrate absorption in man. *Diabetes*. 1981;30(11):951–4.

760. Augustin LSA, Kendall CWC, Jenkins DJA, et al. Glycemic index, glycemic load and glycemic response: an international scientific consensus summit from the International Carbohydrate Quality Consortium (ICQC). *Nutr Metab Cardiovasc Dis*. 2015;25(9):795–815.

761. Schnell O, Weng J, Sheu WH, et al. Acarbose reduces body weight irrespective of glycemic control in patients with diabetes: results of a worldwide, non-interventional, observational study data pool. *J Diabetes Complicat*. 2016;30(4):628–37.

762. Tsunosue M, Mashiko N, Ohta Y, et al. An α-glucosidase inhibitor, acarbose treatment decreases serum levels of glyceraldehyde-derived advanced glycation end products (AGEs) in patients with type 2 diabetes. *Clin Exp Med*. 2010;10(2):139–41.

763. Newman JC, Milman S, Hashmi SK, et al. Strategies and challenges in clinical trials targeting human aging. *J Gerontol A Biol Sci Med Sci*. 2016;71(11):1424–34.

764. Brewer RA, Gibbs VK, Smith DL. Targeting glucose metabolism for healthy aging. *Nutr Healthy Aging*. 2016;4(1):31–46.

765. Jenkins D, Wolever T, Taylor R, Barker H, Fielden H. Exceptionally low blood glucose response to dried beans: comparison with other carbohydrate foods. *BMJ*. 1980;281(6240):578–80.

766. Jenkins DJ, Wolever TM, Taylor RH, et al. Slow release dietary carbohydrate improves second meal tolerance. *Am J Clin Nutr*. 1982;35(6):1339–46.

767. Wolever TM, Jenkins DJ, Ocana AM, Rao VA, Collier GR. Second-meal effect: low-glycemic-index foods eaten at dinner improve subsequent breakfast glycemic response. *Am J Clin Nutr*. 1988;48(4):1041–7.

768. Mollard RC, Wong CL, Luhovyy BL, Anderson GH. First and second meal effects of pulses on blood glucose, appetite, and food intake at a later meal. *Appl Physiol Nutr Metab*. 2011;36(5):634–42.

769. Jenkins DJA, Kendall CWC, Augustin LSA, et al. Effect of legumes as part of a low glycemic index diet on glycemic control and cardiovascular risk factors in type 2 diabetes mellitus: a randomized controlled trial. *Arch Intern Med*. 2012;172(21):1653–60.
770. Sievenpiper JL, Chiavaroli L, de Souza RJ, et al. "Catalytic" doses of fructose may benefit glycaemic control without harming cardiometabolic risk factors: a small meta-analysis of randomised controlled feeding trials. *Br J Nutr.* 2012;108(3):418–23.
771. Christensen AS, Viggers L, Hasselström K, Gregersen S. Effect of fruit restriction on glycemic control in patients with type 2 diabetes—a randomized trial. *Nutr J.* 2013;12:29.
772. Choo VL, Viguiliouk E, Mejia SB, et al. Food sources of fructose-containing sugars and glycaemic control: systematic review and meta-analysis of controlled intervention studies. *BMJ*. 2018;363:k4644.
773. McSwiney FT, Doyle L. Low-carbohydrate ketogenic diets in male endurance athletes demonstrate different micronutrient contents and changes in corpuscular haemoglobin over 12 weeks. *Sports (Basel)*. 2019;7(9):201.
774. Sweeney JS. Dietary factors that influence the dextrose tolerance test: a preliminary study. *Arch Intern Med (Chic)*. 1927;40(6):818–30.
775. Manco M, Bertuzzi A, Salinari S, et al. The ingestion of saturated fatty acid triacylglycerols acutely affects insulin secretion and insulin sensitivity in human subjects. *Br J Nutr*. 2004;92(6):895–903.
776. Koska J, Ozias MK, Deer J, et al. A human model of dietary saturated fatty acid induced insulin resistance. *Metabolism*. 2016;65(11):1621–8.
777. Angeloni C, Zambonin L, Hrelia S. Role of methylglyoxal in Alzheimer's disease. *Biomed Res Int*. 2014;2014:238485.
778. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc.* 2010;110(6):911–16.e12.
779. Beisswenger BG, Delucia EM, Lapoint N, Sanford RJ, Beisswenger PJ. Ketosis leads to increased methylglyoxal production on the Atkins diet. *Ann N Y Acad Sci*. 2005;1043:201–10.

780. Franz MJ. Protein and diabetes: much advice, little research. *Curr Diab Rep*. 2002;2(5):457–64.
781. Jones AW, Rössner S. False-positive breath-alcohol test after a ketogenic diet. *Int J Obes (Lond)*. 2007;31(3):559–61.
782. Beisswenger BG, Delucia EM, Lapoint N, Sanford RJ, Beisswenger PJ. Ketosis leads to increased methylglyoxal production on the Atkins diet. *Ann N Y Acad Sci*. 2005;1043:201–10.
783. Tey SL, Salleh NB, Henry CJ, Forde CG. Effects of non-nutritive (artificial vs natural) sweeteners on 24-h glucose profiles. *Eur J Clin Nutr*. 2017;71(9):1129–32.
784. Coca-Cola. Nutrition facts—original 20 fl oz. https://us.coca-cola.com/products/coca-cola/original. Accessed December 26, 2022.
785. Tey SL, Salleh NB, Henry J, Forde CG. Effects of aspartame-, monk fruit-, stevia- and sucrose-sweetened beverages on postprandial glucose, insulin and energy intake. *Int J Obes (Lond)*. 2017;41(3):450–7.
786. Pepino MY, Tiemann CD, Patterson BW, Wice BM, Klein S. Sucralose affects glycemic and hormonal responses to an oral glucose load. *Diabetes Care*. 2013;36(9):2530–5.
787. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care*. 2008;31(12):2281–3.
788. Brand JC, Nicholson PL, Thorburn AW, Truswell AS. Food processing and the glycemic index. *Am J Clin Nutr*. 1985;42(6):1192–6.
789. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of glycemic index and glycemic load values: 2008. *Diabetes Care*. 2008;31(12):2281–3.
790. Mofidi A, Ferraro ZM, Stewart KA, et al. The acute impact of ingestion of sourdough and whole-grain breads on blood glucose, insulin, and incretins in overweight and obese men. *J Nutr Metab*. 2012;2012:184710.
791. Scazzina F, Siebenhandl-Ehn S, Pellegrini N. The effect of dietary fibre on reducing the glycaemic index of bread. *Br J Nutr*. 2013;109(7):1163–74.

792. Jenkins DJ, Wesson V, Wolever TM, et al. Wholemeal versus wholegrain breads: proportion of whole or cracked grain and the glycaemic response. *BMJ*. 1988;297(6654):958–60.
793. Breen C, Ryan M, Gibney MJ, Corrigan M, O'Shea D. Glycemic, insulinemic, and appetite responses of patients with type 2 diabetes to commonly consumed breads. *Diabetes Educ*. 2013;39(3):376–86.
794. Reynolds AN, Mann J, Elbalshy M, et al. Wholegrain particle size influences postprandial glycemia in type 2 diabetes: a randomized crossover study comparing four wholegrain breads. *Dia Care*. 2020;43(2):476–9.
795. Burton P, Lightowler HJ. The impact of freezing and toasting on the glycaemic response of white bread. *Eur J Clin Nutr*. 2008;62(5):594–9.
796. Scazzina F, Siebenhandl-Ehn S, Pellegrini N. The effect of dietary fibre on reducing the glycaemic index of bread. *Br J Nutr*. 2013;109(7):1163–74.
797. Yadav BS, Sharma A, Yadav RB. Studies on effect of multiple heating/cooling cycles on the resistant starch formation in cereals, legumes and tubers. *Int J Food Sci Nutr*. 2009;60 Suppl 4:258–72.
798. de Morais Cardoso L, Pinheiro SS, Martino HSD, Pinheiro-Sant'Ana HM. Sorghum (*Sorghum bicolor* L.): nutrients, bioactive compounds, and potential impact on human health. *Crit Rev Food Sci Nutr*. 2017;57(2):372–90.
799. Narayanan J, Sanjeevi V, Rohini U, Trueman P, Viswanathan V. Postprandial glycaemic response of foxtail millet *dosa* in comparison to a rice *dosa* in patients with type 2 diabetes. *Indian J Med Res*. 2016;144(5):712–7.
800. Poquette NM, Gu X, Lee SO. Grain sorghum muffin reduces glucose and insulin responses in men. *Food Funct*. 2014;5(5):894–9.
801. Abdelgadir M, Abbas M, Järvi A, Elbagir M, Eltom M, Berne C. Glycaemic and insulin responses of six traditional Sudanese carbohydrate-rich meals in subjects with Type 2 diabetes mellitus. *Diabet Med*. 2005;22(2):213–7.
802. Chen Z, Glisic M, Song M, et al. Dietary protein intake and all-cause and cause-specific mortality: results from the Rotterdam Study and a

meta-analysis of prospective cohort studies. *Eur J Epidemiol*. 2020;35(5):411–29.

803. Mazidi M, Katsiki N, Mikhailidis DP, Pella D, Banach M. Potato consumption is associated with total and cause-specific mortality: a population-based cohort study and pooling of prospective studies with 98,569 participants. *Arch Med Sci*. 2020;16(2):260–72.

804. Fernandes G, Velangi A, Wolever TMS. Glycemic index of potatoes commonly consumed in North America. *J Am Diet Assoc*. 2005;105(4):557–62.

805. Johnston CS, Steplewska I, Long CA, Harris LN, Ryals RH. Examination of the antiglycemic properties of vinegar in healthy adults. *Ann Nutr Metab.* 2010;56(1):74–9.

806. Leeman M, Östman E, Björck I. Vinegar dressing and cold storage of potatoes lowers postprandial glycaemic and insulinaemic responses in healthy subjects. *Eur J Clin Nutr*. 2005;59(11):1266–71.

807. Grussu D, Stewart D, McDougall GJ. Berry polyphenols inhibit α-amylase *in vitro*: identifying active components in rowanberry and raspberry. *J Agric Food Chem*. 2011;59(6):2324–31.

808. Sharma KK, Gupta RK, Gupta S, Samuel KC. Antihyperglycemic effect of onion: effect on fasting blood sugar and induced hyperglycemia in man. *Indian J Med Res*. 1977;65(3):422–9.

809. Haldar S, Chia SC, Lee SH, et al. Polyphenol-rich curry made with mixed spices and vegetables benefits glucose homeostasis in Chinese males (Polyspice Study): a dose-response randomized controlled crossover trial. *Eur J Nutr*. 2019;58(1):301–13.

810. Azzeh FS. Synergistic effect of green tea, cinnamon and ginger combination on enhancing postprandial blood glucose. *Pak J Biol Sci*. 2013;16(2):74–9.

811. Hajizadeh-Sharafabad F, Varshosaz P, Jafari-Vayghan H, Alizadeh M, Maleki V. Chamomile (*Matricaria recutita* L.) and diabetes mellitus, current knowledge and the way forward: a systematic review. *Complement Ther Med*. 2020;48:102284.

812. Rafraf M, Zemestani M, Asghari-Jafarabadi M. Effectiveness of *chamomile* tea on glycemic control and serum lipid profile in patients with type 2 diabetes. *J Endocrinol Invest*. 2015;38(2):163–70.

813. Kermanian S, Mozaffari-Khosravi H, Dastgerdi G, Zavar-Reza J, Rahmanian M. The effect of chamomile tea versus black tea on glycemic control and blood lipid profiles in depressed patients with type 2 diabetes: a randomized clinical trial. *JNFS*, 2018;3(3):157–66.
814. Rafraf M, Zemestani M, Asghari-Jafarabadi M. Effectiveness of *chamomile* tea on glycemic control and serum lipid profile in patients with type 2 diabetes. *J Endocrinol Invest*. 2015;38(2):163–70.
815. Pirouzpanah S, Mahboob S, Sanayei M, Hajaliloo M, Safaeiyan A. The effect of *chamomile* tea consumption on inflammation among rheumatoid arthritis patients: randomized clinical trial. *Prog Nutr*. 2017;19(1-S)27–33.
816. Chang SM, Chen CH. Effects of an intervention with drinking chamomile tea on sleep quality and depression in sleep disturbed postnatal women: a randomized controlled trial. *J Adv Nurs*. 2016;72(2):306–15.
817. Zemestani M, Rafraf M, Asghari-Jafarabadi M. Chamomile tea improves glycemic indices and antioxidants status in patients with type 2 diabetes mellitus. *Nutrition*. 2016;32(1):66–72.
818. Villa-Rodriguez JA, Aydin E, Gauer JS, Pyner A, Williamson G, Kerimi A. Green and chamomile teas, but not acarbose, attenuate glucose and fructose transport via inhibition of GLUT2 and GLUT5. *Mol Nutr Food Res*. 2017;61(12):1700566.
819. Bowen AJ, Reeves RL. Diurnal variation in glucose tolerance. *Arch Intern Med*. 1967;119(3):261–4.
820. Van Cauter E, Polonsky KS, Scheen AJ. Roles of circadian rhythmicity and sleep in human glucose regulation. *Endocr Rev*. 1997;18(5):716–38.
821. Bandín C, Scheer FA, Luque AJ, et al. Meal timing affects glucose tolerance, substrate oxidation and circadian-related variables: a randomized, crossover trial. *Int J Obes (Lond)*. 2015;39(5):828–33.
822. Gibbs M, Harrington D, Starkey S, Williams P, Hampton S. Diurnal postprandial responses to low and high glycaemic index mixed meals. *Clin Nutr*. 2014;33(5):889–94.
823. Colberg SR, Zarrabi L, Bennington L, et al. Postprandial walking is better for lowering the glycemic effect of dinner than pre-dinner

exercise in type 2 diabetic individuals. *J Am Med Dir Assoc*. 2009;10(6):394–7.

824. Haxhi J, Scotto di Palumbo A, Sacchetti M. Exercising for metabolic control: is timing important? *Ann Nutr Metab*. 2013;62(1):14–25.

825. Reynolds AN, Mann JI, Williams S, Venn BJ. Advice to walk after meals is more effective for lowering postprandial glycaemia in type 2 diabetes mellitus than advice that does not specify timing: a randomised crossover study. *Diabetologia*. 2016;59(12):2572–8.

826. Rahmadi A, Steiner N, Münch G. Advanced glycation endproducts as gerontotoxins and biomarkers for carbonyl-based degenerative processes in Alzheimer's disease. *Clin Chem Lab Med*. 2011;49(3):385–91.

827. Green AS. mTOR, glycotoxins and the parallel universe. *Aging (Albany NY)*. 2018;10(12):3654–6.

828. Uribarri J, He JC. The low AGE diet: a neglected aspect of clinical nephrology practice? *Nephron*. 2015;130(1):48–53.

829. Yamagishi S, Nakamura K, Matsui T, Inoue H, Takeuchi M. Oral administration of AST-120 (Kremezin) is a promising therapeutic strategy for advanced glycation end product (AGE)-related disorders. *Med Hypotheses*. 2007;69(3):666–8.

830. MIMS. Kremezin full prescribing information, dosage & side effects. https://www.mims.com/philippines/drug/info/kremezin?type=full. Accessed December 26, 2022.

831. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc*. 2010;110(6):911–6.e12.

832. Cerami C, Founds H, Nicholl I, et al. Tobacco smoke is a source of toxic reactive glycation products. *Proc Natl Acad Sci USA*. 1997;94(25):13915–20.

833. Green AS. mTOR, glycotoxins and the parallel universe. *Aging (Albany NY)*. 2018;10(12):3654–6.

834. Green AS. mTOR, glycotoxins and the parallel universe. *Aging (Albany NY)*. 2018;10(12):3654–6.

835. Kenyon C. The first long-lived mutants: discovery of the insulin/IGF-1 pathway for ageing. *Philos Trans R Soc Lond B Biol Sci.* 2011;366(1561):9–16.

836. Kenyon C, Chang J, Gensch E, Rudner A, Tabtiang R. A *C. elegans* mutant that lives twice as long as wild type. *Nature*. 1993;366(6454):461–4.
837. Kenyon C. The first long-lived mutants: discovery of the insulin/IGF-1 pathway for ageing. *Philos Trans R Soc Lond B Biol Sci.* 2011;366(1561):9–16.
838. Partridge L, Harvey PH. Gerontology. Methuselah among nematodes. *Nature*. 1993;366(6454):404–5.
839. Coffer P. OutFOXing the grim reaper: novel mechanisms regulating longevity by Forkhead transcription factors. *Sci STKE*. 2003;2003(201):PE39.
840. Suh Y, Atzmon G, Cho MO, et al. Functionally significant insulin-like growth factor I receptor mutations in centenarians. *Proc Natl Acad Sci U S A*. 2008;105(9):3438–42.
841. Kenyon C. The first long-lived mutants: discovery of the insulin/IGF-1 pathway for ageing. *Philos Trans R Soc Lond B Biol Sci.* 2011;366(1561):9–16.
842. Laron Z, Kauli R, Lapkina L, Werner H. IGF-I deficiency, longevity and cancer protection of patients with Laron syndrome. *Mutat Res Rev Mutat Res*. 2017;772:123–33.
843. Vitale G, Pellegrino G, Vollery M, Hofland LJ. Role of IGF-1 system in the modulation of longevity: controversies and new insights from a centenarians' perspective. *Front Endocrinol*. 2019;10:27.
844. Kenyon C. The plasticity of aging: insights from long-lived mutants. *Cell*. 2005;120(4):449–60.
845. Junnila RK, List EO, Berryman DE, Murrey JW, Kopchick JJ. The GH/IGF-1 axis in ageing and longevity. *Nat Rev Endocrinol*. 2013;9(6):366–76.
846. Vitale G, Barbieri M, Kamenetskaya M, Paolisso G. GH/IGF-I/insulin system in centenarians. *Mech Ageing Dev*. 2017;165(Pt B):107–14.
847. Vitale G, Brugts MP, Ogliari G, et al. Low circulating IGF-I bioactivity is associated with human longevity: findings in centenarians' offspring. *Aging (Albany NY)*. 2012;4(9):580–9.
848. Vitale G, Barbieri M, Kamenetskaya M, Paolisso G. GH/IGF-I/insulin system in centenarians. *Mech Ageing Dev*. 2017;165(Pt

B):107–14.
849. Pawlikowska L, Hu D, Huntsman S, et al. Association of common genetic variation in the insulin/IGF1 signaling pathway with human longevity. *Aging Cell*. 2009;8(4):460–72.
850. Ben-Avraham D, Govindaraju DR, Budagov T, et al. The GH receptor exon 3 deletion is a marker of male-specific exceptional longevity associated with increased GH sensitivity and taller stature. *Sci Adv*. 2017;3(6):e1602025.
851. Teumer A, Qi Q, Nethander M, et al. Genomewide meta-analysis identifies loci associated with IGF-I and IGFBP-3 levels with impact on age-related traits. *Aging Cell*. 2016;15(5):811–24.
852. Milman S, Atzmon G, Huffman DM, et al. Low insulin-like growth factor-1 level predicts survival in humans with exceptional longevity. *Aging Cell*. 2014;13(4):769–71.
853. van der Spoel E, Rozing MP, Houwing-Duistermaat JJ, et al. Association analysis of insulin-like growth factor-1 axis parameters with survival and functional status in nonagenarians of the Leiden Longevity Study. *Aging (Albany NY)*. 2015;7(11):956–63.
854. Suh Y, Atzmon G, Cho MO, et al. Functionally significant insulin-like growth factor I receptor mutations in centenarians. *Proc Natl Acad Sci U S A*. 2008;105(9):3438–42.
855. Tazearslan C, Huang J, Barzilai N, Suh Y. Impaired IGF1R signaling in cells expressing longevity-associated human *IGF1R* alleles. *Aging Cell*. 2011;10(3):551–4.
856. Bartke A. Healthy aging: is smaller better?—a mini-review. *Gerontology*. 2012;58(4):337–43.
857. Michell AR. Longevity of British breeds of dog and its relationships with sex, size, cardiovascular variables and disease. *Vet Rec*. 1999;145(22):625–9.
858. Sutter NB, Bustamante CD, Chase K, et al. A single *IGF1* allele is a major determinant of small size in dogs. *Science*. 2007;316(5821):112–5.
859. Samaras TT. How height is related to our health and longevity: a review. *Nutr Health*. 2012;21(4):247–61.
860. Sohn K. Now, the taller die earlier: the curse of cancer. *J Gerontol A Biol Sci Med Sci*. 2016;71(6):713–9.

861. Samaras TT. How height is related to our health and longevity: a review. *Nutr Health*. 2012;21(4):247–61.
862. Samaras TT, Elrick H, Storms LH. Is height related to longevity? *Life Sci*. 2003;72(16):1781–802.
863. Samaras TT. How height is related to our health and longevity: a review. *Nutr Health*. 2012;21(4):247–61.
864. Sohn K. Now, the taller die earlier: the curse of cancer. *J Gerontol A Biol Sci Med Sci*. 2016;71(6):713–9.
865. Walter RB, Brasky TM, Buckley SA, Potter JD, White E. Height as an explanatory factor for sex differences in human cancer. *J Natl Cancer Inst*. 2013;105(12):860–8.
866. Shors AR, Solomon C, McTiernan A, White E. Melanoma risk in relation to height, weight, and exercise (United States). *Cancer Causes Control*. 2001;12(7):599–606.
867. Walter RB, Brasky TM, Buckley SA, Potter JD, White E. Height as an explanatory factor for sex differences in human cancer. *J Natl Cancer Inst*. 2013;105(12):860–8.
868. Suh Y, Atzmon G, Cho MO, et al. Functionally significant insulin-like growth factor I receptor mutations in centenarians. *Proc Natl Acad Sci U S A*. 2008;105(9):3438–42.
869. Reed JC. Dysregulation of apoptosis in cancer. *J Clin Oncol*. 1999;17(9):2941–53.
870. Murphy N, Knuppel A, Papadimitriou N, et al. Insulin-like growth factor-1, insulin-like growth factor-binding protein-3, and breast cancer risk: observational and Mendelian randomization analyses with ∼430 000 women. *Ann Oncol*. 2020;31(5):641–9.
871. Chi F, Wu R, Zeng Y, Xing R, Liu Y. Circulation insulin-like growth factor peptides and colorectal cancer risk: an updated systematic review and meta-analysis. *Mol Biol Rep*. 2013;40(5):3583–90.
872. Travis RC, Appleby PN, Martin RM, et al. A meta-analysis of individual participant data reveals an association between circulating levels of IGF-I and prostate cancer risk. *Cancer Res*. 2016;76(8):2288–300.
873. Cao H, Wang G, Meng L, et al. Association between circulating levels of IGF-1 and IGFBP-3 and lung cancer risk: a meta-analysis. *PLoS One*. 2012;7(11):e49884.

874. Li Y, Li Y, Zhang J, et al. Circulating insulin-like growth factor-1 level and ovarian cancer risk. *Cell Physiol Biochem*. 2016;38(2):589–97.
875. Gong Y, Zhang B, Liao Y, et al. Serum insulin-like growth factor axis and the risk of pancreatic cancer: systematic review and meta-analysis. *Nutrients*. 2017;9(4):394.
876. Hankinson SE, Willett WC, Colditz GA, et al. Circulating concentrations of insulin-like growth factor I and risk of breast cancer. *Lancet*. 1998;351(9113):1393–6.
877. Yee D. Insulin-like growth factor receptor inhibitors: baby or the bathwater? *J Natl Cancer Inst*. 2012;104(13):975–81.
878. Quan H, Tang H, Fang L, Bi J, Liu Y, Li H. IGF1(CA)19 and IGFBP-3–202A/C gene polymorphism and cancer risk: a meta-analysis. *Cell Biochem Biophys*. 2014;69(1):169–78.
879. Yokoyama NN, Denmon AP, Uchio EM, Jordan M, Mercola D, Zi X. When anti-aging studies meet cancer chemoprevention: can anti-aging agent kill two birds with one blow? *Curr Pharmacol Rep*. 2015;1(6):420–33.
880. Elia I, Doglioni G, Fendt SM. Metabolic hallmarks of metastasis formation. *Trends Cell Biol*. 2018;28(8):673–84.
881. Kleinberg DL, Wood TL, Furth PA, Lee AV. Growth hormone and insulin-like growth factor-I in the transition from normal mammary development to preneoplastic mammary lesions. *Endocr Rev.* 2009;30(1):51–74.
882. Yang SY, Miah A, Pabari A, Winslet M. Growth factors and their receptors in cancer metastases. *Front Biosci (Landmark Ed)*. 2011;16:531–8.
883. Zhang Y, Ma B, Fan Q. Mechanisms of breast cancer bone metastasis. *Cancer Lett*. 2010;292(1):1–7.
884. Yang SY, Miah A, Pabari A, Winslet M. Growth factors and their receptors in cancer metastases. *Front Biosci (Landmark Ed)*. 2011;16:531–8.
885. Sohn K. Now, the taller die earlier: the curse of cancer. *J Gerontol A Biol Sci Med Sci*. 2016;71(6):713–19.
886. Salvioli S, Capri M, Bucci L, et al. Why do centenarians escape or postpone cancer? The role of IGF-1, inflammation and p53. *Cancer*

Immunol Immunother. 2009;58(12):1909–17.
887. Piantanelli L. Cancer and aging: from the kinetics of biological parameters to the kinetics of cancer incidence and mortality. *Ann N Y Acad Sci*. 1988;521:99–109.
888. Kenyon C. The plasticity of aging: insights from long-lived mutants. *Cell*. 2005;120(4):449–60.
889. Stanta G, Campagner L, Cavallieri F, Giarelli L. Cancer of the oldest old. What we have learned from autopsy studies. *Clin Geriatr Med*. 1997;13(1):55–68.
890. Salvioli S, Capri M, Bucci L, et al. Why do centenarians escape or postpone cancer? The role of IGF-1, inflammation and p53. *Cancer Immunol Immunother*. 2009;58(12):1909–17.
891. Laron Z, Pertzelan A, Mannheimer S. Genetic pituitary dwarfism with high serum concentration of growth hormone: a new inborn error of metabolism? *Isr J Med Sci* 1966;2:152–5.
892. Guevara-Aguirre J, Bautista C, Torres C, et al. Insights from the clinical phenotype of subjects with Laron syndrome in Ecuador. *Rev Endocr Metab Disord*. 2021;22(1):59–70.
893. Laron Z, Kauli R, Lapkina L, Werner H. IGF-I deficiency, longevity and cancer protection of patients with Laron syndrome. *Mutat Res Rev Mutat Res*. 2017;772:123–33.
894. Guevara-Aguirre J, Balasubramanian P, Guevara-Aguirre M, et al. Growth hormone receptor deficiency is associated with a major reduction in pro-aging signaling, cancer, and diabetes in humans. *Sci Transl Med*. 2011;3(70):70ra13.
895. Boguszewski CL, Boguszewski MC da S. Growth hormone's links to cancer. *Endocr Rev*. 2019;40(2):558–74.
896. Guevara-Aguirre J, Balasubramanian P, Guevara-Aguirre M, et al. Growth hormone receptor deficiency is associated with a major reduction in pro-aging signaling, cancer, and diabetes in humans. *Sci Transl Med*. 2011;3(70):70ra13.
897. Laron Z, Kauli R, Lapkina L, Werner H. IGF-I deficiency, longevity and cancer protection of patients with Laron syndrome. *Mutat Res Rev Mutat Res*. 2017;772:123–33.
898. Ma H, Zhang T, Shen H, Cao H, Du J. The adverse events profile of anti-IGF-1R monoclonal antibodies in cancer therapy. *Br J Clin*

Pharmacol. 2014;77(6):917–28.
899. Thissen JP, Ketelslegers JM, Underwood LE. Nutritional regulation of the insulin-like growth factors. *Endocr Rev*. 1994;15(1):80–101.
900. Lee C, Safdie FM, Raffaghello L, et al. Reduced levels of IGF-I mediate differential protection of normal and cancer cells in response to fasting and improve chemotherapeutic index. *Cancer Res*. 2010;70(4):1564–72.
901. Longo VD, Anderson RM. Nutrition, longevity and disease: from molecular mechanisms to interventions. *Cell*. 2022;185(9):1455–70.
902. Dunn SE, Kari FW, French J, et al. Dietary restriction reduces insulin-like growth factor I levels, which modulates apoptosis, cell proliferation, and tumor progression in p53-deficient mice. *Cancer Res*. 1997;57(21):4667–72.
903. Fontana L, Weiss EP, Villareal DT, Klein S, Holloszy JO. Long-term effects of calorie or protein restriction on serum IGF-1 and IGFBP-3 concentration in humans. *Aging Cell*. 2008;7(5):681–7.
904. Schüler R, Markova M, Osterhoff MA, et al. Similar dietary regulation of IGF-1-and IGF-binding proteins by animal and plant protein in subjects with type 2 diabetes. *Eur J Nutr*. https://link.springer.com/article/10.1007/s00394–021–02518-y. Published online March 8, 2021. Accessed June 23, 2021.
905. Allen NE, Appleby PN, Davey GK, Key TJ. Hormones and diet: low insulin-like growth factor-I but normal bioavailable androgens in vegan men. *Br J Cancer*. 2000;83(1):95–7.
906. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. *Cancer Epidemiol Biomarkers Prev*. 2002;11(11):1441–8.
907. Ngo TH, Barnard RJ, Tymchuk CN, Cohen P, Aronson WJ. Effect of diet and exercise on serum insulin, IGF-I, and IGFBP-1 levels and growth of LNCaP cells in vitro (United States). *Cancer Causes Control*. 2002;13(10):929–35.
908. Flood A, Mai V, Pfeiffer R, et al. The effects of a high-fruit and -vegetable, high-fiber, low-fat dietary intervention on serum concentrations of insulin, glucose, IGF-I and IGFBP-3. *Eur J Clin Nutr*. 2008;62(2):186–96.

909. Allen NE, Appleby PN, Davey GK, Key TJ. Hormones and diet: low insulin-like growth factor-I but normal bioavailable androgens in vegan men. *Br J Cancer*. 2000;83(1):95–7.
910. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. *Cancer Epidemiol Biomarkers Prev*. 2002;11(11):1441–8.
911. Berrino F, Bellati C, Secreto G, et al. Reducing bioavailable sex hormones through a comprehensive change in diet: the diet and androgens (DIANA) randomized trial. *Cancer Epidemiol Biomarkers Prev*. 2001;10(1):25–33.
912. Kaaks R, Bellati C, Venturelli E, et al. Effects of dietary intervention on IGF-I and IGF-binding proteins, and related alterations in sex steroid metabolism: the Diet and Androgens (DIANA) Randomised Trial. *Eur J Clin Nutr*. 2003;57(9):1079–88.
913. Pasanisi P, Bruno E, Venturelli E, et al. A dietary intervention to lower serum levels of IGF-I in *BRCA* mutation carriers. *Cancers (Basel)*. 2018;10(9):309.
914. Gulick CN, Peddie MC, Cameron C, Bradbury K, Rehrer NJ. Physical activity, dietary protein and insulin-like growth factor 1: cross-sectional analysis utilising UK Biobank. *Growth Horm IGF Res*. 2020;55:101353.
915. Toden S, Belobrajdic DP, Bird AR, Topping DL, Conlon MA. Effects of dietary beef and chicken with and without high amylose maize starch on blood malondialdehyde, interleukins, IGF-I, insulin, leptin, MMP-2, and TIMP-2 concentrations in rats. *Nutr Cancer*. 2010;62(4):454–65.
916. Qin LQ, He K, Xu JY. Milk consumption and circulating insulin-like growth factor-I level: a systematic literature review. *Int J Food Sci Nutr*. 2009;60(S7):330–40.
917. Hoppe C, Kristensen M, Boiesen M, Kudsk J, Michaelsen KF, Mølgaard C. Short-term effects of replacing milk with cola beverages on insulin-like growth factor-I and insulin–glucose metabolism: a 10 d interventional study in young men. *Br J Nutr*. 2009;102(7):1047–51.

918. Harrison S, Lennon R, Holly J, et al. Does milk intake promote prostate cancer initiation or progression via effects on insulin-like growth factors (IGFs)? A systematic review and meta-analysis. *Cancer Causes Control*. 2017;28(6):497–528.
919. Adams AM, Smith AF. Risk perception and communication: recent developments and implications for anaesthesia. *Anaesthesia*. 2001;56(8):745–55.
920. Harrison S, Lennon R, Holly J, et al. Does milk intake promote prostate cancer initiation or progression via effects on insulin-like growth factors (IGFs)? A systematic review and meta-analysis. *Cancer Causes Control*. 2017;28(6):497–528.
921. Naghshi S, Sadeghi O, Larijani B, Esmaillzadeh A. High vs. low-fat dairy and milk differently affects the risk of all-cause, CVD, and cancer death: a systematic review and dose-response meta-analysis of prospective cohort studies. *Crit Rev Food Sci Nutr*. 2021;Jan 5:1–15.
922. Qin LQ, He K, Xu JY. Milk consumption and circulating insulin-like growth factor-I level: a systematic literature review. *Int J Food Sci Nutr*. 2009;60(7):330–40.
923. Jones CM, Heinrichs J. Growth charts for dairy heifers. Penn State Extension. https://extension.psu.edu/growth-charts-for-dairy-heifers. Updated July 28, 2017. Accessed June 9, 2021.
924. Clatici VG, Voicu C, Voaides C, Roseanu A, Icriverzi M, Jurcoane S. Diseases of civilization—cancer, diabetes, obesity and acne—the implication of milk, IGF-1 and mTORC1. *Maedica (Bucur)*. 2018;13(4):273–81.
925. Honegger A, Humbel RE. Insulin-like growth factors I and II in fetal and adult bovine serum. Purification, primary structures, and immunological cross-reactivities. *J Biol Chem*. 1986;261(2):569–75.
926. Collier RJ, Miller MA, Hildebrandt JR, et al. Factors affecting insulin-like growth factor-I concentration in bovine milk. *J Dairy Sci*. 1991;74(9):2905–11.
927. Kim WK, Ryu YH, Seo DS, Lee CY, Ko Y. Effects of oral administration of insulin-like growth factor-I on circulating concentration of insulin-like growth factor-I and growth of internal organs in weanling mice. *Biol Neonate*. 2006;89(3):199–204.

928. Clatici VG, Voicu C, Voaides C, Roseanu A, Icriverzi M, Jurcoane S. Diseases of civilization—cancer, diabetes, obesity and acne—the implication of milk, IGF-1 and mTORC1. *Maedica (Bucur)*. 2018;13(4):273–81.
929. Allen NE, Key TJ. Re: plasma insulin-like growth factor-I, insulin-like growth factor-binding proteins, and prostate cancer risk: a prospective study. *J Natl Cancer Inst*. 2001;93(8):649–51.
930. Conover CA. Discrepancies in insulin-like growth factor signaling? No, not really. *Growth Horm IGF Res*. 2016;30–31:42–4.
931. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. *Cancer Epidemiol Biomarkers Prev*. 2002;11(11):1441–8.
932. Clemmons DR, Seek MM, Underwood LE. Supplemental essential amino acids augment the somatomedin-C/insulin-like growth factor I response to refeeding after fasting. *Metabolism*. 1985;34(4):391–5.
933. Mariotti F, Gardner CD. Dietary protein and amino acids in vegetarian diets—a review. *Nutrients*. 2019;11(11):2661.
934. Ten Have GAM, Engelen MPKJ, Soeters PB, Deutz NEP. Absence of post-prandial gut anabolism after intake of a low quality protein meal. *Clin Nutr*. 2012;31(2):273–82.
935. Katz DL, Doughty KN, Geagan K, Jenkins DA, Gardner CD. Perspective: the public health case for modernizing the definition of protein quality. *Adv Nutr*. 2019;10(5):755–64.
936. Freda PU, Shen W, Reyes-Vidal CM, et al. Skeletal muscle mass in acromegaly assessed by magnetic resonance imaging and dual-photon x-ray absorptiometry. *J Clin Endocrinol Metab*. 2009;94(8):2880–6.
937. Friedlander AL, Butterfield GE, Moynihan S, et al. One year of insulin-like growth factor I treatment does not affect bone density, body composition, or psychological measures in postmenopausal women. *J Clin Endocrinol Metab*. 2001;86(4):1496–503.
938. Levine ME, Suarez JA, Brandhorst S, et al. Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. *Cell Metab*. 2014;19(3):407–17.

939. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. *Cancer Epidemiol Biomarkers Prev*. 2002;11(11):1441–8.
940. Crimarco A, Springfield S, Petlura C, et al. A randomized crossover trial on the effect of plant-based compared with animal-based meat on trimethylamine-N-oxide and cardiovascular disease risk factors in generally healthy adults: Study With Appetizing Plantfood—Meat Eating Alternative Trial (SWAP-MEAT). *Am J Clin Nutr*. 2020;112(5):1188–99.
941. Arjmandi BH, Khalil DA, Smith BJ, et al. Soy protein has a greater effect on bone in postmenopausal women not on hormone replacement therapy, as evidenced by reducing bone resorption and urinary calcium excretion. *J Clin Endocrinol Metab*. 2003;88(3):1048–54.
942. Khalil DA, Lucas EA, Juma S, Smith BJ, Payton ME, Arjmandi BH. Soy protein supplementation increases serum insulin-like growth factor-I in young and old men but does not affect markers of bone metabolism. *J Nutr*. 2002;132(9):2605–8.
943. Maskarinec G, Takata Y, Murphy SP, Franke AA, Kaaks R. Insulin-like growth factor-1 and binding protein-3 in a 2-year soya intervention among premenopausal women. *Br J Nutr*. 2005;94(3):362–7.
944. Messina M, Magee P. Does soy protein affect circulating levels of unbound IGF-1? *Eur J Nutr*. 2018;57(2):423–32.
945. Nachvak SM, Moradi S, Anjom-Shoae J, et al. Soy, soy isoflavones, and protein intake in relation to mortality from all causes, cancers, and cardiovascular diseases: a systematic review and dose-response meta-analysis of prospective cohort studies. *J Acad Nutr Diet*. 2019;119(9):1483–1500.e17.
946. Applegate CC, Rowles JL III, Ranard KM, Jeon S, Erdman JW Jr. Soy consumption and the risk of prostate cancer: an updated systematic review and meta-analysis. *Nutrients*. 2018;10(1):40.
947. Willcox DC, Willcox BJ, Todoriki H, Suzuki M. The Okinawan diet: health implications of a low-calorie, nutrient-dense, antioxidant-rich

dietary pattern low in glycemic load. *J Am Coll Nutr*. 2009;28(sup4):500S-16S.

948. Lousuebsakul-Matthews V, Thorpe DL, Knutsen R, Beeson WL, Fraser GE, Knutsen SF. Legumes and meat analogues consumption are associated with hip fracture risk independently of meat intake among Caucasian men and women: the Adventist Health Study-2. *Public Health Nutr*. 2014;17(10):2333–43.
949. Mazidi M, Katsiki N, Mikhailidis DP, et al. Lower carbohydrate diets and all-cause and cause-specific mortality: a population-based cohort study and pooling of prospective studies. *Eur Heart J*. 2019;40(34):2870–9.
950. Fung TT, van Dam RM, Hankinson SE, Stampfer M, Willett WC, Hu FB. Low-carbohydrate diets and all-cause and cause-specific mortality: two cohort studies. *Ann Intern Med*. 2010;153(5):289–98.
951. Sun Y, Liu B, Snetselaar LG, et al. Association of major dietary protein sources with all-cause and cause-specific mortality: prospective cohort study. *J Am Heart Assoc*. 2021;10(5):e015553.
952. Huang J, Liao LM, Weinstein SJ, Sinha R, Graubard BI, Albanes D. Association between plant and animal protein intake and overall and cause-specific mortality. *JAMA Intern Med*. 2020;180(9):1173–84.
953. Levine ME, Suarez JA, Brandhorst S, et al. Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. *Cell Metab*. 2014;19(3):407–17.
954. Wu S. Meat and cheese may be as bad as smoking. USC News. https://news.usc.edu/59199/meat-and-cheese-may-be-as-bad-for-you-as-smoking/. Published March 4, 2014. Accessed June 11, 2021.
955. Wu S. Meat and cheese may be as bad as smoking. USC News. https://news.usc.edu/59199/meat-and-cheese-may-be-as-bad-for-you-as-smoking/. Published March 4, 2014. Accessed June 11, 2021.
956. Spiegelhalter D. Using speed of ageing and “microlives” to communicate the effects of lifetime habits and environment. *BMJ*. 2012;345:e8223.
957. Sample I. Diets high in meat, eggs and dairy could be as harmful to health as smoking. *Guardian*. https://www.theguardian.com/science/2014/mar/04/animal-protein-

diets-smoking-meat-eggs-dairy. Published March 5, 2014. Accessed June 9, 2021.
958. Philip Morris, Europe. Second-hand tobacco smoke in perspective. What risks do you take? Philip Morris Records; Master Settlement Agreement. UCSF Industry Documents Library. https://www.industrydocuments.ucsf.edu/docs/pkdl0113. Produced 1994. Accessed February 11, 2023.
959. Ngo TH, Barnard RJ, Tymchuk CN, Cohen P, Aronson WJ. Effect of diet and exercise on serum insulin, IGF-I, and IGFBP-1 levels and growth of LNCaP cells *in vitro* (United States). *Cancer Causes Control*. 2002;13(10):929–35.
960. Soliman S, Aronson WJ, Barnard RJ. Analyzing serum-stimulated prostate cancer cell lines after low-fat, high-fiber diet and exercise intervention. *Evid Based Complement Alternat Med*. 2011;2011:529053.
961. Barnard RJ, Ngo TH, Leung PS, Aronson WJ, Golding LA. A low-fat diet and/or strenuous exercise alters the IGF axis in vivo and reduces prostate tumor cell growth in vitro. *Prostate*. 2003;56(3):201–6.
962. Ornish D, Weidner G, Fair WR, et al. Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol*. 2005;174(3):1065–9.
963. Ornish D, Magbanua MJM, Weidner G, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. *Proc Natl Acad Sci U S A*. 2008;105(24):8369–74.
964. Yang M, Kenfield SA, Van Blarigan EL, et al. Dairy intake after prostate cancer diagnosis in relation to disease-specific and total mortality. *Int J Cancer*. 2015;137(10):2462–9.
965. Tantamango-Bartley Y, Jaceldo-Siegl K, Fan J, Fraser G. Vegetarian diets and the incidence of cancer in a low-risk population. *Cancer Epidemiol Biomarkers Prev*. 2013;22(2):286–94.
966. Mucci LA, Tamimi R, Lagiou P, et al. Are dietary influences on the risk of prostate cancer mediated through the insulin-like growth factor system? *BJU Int*. 2001;87(9):814–20.
967. Gunnell D, Oliver SE, Peters TJ, et al. Are diet–prostate cancer associations mediated by the IGF axis? A cross-sectional analysis of

diet, IGF-I and IGFBP-3 in healthy middle-aged men. *Br J Cancer*. 2003;88(11):1682–6.

968. Walfisch S, Walfisch Y, Kirilov E, et al. Tomato lycopene extract supplementation decreases insulin-like growth factor-I levels in colon cancer patients. *Eur J Cancer Prev*. 2007;16(4):298–303.

969. Xie Z, Yang F. The effects of lycopene supplementation on serum insulin-like growth factor 1 (IGF-1) levels and cardiovascular disease: a dose-response meta-analysis of clinical trials. *Complement Ther Med*. 2021;56:102632.

970. Rickard SE, Yuan YV, Thompson LU. Plasma insulin-like growth factor I levels in rats are reduced by dietary supplementation of flaxseed or its lignan secoisolariciresinol diglycoside. *Cancer Lett*. 2000;161(1):47–55.

971. Sturgeon SR, Volpe SL, Puleo E, et al. Dietary intervention of flaxseed: effect on serum levels of IGF-1, IGF-BP3, and C-peptide. *Nutr Cancer*. 2011;63(3):376–80.

972. Zhou JR, Yu L, Mai Z, Blackburn GL. Combined inhibition of estrogen-dependent human breast carcinoma by soy and tea bioactive components in mice. *Int J Cancer*. 2004;108(1):8–14.

973. Biernacka KM, Holly JMP, Martin RM, et al. Effect of green tea and lycopene on the insulin-like growth factor system: the ProDiet randomized controlled trial. *Eur J Cancer Prev*. 2019;28(6):569–75.

974. Samavat H, Wu AH, Ursin G, et al. Green tea catechin extract supplementation does not influence circulating sex hormones and insulin-like growth factor axis proteins in a randomized controlled trial of postmenopausal women at high risk of breast cancer. *J Nutr*. 2019;149(4):619–27.

975. Teas J, Irhimeh MR, Druker S, et al. Serum IGF-1 concentrations change with soy and seaweed supplements in healthy postmenopausal American women. *Nutr Cancer*. 2011;63(5):743–8.

976. Burgers AMG, Biermasz NR, Schoones JW, et al. Meta-analysis and dose-response metaregression: circulating insulin-like growth factor I (IGF-I) and mortality. *J Clin Endocrinol Metab*. 2011;96(9):2912–20.

977. LeRoith D. IGF-I: panacea or poison? *J Clin Endocrinol Metab.* 2010;95(10):4549–51.

978. Zhang WB, Aleksic S, Gao T, et al. Insulin-like growth factor-1 and IGF binding proteins predict all-cause mortality and morbidity in older adults. *Cells*. 2020;9(6):1368.
979. Larsson SC, Michaëlsson K, Burgess S. IGF-1 and cardiometabolic diseases: a Mendelian randomisation study. *Diabetologia*. 2020;63(9):1775–82.
980. Hartley A, Sanderson E, Paternoster L, et al. Mendelian randomization provides evidence for a causal effect of higher serum IGF-1 concentration on risk of hip and knee osteoarthritis. *Rheumatology (Oxford)*. 2020;60(4):1676–86.
981. Larsson SC, Michaëlsson K, Burgess S. IGF-1 and cardiometabolic diseases: a Mendelian randomisation study. *Diabetologia*. 2020;63(9):1775–82.
982. Fan M, Li Y, Wang C, et al. Dietary protein consumption and the risk of type 2 diabetes: adose-response *[sic]* meta-analysis of prospective studies. *Nutrients*. 2019;11(11):2783.
983. Teumer A, Qi Q, Nethander M, et al. Genomewide meta-analysis identifies loci associated with IGF-I and IGFBP-3 levels with impact on age-related traits. *Aging Cell*. 2016;15(5):811–24.
984. Milman S, Atzmon G, Huffman DM, et al. Low insulin-like growth factor-1 level predicts survival in humans with exceptional longevity. *Aging Cell*. 2014;13(4):769–71.
985. Pawlikowska L, Hu D, Huntsman S, et al. Association of common genetic variation in the insulin/IGF1 signaling pathway with human longevity. *Aging Cell*. 2009;8(4):460–72.
986. Fontana L, Cummings NE, Arriola Apelo SI, et al. Decreased consumption of branched-chain amino acids improves metabolic health. *Cell Rep*. 2016;16(2):520–30.
987. Chainani-Wu N, Weidner G, Purnell DM, et al. Changes in emerging cardiac biomarkers after an intensive lifestyle intervention. *Am J Cardiol*. 2011;108(4):498–507.
988. Levine ME, Suarez JA, Brandhorst S, et al. Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. *Cell Metab*. 2014;19(3):407–17.

989. Werner H, Laron Z. Role of the GH-IGF1 system in progression of cancer. *Mol Cell Endocrinol*. 2020;518:111003.
990. McCarty MF. A low-fat, whole-food vegan diet, as well as other strategies that down-regulate IGF-I activity, may slow the human aging process. *Med Hypotheses*. 2003;60(6):784–92.
991. Longo VD, Lieber MR, Vijg J. Turning anti-ageing genes against cancer. *Nat Rev Mol Cell Biol*. 2008;9(11):903–10.
992. McCarty MF. GCN2 and FGF21 are likely mediators of the protection from cancer, autoimmunity, obesity, and diabetes afforded by vegan diets. *Med Hypotheses*. 2014;83(3):365–71.
993. Piper MDW, Soultoukis GA, Blanc E, et al. Matching dietary amino acid balance to the in silico–translated exome optimizes growth and reproduction without cost to lifespan. *Cell Metab*. 2017;25(3):610–21.
994. Slavich GM. Understanding inflammation, its regulation, and relevance for health: a top scientific and public priority. *Brain Behav Immun*. 2015;45:13–4.
995. Egger G. In search of a germ theory equivalent for chronic disease. *Prev Chronic Dis*. 2012;9:E95.
996. Rubio-Ruiz ME, Peredo-Escárcega AE, Cano-Martínez A, Guarner-Lans V. An evolutionary perspective of nutrition and inflammation as mechanisms of cardiovascular disease. *Int J Evol Biol*. 2015:2015:179791.
997. Rogers J. The inflammatory response in Alzheimer's disease. *J Periodontol*. 2008;79(8 Suppl):1535–43.
998. Egger G. In search of a germ theory equivalent for chronic disease. *Prev Chronic Dis*. 2012;9:E95.
999. Ridker PM. C-reactive protein: a simple test to help predict risk of heart attack and stroke. *Circulation*. 2003;108(12):e81–5.
1000. Bray C, Bell LN, Liang H, et al. Erythrocyte sedimentation rate and C-reactive protein measurements and their relevance in clinical medicine. *WMJ*. 2016;115(6):317–21.
1001. Ridker PM. C-reactive protein: a simple test to help predict risk of heart attack and stroke. *Circulation*. 2003;108(12):e81–5.
1002. Bottazzi B, Riboli E, Mantovani A. Aging, inflammation and cancer. *Semin Immunol*. 2018;40:74–82.

1003. National Center for Injury Prevention and Control, CDC using WISQARS™.10 leading causes of death by age group, United States —2018. Centers for Disease Control and Prevention. https://www.cdc.gov/injury/images/lc-charts/leading_causes_of_death_by_age_group_2018_1100w850h.jpg. Accessed June 29, 2021.
1004. Weyh C, Krüger K, Strasser B. Physical activity and diet shape the immune system during aging. *Nutrients*. 2020;12(3):622.
1005. Fagiolo U, Cossarizza A, Scala E, et al. Increased cytokine production in mononuclear cells of healthy elderly people. *Eur J Immunol*. 1993;23(9):2375–8.
1006. Fulop T, Larbi A, Dupuis G, et al. Immunosenescence and inflamm-aging as two sides of the same coin: friends or foes? *Front Immunol*. 2018;8:1960.
1007. Cevenini E, Monti D, Franceschi C. Inflamm-ageing. *Curr Opin Clin Nutr Metab Care*. 2013;16(1):14–20.
1008. Franceschi C, Bonafè M, Valensin S, et al. Inflamm-aging: an evolutionary perspective on immunosenescence. *Ann N Y Acad Sci*. 2000;908(1):244–54.
1009. Tang Y, Fung E, Xu A, Lan HY. C-reactive protein and ageing. *Clin Exp Pharmacol Physiol*. 2017;44(S1):9–14.
1010. Tait JL, Duckham RL, Milte CM, Main LC, Daly RM. Associations between inflammatory and neurological markers with quality of life and well-being in older adults. *Exp Gerontol*. 2019;125:110662.
1011. Tang Y, Fung E, Xu A, Lan HY. C-reactive protein and ageing. *Clin Exp Pharmacol Physiol*. 2017;44(S1):9–14.
1012. Rajasekaran S, Tangavel C, Anand SV KS, et al. Inflammaging determines health and disease in lumbar discs—evidence from differing proteomic signatures of healthy, aging, and degenerating discs. *Spine J*. 2020;20(1):48–59.
1013. Pedersen BK. Anti-inflammation—just another word for anti-ageing? *J Physiol*. 2009;587(Pt 23):5515.
1014. Barron E, Lara J, White M, Mathers JC. Blood-borne biomarkers of mortality risk: systematic review of cohort studies. *PLoS ONE*. 2015;10(6):e0127550.

1015. Bottazzi B, Riboli E, Mantovani A. Aging, inflammation and cancer. *Semin Immunol*. 2018;40:74–82.
1016. Franceschi C, Bonafè M, Valensin S, et al. Inflamm-aging: an evolutionary perspective on immunosenescence. *Ann N Y Acad Sci*. 2000;908(1):244–54.
1017. Puzianowska-Kuźnicka M, Owczarz M, Wieczorowska-Tobis K, et al. Interleukin-6 and C-reactive protein, successful aging, and mortality: the PolSenior study. *Immun Ageing*. 2016;13:21.
1018. Franceschi C, Ostan R, Santoro A. Nutrition and inflammation: are centenarians similar to individuals on calorie-restricted diets? *Annu Rev Nutr*. 2018;38:329–56.
1019. Bonafè M, Olivieri F, Cavallone L, et al. A gender–dependent genetic predisposition to produce high levels of IL-6 is detrimental for longevity. *Eur J Immunol*. 2001;31(8):2357–61.
1020. Man MQ, Elias PM. Could inflammaging and its sequelae be prevented or mitigated? *Clin Interv Aging*. 2019;14:2301–4.
1021. Man MQ, Elias PM. Could inflammaging and its sequelae be prevented or mitigated? *Clin Interv Aging*. 2019;14:2301–4.
1022. Hu L, Mauro TM, Dang E, et al. Epidermal dysfunction leads to an age-associated increase in levels of serum inflammatory cytokines. *J Invest Dermatol*. 2017;137(6):1277–85.
1023. Ye L, Mauro TM, Dang E, et al. Topical applications of an emollient reduce circulating pro-inflammatory cytokine levels in chronically aged humans: a pilot clinical study. *J Eur Acad Dermatol Venereol*. 2019;33(11):2197–201.
1024. Arai Y, Martin-Ruiz CM, Takayama M, et al. Inflammation, but not telomere length, predicts successful ageing at extreme old age: a longitudinal study of semi-supercentenarians. *EBioMedicine*. 2015;2(10):1549–58.
1025. Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. *Nat Med*. 2019;25(12):1822–32.
1026. Chambers ES, Akbar AN. Can blocking inflammation enhance immunity during aging? *J Allergy Clin Immunol*. 2020;145(5):1323–31.

1027. Franceschi C, Garagnani P, Vitale G, Capri M, Salvioli S. Inflammaging and 'garb-aging.' *Trends Endocrinol. Metab*. 2017;28(3):199–212.
1028. Monti D, Ostan R, Borelli V, Castellani G, Franceschi C. Inflammaging and human longevity in the omics era. *Mech Ageing Dev*. 2017;165(Pt B):129–38.
1029. Meydani SN, Das SK, Pieper CF, et al. Long-term moderate calorie restriction inhibits inflammation without impairing cell-mediated immunity: a randomized controlled trial in non-obese humans. *Aging (Albany NY)*. 2016;8(7):1416–31.
1030. Choi J, Joseph L, Pilote L. Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. *Obes Rev*. 2013;14(3):232–44.
1031. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci*. 2017;13(4):851–63.
1032. Pasarica M, Sereda OR, Redman LM, et al. Reduced adipose tissue oxygenation in human obesity: evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response. *Diabetes*. 2009;58(3):718–25.
1033. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest*. 2003;112(12):1796–808.
1034. Cinti S, Mitchell G, Barbatelli G, et al. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. *J Lipid Res*. 2005;46(11):2347–55.
1035. Bays HE, González-Campoy JM, Bray GA, et al. Pathogenic potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. *Expert Rev Cardiovasc Ther*. 2008;6(3):343–68.
1036. Welsh P, Polisecki E, Robertson M, et al. Unraveling the directional link between adiposity and inflammation: a bidirectional Mendelian randomization approach. *J Clin Endocrinol Metab*. 2010;95(1):93–9.
1037. Timpson NJ, Nordestgaard BG, Harbord RM, et al. C-reactive protein levels and body mass index: elucidating direction of causation

through reciprocal Mendelian randomization. *Int J Obes (Lond)*. 2011;35(2):300–8.
1038. Chung S, Parks JS. Dietary cholesterol effects on adipose tissue inflammation. *Curr Opin Lipidol*. 2016;27(1):19–25.
1039. Chung S, Cuffe H, Marshall SM, et al. Dietary cholesterol promotes adipocyte hypertrophy and adipose tissue inflammation in visceral, but not in subcutaneous, fat in monkeys. *Arterioscler Thromb Vasc Biol*. 2014;34(9):1880–7.
1040. Chung S, Parks JS. Dietary cholesterol effects on adipose tissue inflammation. *Curr Opin Lipidol*. 2016;27(1):19–25.
1041. Chung S, Cuffe H, Marshall SM, et al. Dietary cholesterol promotes adipocyte hypertrophy and adipose tissue inflammation in visceral, but not in subcutaneous, fat in monkeys. *Arterioscler Thromb Vasc Biol*. 2014;34(9):1880–7.
1042. Xu Z, McClure ST, Appel LJ. Dietary cholesterol intake and sources among U.S. adults: results from National Health and Nutrition Examination Surveys (NHANES), 2001–2014. *Nutrients*. 2018;10(6):E771.
1043. Morgan-Bathke ME, Jensen MD. Preliminary evidence for reduced adipose tissue inflammation in vegetarians compared with omnivores. *Nutr J*. 2019;18(1):45.
1044. Hegsted DM. Dietary goals—a progressive view. *Am J Clin Nutr*. 1978;31(9):1504–9.
1045. Trumbo PR, Shimakawa T. Tolerable upper intake levels for trans fat, saturated fat, and cholesterol. *Nutr Rev*. 2011;69(5):270–8.
1046. Chambers ES, Akbar AN. Can blocking inflammation enhance immunity during aging? *J Allergy Clin Immunol*. 2020;145(5):1323–31.
1047. Zamboni M, Nori N, Brunelli A, Zoico E. How does adipose tissue contribute to inflammageing? *Exp Gerontol*. 2021;143:111162.
1048. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA*. 2004;292(14):1724–37.
1049. Rao SR. Inflammatory markers and bariatric surgery: a meta-analysis. *Inflamm Res*. 2012;61(8):789–807.
1050. Meydani SN, Das SK, Pieper CF, et al. Long-term moderate calorie restriction inhibits inflammation without impairing cell-mediated

immunity: a randomized controlled trial in non-obese humans. *Aging (Albany NY)*. 2016;8(7):1416–31.

1051. Chambers ES, Akbar AN. Can blocking inflammation enhance immunity during aging? *J Allergy Clin Immunol*. 2020;145(5):1323–31.

1052. Egger G. In search of a germ theory equivalent for chronic disease. *Prev Chronic Dis*. 2012;9:E95.

1053. Egger G, Dixon J. Non-nutrient causes of low-grade, systemic inflammation: support for a 'canary in the mineshaft' view of obesity in chronic disease. *Obes Rev*. 2011;12(5):339–45.

1054. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8):1689–96.

1055. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8):1689–96.

1056. Ryu S, Shivappa N, Veronese N, et al. Secular trends in Dietary Inflammatory Index among adults in the United States, 1999–2014. *Eur J Clin Nutr*. 2019;73(10):1343–51.

1057. Xu H, Sjögren P, Ärnlöv J, et al. A proinflammatory diet is associated with systemic inflammation and reduced kidney function in elderly adults. *J Nutr*. 2015;145(4):729–35.

1058. Han YY, Forno E, Shivappa N, Wirth MD, Hébert JR, Celedón JC. The Dietary Inflammatory Index and current wheeze among children and adults in the United States. *J Allergy Clin Immunol Pract*. 2018;6(3):834–41.

1059. Cantero I, Abete I, Babio N, et al. Dietary Inflammatory Index and liver status in subjects with different adiposity levels within the PREDIMED trial. *Clin Nutr*. 2018;37(5):1736–43.

1060. Shivappa N, Godos J, Hébert JR, et al. Dietary Inflammatory Index and cardiovascular risk and mortality—a meta-analysis. *Nutrients*. 2018;10(2):200.

1061. Shivappa N, Wirth MD, Hurley TG, Hébert JR. Association between the dietary inflammatory index (DII) and telomere length and C-reactive protein from the National Health and Nutrition Examination Survey—1999–2002. *Mol Nutr Food Res*. 2017;61(4).

1062. García-Calzón S, Zalba G, Ruiz-Canela M, et al. Dietary inflammatory index and telomere length in subjects with a high cardiovascular disease risk from the PREDIMED-NAVARRA study: cross-sectional and longitudinal analyses over 5 y. *Am J Clin Nutr*. 2015;102(4):897–904.
1063. Shivappa N, Stubbs B, Hébert JR, et al. The relationship between the Dietary Inflammatory Index and incident frailty: a longitudinal cohort study. *J Am Med Dir Assoc*. 2018;19(1):77–82.
1064. Cervo MMC, Scott D, Seibel MJ, et al. Proinflammatory diet increases circulating inflammatory biomarkers and falls risk in community-dwelling older men. *J Nutr*. 2020;150(2):373–81.
1065. Kheirouri S, Alizadeh M. Dietary inflammatory potential and the risk of neurodegenerative diseases in adults. *Epidemiol Rev*. 2019;41(1):109–20.
1066. Phillips CM, Shivappa N, Hébert JR, Perry IJ. Dietary inflammatory index and mental health: a cross-sectional analysis of the relationship with depressive symptoms, anxiety and well-being in adults. *Clin Nutr*. 2018;37(5):1485–91.
1067. Godos J, Ferri R, Caraci F, et al. Dietary inflammatory index and sleep quality in southern Italian adults. *Nutrients*. 2019;11(6):1324.
1068. Shivappa N, Jackson MD, Bennett F, Hébert JR. Increased dietary inflammatory index (DII) is associated with increased risk of prostate cancer in Jamaican men. *Nutr Cancer*. 2015;67(6):941–8.
1069. Shivappa N, Hébert JR, Jalilpiran Y, Faghih S. Association between dietary inflammatory index and prostate cancer in Shiraz province of Iran. *Asian Pac J Cancer Prev*. 2018;19(2):415–20.
1070. Shivappa N, Miao Q, Walker M, Hébert JR, Aronson KJ. Association between a dietary inflammatory index and prostate cancer risk in Ontario, Canada. *Nutr Cancer*. 2017;69(6):825–32.
1071. Huang WQ, Mo XF, Ye YB, et al. A higher Dietary Inflammatory Index score is associated with a higher risk of breast cancer among Chinese women: a case-control study. *Br J Nutr*. 2017;117(10):1358–67.
1072. Shivappa N, Sandin S, Löf M, Hébert JR, Adami HO, Weiderpass E. Prospective study of dietary inflammatory index and risk of breast cancer in Swedish women. *Br J Cancer*. 2015;113(7):1099–103.

1073. Shivappa N, Hébert JR, Zucchetto A, et al. Dietary inflammatory index and endometrial cancer risk in an Italian case-control study. *Br J Nutr*. 2016;115(1):138–46.
1074. Shivappa N, Hébert JR, Rosato V, et al. Dietary inflammatory index and ovarian cancer risk in a large Italian case-control study. *Cancer Causes Control*. 2016;27(7):897–906.
1075. Shivappa N, Zucchetto A, Serraino D, Rossi M, La Vecchia C, Hébert JR. Dietary inflammatory index and risk of esophageal squamous cell cancer in a case-control study from Italy. *Cancer Causes Control*. 2015;26(10):1439–47.
1076. Shivappa N, Hébert JR, Ferraroni M, La Vecchia C, Rossi M. Association between dietary inflammatory index and gastric cancer risk in an Italian case-control study. *Nutr Cancer*. 2016;68(8):1262–8.
1077. Shivappa N, Hébert JR, Polesel J, et al. Inflammatory potential of diet and risk for hepatocellular cancer in a case-control study from Italy. *Br J Nutr*. 2016;115(2):324–31.
1078. Shivappa N, Bosetti C, Zucchetto A, Serraino D, La Vecchia C, Hébert JR. Dietary inflammatory index and risk of pancreatic cancer in an Italian case-control study. *Br J Nutr*. 2015;113(2):292–8.
1079. Shivappa N, Godos J, Hébert JR, et al. Dietary inflammatory index and colorectal cancer risk—a meta-analysis. *Nutrients*. 2017 Sep 20;9(9):1043.
1080. Shivappa N, Hébert JR, Rosato V, et al. Dietary inflammatory index and renal cell carcinoma risk in an Italian case-control study. *Nutr Cancer*. 2017;69(6):833–9.
1081. Shivappa N, Hébert JR, Rosato V, et al. Dietary inflammatory index and risk of bladder cancer in a large Italian case-control study. *Urology*. 2017;100:84–9.
1082. Shivappa N, Hébert JR, Taborelli M, et al. Dietary inflammatory index and non-Hodgkin lymphoma risk in an Italian case-control study. *Cancer Causes Control*. 2017;28(7):791–9.
1083. Fowler ME, Akinyemiju TF. Meta-analysis of the association between dietary inflammatory index (DII) and cancer outcomes. *Int J Cancer*. 2017;141(11):2215–27.
1084. Shivappa N, Hebert JR, Kivimaki M, Akbaraly T. Alternate Healthy Eating Index 2010, Dietary Inflammatory Index and risk of mortality:

results from the Whitehall II cohort study and meta-analysis of previous Dietary Inflammatory Index and mortality studies. *Br J Nutr*. 2017;118(3):210–21.

1085. Edwards MK, Shivappa N, Mann JR, Hébert JR, Wirth MD, Loprinzi PD. The association between physical activity and dietary inflammatory index on mortality risk in U.S. adults. *Phys Sportsmed*. 2018;46(2):249–54.

1086. Shivappa N, Harris H, Wolk A, Hebert JR. Association between inflammatory potential of diet and mortality among women in the Swedish Mammography Cohort. *Eur J Nutr*. 2016;55(5):1891–900.

1087. Shivappa N, Blair CK, Prizment AE, Jacobs DR, Steck SE, Hébert JR. Association between inflammatory potential of diet and mortality in the Iowa Women's Health study. *Eur J Nutr*. 2016;55(4):1491–502.

1088. Tomata Y, Shivappa N, Zhang S, et al. Dietary inflammatory index and disability-free survival in community-dwelling older adults. *Nutrients*. 2018;10(12):1896.

1089. Garcia-Arellano A, Martínez-González MA, Ramallal R, et al. Dietary inflammatory index and all-cause mortality in large cohorts: the SUN and PREDIMED studies. *Clin Nutr*. 2019;38(3):1221–31.

1090. Nilsson MI, Bourgeois JM, Nederveen JP, et al. Lifelong aerobic exercise protects against inflammaging and cancer. *PLoS One*. 2019;14(1):e0210863.

1091. Bautmans I, Salimans L, Njemini R, Beyer I, Lieten S, Liberman K. The effects of exercise interventions on the inflammatory profile of older adults: a systematic review of the recent literature. *Exp Gerontol*. 2021;146:111236.

1092. Ferrer MD, Capó X, Martorell M, et al. Regular practice of moderate physical activity by older adults ameliorates their anti-inflammatory status. *Nutrients*. 2018;10(11):1780.

1093. Piercy KL, Troiano RP, Ballard RM, et al. The Physical Activity Guidelines for Americans. *JAMA*. 2018;320(19):2020–8.

1094. Harvard T.H. Chan School of Public Health. Top food sources of saturated fat in the U.S. https://puntocritico.com/ausajpuntocritico/documentos/The_Nutrition_Source.pdf. Accessed November 23, 2021.

1095. Exler J, Lemar L, Smith J. Fat and fatty acid content of selected foods containing trans-fatty acids: special purpose table no. 1. Agricultural Research Service, United States Department of Agriculture. https://www.ars.usda.gov/arsuserfiles/80400525/data/classics/trans_fa.pdf. Published January 1996. Accessed June 20, 2021.
1096. Vogel RA, Corretti MC, Plotnick GD. Effect of a single high-fat meal on endothelial function in healthy subjects. *Am J Cardiol*. 1997;79(3):350–4.
1097. Deopurkar R, Ghanim H, Friedman J, et al. Differential effects of cream, glucose, and orange juice on inflammation, endotoxin, and the expression of Toll-like receptor-4 and suppressor of cytokine signaling-3. *Diabetes Care*. 2010;33(5):991–7.
1098. Kesteloot HE, Sasaki S. Nutrition and the aging process: a population study. *Am J Geriatr Cardiol*. 1994;3(2):8–19.
1099. Emerson SR, Kurti SP, Harms CA, et al. Magnitude and timing of the postprandial inflammatory response to a high-fat meal in healthy adults: a systematic review. *Adv Nutr*. 2017;8(2):213–25.
1100. Harris TB, Ferrucci L, Tracy RP, et al. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *Am J Med*. 1999;106(5):506–12.
1101. Jonnalagadda SS, Egan SK, Heimbach JT, et al. Fatty acid consumption pattern of Americans: 1987–1988 USDA Nationwide Food Consumption Survey. *Nutr Res.* 1995;15(12):1767–81.
1102. Carta G, Murru E, Banni S, Manca C. Palmitic acid: physiological role, metabolism and nutritional implications. *Front Physiol*. 2017;8:902.
1103. Korbecki J, Bajdak-Rusinek K. The effect of palmitic acid on inflammatory response in macrophages: an overview of molecular mechanisms. *Inflamm Res*. 2019;68(11):915–32.
1104. Deopurkar R, Ghanim H, Friedman J, et al. Differential effects of cream, glucose, and orange juice on inflammation, endotoxin, and the expression of Toll-like receptor-4 and suppressor of cytokine signaling-3. *Diabetes Care*. 2010;33(5):991–7.
1105. Erridge C. Accumulation of stimulants of Toll-like receptor (TLR)-2 and TLR4 in meat products stored at 5 °C. *J Food Sci*. 2011;76(2):H72–9.

1106. Erridge C. The capacity of foodstuffs to induce innate immune activation of human monocytes *in vitro* is dependent on food content of stimulants of Toll-like receptors 2 and 4. *Br J Nutr*. 2011;105(1):15–23.
1107. Deopurkar R, Ghanim H, Friedman J, et al. Differential effects of cream, glucose, and orange juice on inflammation, endotoxin, and the expression of Toll-like receptor-4 and suppressor of cytokine signaling-3. *Diabetes Care*. 2010;33(5):991–7.
1108. Herieka M, Faraj TA, Erridge C. Reduced dietary intake of pro-inflammatory Toll-like receptor stimulants favourably modifies markers of cardiometabolic risk in healthy men. *Nutr Metab Cardiovasc Dis*. 2016;26(3):194–200.
1109. Wassenaar TM, Zimmermann K. Lipopolysaccharides in food, food supplements, and probiotics: should we be worried? *Eur J Microbiol Immunol (Bp)*. 2018;8(3):63–9.
1110. Ghoshal S, Witta J, Zhong J, de Villiers W, Eckhardt E. Chylomicrons promote intestinal absorption of lipopolysaccharides. *J Lipid Res*. 2009;50(1):90–7.
1111. Ghezzal S, Postal BG, Quevrain E, et al. Palmitic acid damages gut epithelium integrity and initiates inflammatory cytokine production. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2020;1865(2):158530.
1112. Harte AL, Varma MC, Tripathi G, et al. High fat intake leads to acute postprandial exposure to circulating endotoxin in type 2 diabetic subjects. *Diabetes Care*. 2012;35(2):375–82.
1113. Erridge C. The capacity of foodstuffs to induce innate immune activation of human monocytes *in vitro* is dependent on food content of stimulants of Toll-like receptors 2 and 4. *Br J Nutr*. 2011;105(1):15–23.
1114. Cho B, Kim MS, Chao K, Lawrence K, Park B, Kim K. Detection of fecal residue on poultry carcasses by laser-induced fluorescence imaging. *J Food Sci*. 2009;74(3):E154–9.
1115. Giombelli A, Gloria MB. Prevalence of *Salmonella* and *Campylobacter* on broiler chickens from farm to slaughter and efficiency of methods to remove visible fecal contamination. *J Food Prot*. 2014;77(11):1851–9.

1116. Erridge C. Accumulation of stimulants of Toll-like receptor (TLR)-2 and TLR4 in meat products stored at 5 °C. *J Food Sci*. 2011;76(2):H72–9.
1117. Erridge C. Stimulants of Toll-like receptor (TLR)-2 and TLR-4 are abundant in certain minimally-processed vegetables. *Food Chem Toxicol*. 2011;49(6):1464–7.
1118. Tournas VH. Spoilage of vegetable crops by bacteria and fungi and related health hazards. *Crit Rev Microbiol*. 2005;31(1):33–44.
1119. Herieka M, Faraj TA, Erridge C. Reduced dietary intake of pro-inflammatory Toll-like receptor stimulants favourably modifies markers of cardiometabolic risk in healthy men. *Nutr Metab Cardiovasc Dis*. 2016;26(3):194–200.
1120. Herieka M, Faraj TA, Erridge C. Reduced dietary intake of pro-inflammatory Toll-like receptor stimulants favourably modifies markers of cardiometabolic risk in healthy men. *Nutr Metab Cardiovasc Dis*. 2016;26(3):194–200.
1121. Erridge C. Stimulants of Toll-like receptor (TLR)-2 and TLR-4 are abundant in certain minimally-processed vegetables. *Food Chem Toxicol*. 2011;49(6):1464–7.
1122. Neale EP, Tapsell LC, Guan V, Batterham MJ. The effect of nut consumption on markers of inflammation and endothelial function: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open*. 2017;7(11):e016863.
1123. Chen CYO, Holbrook M, Duess MA, et al. Effect of almond consumption on vascular function in patients with coronary artery disease: a randomized, controlled, cross-over trial. *Nutr J*. 2015;14:61.
1124. Li Z, Wong A, Henning SM, et al. Hass avocado modulates postprandial vascular reactivity and postprandial inflammatory responses to a hamburger meal in healthy volunteers. *Food Funct*. 2013;4(3):384–91.
1125. Haskins CP, Henderson G, Champ CE. Meat, eggs, full-fat dairy, and nutritional boogeymen: does the way in which animals are raised affect health differently in humans? *Crit Rev Food Sci Nutr*. 2019;59(17):2709–19.
1126. Eaton SB. Humans, lipids and evolution. *Lipids*. 1992;27(10):814–20.

1127. Arya F, Egger S, Colquhoun D, Sullivan D, Pal S, Egger G. Differences in postprandial inflammatory responses to a 'modern' *v*. traditional meat meal: a preliminary study. *Br J Nutr*. 2010;104(5):724–8.
1128. Wang Y, Lehane C, Ghebremeskel K, et al. Modern organic and broiler chickens sold for human consumption provide more energy from fat than protein. *Public Health Nutr*. 2010;13(3):400–8.
1129. Kollander B, Widemo F, Ågren E, Larsen EH, Löschner K. Detection of lead nanoparticles in game meat by single particle ICP-MS following use of lead-containing bullets. *Anal Bioanal Chem*. 2017;409(7):1877–85.
1130. Metryka E, Chibowska K, Gutowska I, et al. Lead (Pb) exposure enhances expression of factors associated with inflammation. *Int J Mol Sci*. 2018;19(6):1813.
1131. Harte AL, Varma MC, Tripathi G, et al. High fat intake leads to acute postprandial exposure to circulating endotoxin in type 2 diabetic subjects. *Diabetes Care*. 2012;35(2):375–82.
1132. National Cancer Institute. Identification of top food sources of various dietary components. Epidemiology and Genomics Research Program website. https://epi.grants.cancer.gov/diet/foodsources. Updated November 30, 2019. Accessed June 20, 2021.
1133. Ghanim H, Batra M, Abuaysheh S, et al. Antiinflammatory and ROS suppressive effects of the addition of fiber to a high-fat high-calorie meal. *J Clin Endocrinol Metab*. 2017;102(3):858–69.
1134. Simon AH, Lima PR, Almerinda M, Alves VF, Bottini PV, de Faria JB. Renal haemodynamic responses to a chicken or beef meal in normal individuals. *Nephrol Dial Transplant*. 1998;13(9):2261–4.
1135. Kontessis P, Jones S, Dodds R, et al. Renal, metabolic and hormonal responses to ingestion of animal and vegetable proteins. *Kidney Int*. 1990 Jul;38(1):136–44.
1136. Liu Z, Ho SC, Chen Y, Tang N, Woo J. Effect of whole soy and purified isoflavone daidzein on renal function—a 6-month randomized controlled trial in equol-producing postmenopausal women with prehypertension. *Clin Biochem*. 2014;47(13–14):1250–6.

1137. Fioretto P, Trevisan R, Valerio A, et al. Impaired renal response to a meat meal in insulin-dependent diabetes: role of glucagon and prostaglandins. *Am J Physiol*. 1990;258(3 Pt 2):F675–83.
1138. Varki A. Are humans prone to autoimmunity? Implications from evolutionary changes in hominin sialic acid biology. *J Autoimmun*. 2017;83:134–42.
1139. Pham T, Gregg CJ, Karp F, et al. Evidence for a novel human-specific xeno-auto-antibody response against vascular endothelium. *Blood*. 2009;114(25):5225–35.
1140. Alisson-Silva F, Kawanishi K, Varki A. Human risk of diseases associated with red meat intake: analysis of current theories and proposed role for metabolic incorporation of a non-human sialic acid. *Mol Aspects Med*. 2016;51:16–30.
1141. Peri S, Kulkarni A, Feyertag F, Berninsone PM, Alvarez-Ponce D. Phylogenetic distribution of CMP-Neu5Ac hydroxylase (CMAH), the enzyme synthetizing the proinflammatory human xenoantigen Neu5Gc. *Genome Biol Evol*. 2018;10(1):207–19.
1142. Samraj AN, Pearce OMT, Läubli H, et al. A red meat-derived glycan promotes inflammation and cancer progression. *Proc Natl Acad Sci U S A*. 2015;112(2):542–7.
1143. Peri S, Kulkarni A, Feyertag F, Berninsone PM, Alvarez-Ponce D. Phylogenetic distribution of CMP-Neu5Ac hydroxylase (CMAH), the enzyme synthetizing the proinflammatory human xenoantigen Neu5Gc. *Genome Biol Evol*. 2018;10(1):207–19.
1144. Jahan M, Thomson PC, Wynn PC, Wang B. The non-human glycan, *N*-glycolylneuraminic acid (Neu5Gc), is not expressed in all organs and skeletal muscles of nine animal species. *Food Chem*. 2021;343:128439.
1145. Peri S, Kulkarni A, Feyertag F, Berninsone PM, Alvarez-Ponce D. Phylogenetic distribution of CMP-Neu5Ac hydroxylase (CMAH), the enzyme synthetizing the proinflammatory human xenoantigen Neu5Gc. *Genome Biol Evol*. 2018;10(1):207–19.
1146. Jahan M, Thomson PC, Wynn PC, Wang B. The non-human glycan, *N*-glycolylneuraminic acid (Neu5Gc), is not expressed in all organs and skeletal muscles of nine animal species. *Food Chem*. 2021;343:128439.

1147. Alisson-Silva F, Kawanishi K, Varki A. Human risk of diseases associated with red meat intake: analysis of current theories and proposed role for metabolic incorporation of a non-human sialic acid. *Mol Aspects Med*. 2016;51:16–30.
1148. MacGregor GA, Markandu ND, Best FE, et al. Double-blind randomised crossover trial of moderate sodium restriction in essential hypertension. *Lancet*. 1982;1(8268):351–5.
1149. Yi B, Titze J, Rykova M, et al. Effects of dietary salt levels on monocytic cells and immune responses in healthy human subjects: a longitudinal study. *Transl Res*. 2015;166(1):103–10.
1150. Mickleborough TD, Lindley MR, Ray S. Dietary salt, airway inflammation, and diffusion capacity in exercise-induced asthma. *Med Sci Sports Exerc*. 2005;37(6):904–14.
1151. Farez MF, Fiol MP, Gaitán MI, Quintana FJ, Correale J. Sodium intake is associated with increased disease activity in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2015;86(1):26–31.
1152. Krajina I, Stupin A, Šola M, Mihalj M. Oxidative stress induced by high salt diet—possible implications for development and clinical manifestation of cutaneous inflammation and endothelial dysfunction in *Psoriasis vulgaris*. *Antioxidants (Basel)*. 2022;11(7):1269.
1153. Carranza-León DA, Oeser A, Marton A, et al. Tissue sodium content in patients with systemic lupus erythematosus: association with disease activity and markers of inflammation. *Lupus*. 2020;29(5):455–62.
1154. Jung SM, Kim Y, Kim J, et al. Sodium chloride aggravates arthritis via Th17 polarization. *Yonsei Med J*. 2019;60(1):88–97.
1155. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8):1689–96.
1156. United States Department of Health and Human Services, United States Department of Agriculture. Appendix 13. Food sources of dietary fiber. In: *2015–2020 Dietary Guidelines for Americans. 8th ed.* DietaryGuidelines.gov. 2015:114–8.
1157. Hostetler GL, Ralston RA, Schwartz SJ. Flavones: food sources, bioavailability, metabolism, and bioactivity. *Adv Nutr*. 2017;8(3):423–35.

1158. Haytowitz DB, Bhagwat S, Harnly J, Holden JM, Gebhardt SE. Sources of flavonoids in the U.S. diet using USDA's updated database on the flavonoid content of selected foods. Agricultural Research Service, United States Department of Agriculture. https://www.ars.usda.gov/ARSUserFiles/80400525/Articles/AICR06_flav.pdf. Published 2006. Accessed July 20, 2021.
1159. Hostetler GL, Ralston RA, Schwartz SJ. Flavones: food sources, bioavailability, metabolism, and bioactivity. *Adv Nutr*. 2017;8(3):423–35.
1160. Tan J, McKenzie C, Potamitis M, Thorburn AN, Mackay CR, Macia L. The role of short-chain fatty acids in health and disease. In: Alt FW, ed. *Advances in Immunology*. Vol 121. Academic Press, Elsevier; 2014:91–119.
1161. Pukatzki S, Provenzano D. *Vibrio cholerae* as a predator: lessons from evolutionary principles. *Front Microbiol*. 2013;4.
1162. Chang PV, Hao L, Offermanns S, Medzhitov R. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. *Proc Natl Acad Sci U S A*. 2014;111(6):2247–52.
1163. McRorie JW. Evidence-based approach to fiber supplements and clinically meaningful health benefits, part 1: what to look for and how to recommend an effective fiber therapy. *Nutr Today.* 2015;50(2):82–9.
1164. Nilsson AC, Östman EM, Knudsen KEB, Holst JJ, Björck IME. A cereal-based evening meal rich in indigestible carbohydrates increases plasma butyrate the next morning. *J Nutr*. 2010;140(11):1932–6.
1165. Meijer K, de Vos P, Priebe MG. Butyrate and other short-chain fatty acids as modulators of immunity: what relevance for health? *Curr Opin Clin Nutr Metab Care*. 2010;13(6):715–21.
1166. Dai Z, Lu N, Niu J, Felson DT, Zhang Y. Dietary fiber intake in relation to knee pain trajectory. *Arthritis Care Res (Hoboken)*. 2017;69(9):1331–9.
1167. Dai Z, Niu J, Zhang Y, Jacques P, Felson DT. Dietary intake of fibre and risk of knee osteoarthritis in two US prospective cohorts

[published correction appears in *Ann Rheum Dis.* 2017;76(12):2103]. *Ann Rheum Dis*. 2017;76(8):1411–9.

1168. Vaughan A, Frazer ZA, Hansbro PM, Yang IA. COPD and the gut-lung axis: the therapeutic potential of fibre. *J Thorac Dis*. 2019;11(Suppl 17):S2173–80.

1169. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. Lancet. 2019;393(10170):434-45.

1170. Brewer RA, Gibbs VK, Smith DL Jr. Targeting glucose metabolism for healthy aging. *Nutr Healthy Aging*. 2016;4(1):31–46.

1171. Su B, Liu H, Li J, et al. Acarbose treatment affects the serum levels of inflammatory cytokines and the gut content of bifidobacteria in Chinese patients with type 2 diabetes mellitus. *J Diabetes*. 2015;7(5):729–39.

1172. Zhang X, Fang Z, Zhang C, et al. Effects of acarbose on the gut microbiota of prediabetic patients: a randomized, double-blind, controlled crossover trial. *Diabetes Ther*. 2017;8(2):293–307.

1173. Wolever TMS, Chiasson JL. Acarbose raises serum butyrate in human subjects with impaired glucose tolerance. *Br J Nutr*. 2000;84(1):57–61.

1174. McCay CM, Ku CC, Woodward JC, Sehgal BS. Cellulose in the diet of rats and mice: two figures. *J Nutr*. 1934;8(4):435–47.

1175. Smith BJ, Miller RA, Ericsson AC, Harrison DC, Strong R, Schmidt TM. Changes in the gut microbiome and fermentation products concurrent with enhanced longevity in acarbose-treated mice. *BMC Microbiol*. 2019;19(1):130.

1176. Hovey AL, Jones GP, Devereux HM, Walker KZ. Whole cereal and legume seeds increase faecal short chain fatty acids compared to ground seeds. *Asia Pac J Clin Nutr*. 2003;12(4):477–82.

1177. Stephen AM, Cummings JH. The microbial contribution to human faecal mass. *J Med Microbiol.* 1980;13(1):45–56.

1178. Singh RK, Chang HW, Yan D, et al. Influence of diet on the gut microbiome and implications for human health. *J Transl Med.* 2017;15(1):73.

1179. Franceschi C, Ostan R, Santoro A. Nutrition and inflammation: are centenarians similar to individuals on calorie-restricted diets? *Annu*

Rev Nutr. 2018;38(1):329–56.
1180. Minciullo PL, Catalano A, Mandraffino G, et al. Inflammaging and anti-inflammaging: the role of cytokines in extreme longevity. *Arch Immunol Ther Exp (Warsz)*. 2016;64(2):111–26.
1181. Minciullo PL, Catalano A, Mandraffino G, et al. Inflammaging and anti-inflammaging: the role of cytokines in extreme longevity. *Arch Immunol Ther Exp (Warsz)*. 2016;64(2):111–26.
1182. Säemann MD, Böhmig GA, Österreicher CH, et al. Anti-inflammatory effects of sodium butyrate on human monocytes: potent inhibition of IL-12 and up-regulation of IL-10 production. *FASEB J*. 2000;14(15):2380–2.
1183. Vitaglione P, Mennella I, Ferracane R, et al. Whole-grain wheat consumption reduces inflammation in a randomized controlled trial on overweight and obese subjects with unhealthy dietary and lifestyle behaviors: role of polyphenols bound to cereal dietary fiber. *Am J Clin Nutr*. 2015;101(2):251–61.
1184. Kohl A, Gögebakan Ö, Möhlig M, et al. Increased interleukin-10 but unchanged insulin sensitivity after 4 weeks of (1, 3)(1, 6)-β-glycan consumption in overweight humans. *Nutr Res*. 2009;29(4):248–54.
1185. Barclay GR, McKenzie H, Pennington J, Parratt D, Pennington CR. The effect of dietary yeast on the activity of stable chronic Crohn's disease. *Scand J Gastroenterol*. 1992;27(3):196–200.
1186. Cannistrà C, Finocchi V, Trivisonno A, Tambasco D. New perspectives in the treatment of hidradenitis suppurativa: surgery and brewer's yeast-exclusion diet. *Surgery*. 2013;154(5):1126–30.
1187. Franceschi C, Ostan R, Santoro A. Nutrition and inflammation: are centenarians similar to individuals on calorie-restricted diets? *Annu Rev Nutr*. 2018;38(1):329–56.
1188. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8):1689–96.
1189. Barbaresko J, Koch M, Schulze MB, Nöthlings U. Dietary pattern analysis and biomarkers of low-grade inflammation: a systematic literature review. *Nutr Rev*. 2013;71(8):511–27.
1190. Eichelmann F, Schwingshackl L, Fedirko V, Aleksandrova K. Effect of plant-based diets on obesity-related inflammatory profiles: a

systematic review and meta-analysis of intervention trials. *Obes Rev*. 2016;17(11):1067–79.
1191. Sutliffe JT, Wilson LD, de Heer HD, Foster RL, Carnot MJ. C-reactive protein response to a vegan lifestyle intervention. *Complement Ther Med*. 2015;23(1):32–7.
1192. Macknin M, Kong T, Weier A, et al. Plant-based, no-added-fat or American Heart Association diets: impact on cardiovascular risk in obese children with hypercholesterolemia and their parents. *J Pediatr*. 2015;166(4):953–9.e1–3.
1193. Hosseinpour-Niazi S, Mirmiran P, Fallah-Ghohroudi A, Azizi F. Non-soya legume-based therapeutic lifestyle change diet reduces inflammatory status in diabetic patients: a randomised cross-over clinical trial. *Br J Nutr*. 2015;114(2):213–9.
1194. Watzl B, Kulling SE, Möseneder J, Barth SW, Bub A. A 4-wk intervention with high intake of carotenoid-rich vegetables and fruit reduces plasma C-reactive protein in healthy, nonsmoking men. *Am J Clin Nutr*. 2005;82(5):1052–8.
1195. Lee-Kwan SH, Moore LV, Blanck HM, Harris DM, Galuska D. Disparities in state-specific adult fruit and vegetable consumption—United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2017;66:1241–7.
1196. Baden MY, Satija A, Hu FB, Huang T. Change in plant-based diet quality is associated with changes in plasma adiposity-associated biomarker concentrations in women. *J Nutr*. 2019;149(4):676–86.
1197. Ricker MA, Haas WC. Anti-inflammatory diet in clinical practice: a review. *Nutr Clin Pract*. 2017;32(3):318–25.
1198. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8):1689–96.
1199. Li K, Huang T, Zheng J, Wu K, Li D. Effect of marine-derived n-3 polyunsaturated fatty acids on C-reactive protein, interleukin 6 and tumor necrosis factor α: a meta-analysis. *PLoS ONE*. 2014;9(2):e88103.
1200. Agricultural Research Service, United States Department of Agriculture. Search results: PUFA 22:6 n-3 (DHA) (g). FoodData

Central. https://fdc.nal.usda.gov/fdc-app.html#/?component=1272. Published April 1, 2019. Accessed July 19, 2021.
1201. Stella AB, Cappellari GG, Barazzoni R, Zanetti M. Update on the impact of omega 3 fatty acids on inflammation, insulin resistance and sarcopenia: a review. *Int J Mol Sci*. 2018;19(1):218.
1202. Alhassan A, Young J, Lean MEJ, Lara J. Consumption of fish and vascular risk factors: a systematic review and meta-analysis of intervention studies. *Atherosclerosis*. 2017;266:87–94.
1203. Gopinath B, Buyken AE, Flood VM, Empson M, Rochtchina E, Mitchell P. Consumption of polyunsaturated fatty acids, fish, and nuts and risk of inflammatory disease mortality. *Am J Clin Nutr*. 2011;93(5):1073–9.
1204. Raymond MR, Christensen KY, Thompson BA, Anderson HA. Associations between fish consumption and contaminant biomarkers with cardiovascular conditions among older male anglers in Wisconsin. *J Occup Environ Med*. 2016;58(7):676–82.
1205. Tabung FK, Smith-Warner SA, Chavarro JE, et al. Development and validation of an empirical dietary inflammatory index. *J Nutr*. 2016;146(8):1560–70.
1206. Hjartåker A, Knudsen MD, Tretli S, Weiderpass E. Consumption of berries, fruits and vegetables and mortality among 10,000 Norwegian men followed for four decades. *Eur J Nutr*. 2015;54(4):599–608.
1207. Cassidy A, Rogers G, Peterson JJ, Dwyer JT, Lin H, Jacques PF. Higher dietary anthocyanin and flavonol intakes are associated with anti-inflammatory effects in a population of US adults. *Am J Clin Nutr*. 2015;102(1):172–81.
1208. Nair AR, Mariappan N, Stull AJ, Francis J. Blueberry supplementation attenuates oxidative stress within monocytes and modulates immune cell levels in adults with metabolic syndrome: a randomized, double-blind, placebo-controlled trial. *Food Funct*. 2017;8(11):4118–28.
1209. Moazen S, Amani R, Homayouni Rad A, Shahbazian H, Ahmadi K, Taha Jalali M. Effects of freeze-dried strawberry supplementation on metabolic biomarkers of atherosclerosis in subjects with type 2 diabetes: a randomized double-blind controlled trial. *Ann Nutr Metab*. 2013;63(3):256–64.

1210. Moylan S, Berk M, Dean OM, et al. Oxidative & nitrosative stress in depression: why so much stress? *Neurosci Biobehav Rev*. 2014;45:46–62.
1211. Franzini L, Ardigi D, Valtueña S, et al. Food selection based on high total antioxidant capacity improves endothelial function in a low cardiovascular risk population. *Nutr Metab Cardiovasc Dis*. 2012;22(1):50–7.
1212. Sun CH, Li Y, Zhang YB, Wang F, Zhou XL, Wang F. The effect of vitamin–mineral supplementation on CRP and IL-6: a systemic review and meta-analysis of randomised controlled trials. *Nutr Metab Cardiovasc Dis*. 2011;21(8):576–83.
1213. Fallah AA, Sarmast E, Fatehi P, Jafari T. Impact of dietary anthocyanins on systemic and vascular inflammation: systematic review and meta-analysis on randomised clinical trials. *Food Chem Toxicol*. 2020;135:110922.
1214. do Rosario VA, Chang C, Spencer J, et al. Anthocyanins attenuate vascular and inflammatory responses to a high fat high energy meal challenge in overweight older adults: a cross-over, randomized, double-blind clinical trial. *Clin Nutr*. 2021;40(3):879–89.
1215. O'Hara C, Ojo B, Emerson SR, et al. Acute freeze-dried mango consumption with a high-fat meal has minimal effects on postprandial metabolism, inflammation and antioxidant enzymes. *Nutr Metab Insights*. 2019;12:1178638819869946.
1216. Wang P, Zhang Q, Hou H, et al. The effects of pomegranate supplementation on biomarkers of inflammation and endothelial dysfunction: a meta-analysis and systematic review. *Complement Ther Med*. 2020;49:102358.
1217. Aptekmann NP, Cesar TB. Orange juice improved lipid profile and blood lactate of overweight middle-aged women subjected to aerobic training. *Maturitas*. 2010;67(4):343–7.
1218. McAnulty LS, Nieman DC, Dumke CL, et al. Effect of blueberry ingestion on natural killer cell counts, oxidative stress, and inflammation prior to and after 2.5 h of running. *Appl Physiol Nutr Metab*. 2011;36(6):976–84.
1219. Connolly DA, McHugh MP, Padilla-Zakour OI, Carlson L, Sayers SP. Efficacy of a tart cherry juice blend in preventing the symptoms of

muscle damage. *Br J Sports Med*. 2006;40(8):679–83.
1220. Peake JM, Suzuki K, Coombes JS. The influence of antioxidant supplementation on markers of inflammation and the relationship to oxidative stress after exercise. *J Nutr Biochem*. 2007;18(6):357–71.
1221. Childs A, Jacobs C, Kaminski T, Halliwell B, Leeuwenburgh C. Supplementation with vitamin C and N-acetyl-cysteine increases oxidative stress in humans after an acute muscle injury induced by eccentric exercise. *Free Radic Biol Med*. 2001;31(6):745–53.
1222. McHugh M. The health benefits of cherries and potential applications in sports. *Scand J Med Sci Sports*. 2011;21(5):615–6.
1223. Blau LW. Cherry diet control for gout and arthritis. *Tex Rep Biol Med.* 1950;8(3):309–11.
1224. Overman T. Pegloticase: a new treatment for gout. *Pharmacotherapy Update.* 2011;14(2):1–3.
1225. Finkelstein Y, Aks SE, Hutson JR, et al. Colchicine poisoning: the dark side of an ancient drug. *Clin Toxicol (Phila)*. 2010;48(5):407–14.
1226. Fritsch PO, Sidoroff A. Drug-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. *Am J Clin Dermatol.* 2000;1(6):349–60.
1227. Wang M, Jiang X, Wu W, Zhang D. A meta-analysis of alcohol consumption and the risk of gout. *Clin Rheumatol*. 2013;32(11):1641–8.
1228. Zhang Y, Chen C, Choi H, et al. Purine-rich foods intake and recurrent gout attacks. *Ann Rheum Dis.* 2012;71(9):1448–53.
1229. Menzel J, Jabakhanji A, Biemann R, Mai K, Abraham K, Weikert C. Systematic review and meta-analysis of the associations of vegan and vegetarian diets with inflammatory biomarkers. *Sci Rep*. 2020;10:21736.
1230. Eichelmann F, Schwingshackl L, Fedirko V, Aleksandrova K. Effect of plant-based diets on obesity-related inflammatory profiles: a systematic review and meta-analysis of intervention trials. *Obes Rev*. 2016;17(11):1067–79.
1231. Tran E, Dale HF, Jensen C, Lied GA. Effects of plant-based diets on weight status: a systematic review. *Diabetes Metab Syndr Obes*. 2020;13:3433–48.

1232. Shah B, Newman JD, Woolf K, et al. Anti-inflammatory effects of a vegan diet versus the American Heart Association–recommended diet in coronary artery disease trial. *J Am Heart Assoc*. 2018;7(23):e011367.
1233. Margolis KL, Manson JE, Greenland P, et al. Leukocyte count as a predictor of cardiovascular events and mortality in postmenopausal women: the Women's Health Initiative Observational Study. *Arch Intern Med*. 2005;165(5):500–8.
1234. Leng SX, Xue QL, Huang Y, Ferrucci L, Fried LP, Walston JD. Baseline total and specific differential white blood cell counts and 5-year all-cause mortality in community-dwelling older women. *Exp Gerontol*. 2005;40(12):982–7.
1235. Gkrania-Klotsas E, Ye Z, Cooper AJ, et al. Differential white blood cell count and type 2 diabetes: systematic review and meta-analysis of cross-sectional and prospective studies. *PLoS One*. 2010;5(10):e13405.
1236. Leng SX, Xue QL, Huang Y, Ferrucci L, Fried LP, Walston JD. Baseline total and specific differential white blood cell counts and 5-year all-cause mortality in community-dwelling older women. *Exp Gerontol*. 2005;40(12):982–7.
1237. de Labry LO, Campion EW, Glynn RJ, Vokonas PS. White blood cell count as a predictor of mortality: results over 18 years from the Normative Aging Study. *J Clin Epidemiol*. 1990;43(2):153–7.
1238. Panagiotakos DB, Pitsavos C, Chrysohoou C, et al. Effect of exposure to secondhand smoke on markers of inflammation: the ATTICA study. *Am J Med*. 2004;116(3):145–50.
1239. Swanson E. Prospective clinical study reveals significant reduction in triglyceride level and white blood cell count after liposuction and abdominoplasty and no change in cholesterol levels. *Plast Reconstr Surg*. 2011;128(3):182e-97e.
1240. Domene PA, Moir HJ, Pummell E, Knox A, Easton C. The health-enhancing efficacy of Zumba® fitness: an 8-week randomised controlled study. *J Sports Sci*. 2016;34(15):1396–404.
1241. Kjeldsen-Kragh J. Rheumatoid arthritis treated with vegetarian diets. *Am J Clin Nutr*. 1999;70(3 Suppl):594S-600S.

1242. Schultz H, Ying GS, Dunaief JL, Dunaief DM. Rising plasma beta-carotene is associated with diminishing C-reactive protein in patients consuming a dark green leafy vegetable–rich, Low Inflammatory Foods Everyday (LIFE) diet. *Am J Lifestyle Med*. https://journals.sagepub.com/doi/10.1177/1559827619894954. Published December 21, 2019. Accessed June 26, 2021.

1243. Perzia B, Ying GS, Dunaief JL, Dunaief DM. Once-daily Low Inflammatory Foods Everyday (LIFE) smoothie or the full LIFE diet lowers C-reactive protein and raises plasma beta-carotene in 7 days. *Am J Lifestyle Med*. https://journals.sagepub.com/doi/10.1177/1559827620962458. Published October 5, 2020. Accessed June 26, 2021.

1244. Castenmiller JJM, West CE, Linssen JPH, van het Hof KH, Voragen AGJ. The food matrix of spinach is a limiting factor in determining the bioavailability of β-carotene and to a lesser extent of lutein in humans. *J Nutr*. 1999;129(2):349–55.

1245. Lin KH, Hsu CY, Huang YP, et al. Chlorophyll-related compounds inhibit cell adhesion and inflammation in human aortic cells. *J Med Food*. 2013;16(10):886–98.

1246. Subramoniam A, Asha VV, Nair SA, et al. Chlorophyll revisited: anti-inflammatory activities of chlorophyll a and inhibition of expression of TNF-α gene by the same. *Inflammation*. 2012;35(3):959–66.

1247. Jiang Y, Wu SH, Shu XO, et al. Cruciferous vegetable intake is inversely correlated with circulating levels of proinflammatory markers in women. *J Acad Nutr Diet*. 2014;114(5):700–8.e2.

1248. Zhang X, Shu XO, Xiang YB, et al. Cruciferous vegetable consumption is associated with a reduced risk of total and cardiovascular disease mortality. *Am J Clin Nutr*. 2011;94(1):240–6.

1249. Navarro SL, Schwarz Y, Song X, et al. Cruciferous vegetables have variable effects on biomarkers of systemic inflammation in a randomized controlled trial in healthy young adults. *J Nutr*. 2014;144(11):1850–7.

1250. López-Chillón MT, Carazo-Díaz C, Prieto-Merino D, Zafrilla P, Moreno DA, Villaño D. Effects of long-term consumption of broccoli sprouts on inflammatory markers in overweight subjects. *Clin Nutr*. 2019;38(2):745–52.

1251. Bentley J. Potatoes and tomatoes account for over half of U.S. vegetable availability. Economic Research Service, United States Department of Agriculture. https://www.ers.usda.gov/amber-waves/2015/september/potatoes-and-tomatoes-account-for-over-half-of-us-vegetable-availability. Published September 8, 2015. Accessed June 20, 2021.
1252. Ghavipour M, Saedisomeolia A, Djalali M, et al. Tomato juice consumption reduces systemic inflammation in overweight and obese females. *Br J Nutr*. 2013;109(11):2031–5.
1253. Burton-Freeman B, Talbot J, Park E, Krishnankutty S, Edirisinghe I. Protective activity of processed tomato products on postprandial oxidation and inflammation: a clinical trial in healthy weight men and women. *Mol Nutr Food Res*. 2012;56(4):622–31.
1254. Markovits N, Ben Amotz A, Levy Y. The effect of tomato-derived lycopene on low carotenoids and enhanced systemic inflammation and oxidation in severe obesity. *Isr Med Assoc J*. 2009;11(10):598–601.
1255. Dai X, Stanilka JM, Rowe CA, et al. Consuming *Lentinula edodes* (shiitake) mushrooms daily improves human immunity: a randomized dietary intervention in healthy young adults. *J Am Coll Nutr*. 2015;34(6):478–87.
1256. World Cancer Research Fund / American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. American Institute for Cancer Research; 2007.
1257. American Heart Association. Types of whole grains. Heart.org. https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics/types-of-whole-grains. Published January 1, 2015. Accessed November 5, 2021.
1258. Aune D, Keum N, Giovannucci E, et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ*. 2016;353:i2716.
1259. Jacobs DR, Andersen LF, Blomhoff R. Whole-grain consumption is associated with a reduced risk of noncardiovascular, noncancer death

attributed to inflammatory diseases in the Iowa Women's Health Study. *Am J Clin Nutr.* 2007;85(6):1606–14.
1260. Aune D, Keum N, Giovannucci E, et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ*. 2016;353:i2716.
1261. Afshin A, Sun PJ, Fay KA, et al. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2019;393(10184):1958–72.
1262. Yu Z, Malik VS, Keum NN, et al. Associations between nut consumption and inflammatory biomarkers. *Am J Clin Nutr*. 2016;104(3):722–8.
1263. Gopinath B, Buyken AE, Flood VM, Empson M, Rochtchina E, Mitchell P. Consumption of polyunsaturated fatty acids, fish, and nuts and risk of inflammatory disease mortality. *Am J Clin Nutr*. 2011;93(5):1073–9.
1264. Chen GC, Zhang R, Martínez-González MA, et al. Nut consumption in relation to all-cause and cause-specific mortality: a meta-analysis 18 prospective studies. *Food Funct*. 2017;8(11):3893–905.
1265. Xiao Y, Xia J, Ke Y, et al. Effects of nut consumption on selected inflammatory markers: a systematic review and meta-analysis of randomized controlled trials. *Nutrition*. 2018;54:129–43.
1266. Eftekhar Sadat B, Khadem Haghighian M, Alipoor B, Malek Mahdavi A, Asghari Jafarabadi M, Moghaddam A. Effects of sesame seed supplementation on clinical signs and symptoms in patients with knee osteoarthritis. *Int J Rheum Dis*. 2013;16(5):578–82.
1267. Rodriguez-Leyva D, Weighell W, Edel AL, et al. Potent antihypertensive action of dietary flaxseed in hypertensive patients. *Hypertension*. 2013;62(6):1081–9.
1268. Rahimlou M, Jahromi NB, Hasanyani N, Ahmadi AR. Effects of flaxseed interventions on circulating inflammatory biomarkers: a systematic review and meta-analysis of randomized controlled trials. *Adv Nutr*. 2019;10(6):1108–19.
1269. Caligiuri SPB, Parikh M, Stamenkovic A, Pierce GN, Aukema HM. Dietary modulation of oxylipins in cardiovascular disease and aging. *Am J Physiol Heart Circ Physiol*. 2017;313(5):H903–18.

1270. Caligiuri SPB, Aukema HM, Ravandi A, Pierce GN. Elevated levels of pro-inflammatory oxylipins in older subjects are normalized by flaxseed consumption. *Exp Gerontol*. 2014;59:51–7.
1271. Srinivasan K. Anti-inflammatory influences of culinary spices and their bioactives. *Food Rev Int*. 2020;Nov:1–17.
1272. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8):1689–96.
1273. Allijn IE, Vaessen SF, Quarles van Ufford LC, et al. Head-to-head comparison of anti-inflammatory performance of known natural products *in vitro*. *PLoS ONE*. 2016;11(5):e0155325.
1274. Daily JW, Yang M, Park S. Efficacy of turmeric extracts and curcumin for alleviating the symptoms of joint arthritis: a systematic review and meta-analysis of randomized clinical trials. *J Med Food*. 2016;19(8):717–29.
1275. Abidi A, Gupta S, Agarwal M, Bhalla HL, Saluja M. Evaluation of efficacy of curcumin as an add-on therapy in patients of bronchial asthma. *J Clin Diagn Res*. 2014;8(8):HC19–24.
1276. Panahi Y, Sahebkar A, Parvin S, Saadat A. A randomized controlled trial on the anti-inflammatory effects of curcumin in patients with chronic sulphur mustard-induced cutaneous complications. *Ann Clin Biochem*. 2012;49(Pt 6):580–8.
1277. Garg SK, Ahuja V, Sankar MJ, Kumar A, Moss AC. Curcumin for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2012;10:CD008424.
1278. Khajehdehi P, Zanjaninejad B, Aflaki E, et al. Oral supplementation of turmeric decreases proteinuria, hematuria, and systolic blood pressure in patients suffering from relapsing or refractory lupus nephritis: a randomized and placebo-controlled study. *J Ren Nutr*. 2012;22(1):50–7.
1279. Vors C, Couillard C, Paradis ME, et al. Supplementation with resveratrol and curcumin does not affect the inflammatory response to a high-fat meal in older adults with abdominal obesity: a randomized, placebo-controlled crossover trial. *J Nutr*. 2018;148(3):379–88.

1280. Derosa G, Maffioli P, Simental-Mendía LE, Bo S, Sahebkar A. Effect of curcumin on circulating interleukin-6 concentrations: a systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res*. 2016;111:394–404.
1281. Sahebkar A, Cicero AFG, Simental-Mendía LE, Aggarwal BB, Gupta SC. Curcumin downregulates human tumor necrosis factor-α levels: a systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res*. 2016;107:234–42.
1282. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8):1689–96.
1283. Morvaridzadeh M, Fazelian S, Agah S, et al. Effect of ginger (Zingiber officinale) on inflammatory markers: a systematic review and *meta*-analysis of randomized controlled trials. *Cytokine*. 2020;135:155224.
1284. Aryaeian N, Shahram F, Mahmoudi M, et al. The effect of ginger supplementation on some immunity and inflammation intermediate genes expression in patients with active Rheumatoid Arthritis. *Gene*. 2019;698:179–185.
1285. Bartels EM, Folmer VN, Bliddal H, et al. Efficacy and safety of ginger in osteoarthritis patients: a meta-analysis of randomized placebo-controlled trials. *Osteoar Cartil*. 2015;23(1):13–21.
1286. Haghighi M, Khalvat A, Toliat T, Jallaei SH. Comparing the effects of ginger (Zingiber officinale) extract and ibuprofen on patients with osteoarthritis. *Arch Iran Med*. 2005;8(4):267–71.
1287. Haniadka R, Saldanha E, Sunita V, Palatty PL, Fayad R, Baliga MS. A review of the gastroprotective effects of ginger (*Zingiber officinale* Roscoe). *Food Funct*. 2013;4(6):845–55.
1288. Caunedo-Alvarez A, Gómez-Rodríguez BJ, Romero-Vázquez J, et al. Macroscopic small bowel mucosal injury caused by chronic nonsteroidal anti-inflammatory drugs (NSAID) use as assessed by capsule endoscopy. *Rev Esp Enferm Dig*. 2010;102(2):80–5.
1289. Maghbooli M, Golipour F, Moghimi Esfandabadi A, Yousefi M. Comparison between the efficacy of ginger and sumatriptan in the ablative treatment of the common migraine. *Phytother Res*. 2014;28(3):412–5.

1290. Kashefi F, Khajehei M, Alavinia M, Golmakani E, Asili J. Effect of ginger (Zingiber officinale) on heavy menstrual bleeding: a placebo-controlled, randomized clinical trial. *Phytother Res*. 2015;29(1):114–9.
1291. Dugasani S, Pichika MR, Nadarajah VD, Balijepalli MK, Tandra S, Korlakunta JN. Comparative antioxidant and anti-inflammatory effects of [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol. *J Ethnopharmacol*. 2010;127(2):515–20.
1292. Darooghegi Mofrad M, Milajerdi A, Koohdani F, Surkan PJ, Azadbakht L. Garlic supplementation reduces circulating C-reactive protein, tumor necrosis factor, and interleukin-6 in adults: a systematic review and meta-analysis of randomized controlled trials. *J Nutr*. 2019;149(4):605–18.
1293. Moosavian SP, Paknahad Z, Habibagahi Z, Maracy M. The effects of garlic (*Allium sativum*) supplementation on inflammatory biomarkers, fatigue, and clinical symptoms in patients with active rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. *Phytother Res*. 2020;34(11):2953–62.
1294. Taghizadeh M, Hamedifard Z, Jafarnejad S. Effect of garlic supplementation on serum C-reactive protein level: a systematic review and meta-analysis of randomized controlled trials. *Phytother Res*. 2019;33(2):243–52.
1295. Percival SS, Vanden Heuvel JP, Nieves CJ, Montero C, Migliaccio AJ, Meadors J. Bioavailability of herbs and spices in humans as determined by *ex vivo* inflammatory suppression and DNA strand breaks. *J Am Coll Nutr*. 2012;31(4):288–94.
1296. Payahoo L, Ostadrahimi A, Mobasseri M, et al. *Anethum graveolens* L. supplementation has anti-inflammatory effect in type 2 diabetic patients. *Indian J Tradit Knowl*. 2014:13(3):461–5.
1297. Vallianou N, Tsang C, Taghizadeh M, Davoodvandi A, Jafarnejad S. Effect of cinnamon (*Cinnamomum zeylanicum*) supplementation on serum C-reactive protein concentrations: a meta-analysis and systematic review. *Complement Ther Med*. 2019;42:271–8.
1298. Vallianou N, Tsang C, Taghizadeh M, Davoodvandi A, Jafarnejad S. Effect of cinnamon (*Cinnamomum Zeylanicum*) supplementation on

serum C-reactive protein concentrations: a meta-analysis and systematic review. *Complement Ther Med*. 2019;42:271–8.

1299. Vázquez-Agell M, Urpi-Sarda M, Sacanella E, et al. Cocoa consumption reduces NF-κB activation in peripheral blood mononuclear cells in humans. *Nutr Metab Cardiovasc Dis*. 2013;23(3):257–63.

1300. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8):1689–96.

1301. Eshghpour M, Mortazavi H, Mohammadzadeh Rezaei NM, Nejat AH. Effectiveness of green tea mouthwash in postoperative pain control following surgical removal of impacted third molars: double blind randomized clinical trial. *Daru*. 2013;21(1):59.

1302. Sridharan S, Archer N, Manning N. Premature constriction of the fetal ductus arteriosus following the maternal consumption of camomile herbal tea. *Ultrasound Obstet Gynecol*. 2009;34(3):358–9.

1303. Burkewitz K, Weir HJM, Mair WB. AMPK as a pro-longevity target. In: Cordero MD, Viollet B, eds. *AMP-Activated Protein Kinase. Experientia Supplementum*. Vol 107. Springer; 2016:227–56.

1304. Duthie GG, Wood AD. Natural salicylates: foods, functions and disease prevention. *Food Funct*. 2011;2(9):515–20.

1305. Fuster V, Sweeny JM. Aspirin: a historical and contemporary therapeutic overview. *Circulation*. 2011;123(7):768–78.

1306. Saad M, Abdelaziz HK, Mehta JL. Aspirin for primary prevention in the elderly. *Aging (Albany NY)*. 2019;11(17):6618–9.

1307. Patrono C, Baigent C. Role of aspirin in primary prevention of cardiovascular disease. *Nat Rev Cardiol.* 2019;16(11):675–86.

1308. Duthie GG, Wood AD. Natural salicylates: foods, functions and disease prevention. *Food Funct*. 2011;2(9):515–20.

1309. Duthie GG, Wood AD. Natural salicylates: foods, functions and disease prevention. *Food Funct*. 2011;2(9):515–20.

1310. Blacklock CJ, Lawrence JR, Wiles D, et al. Salicylic acid in the serum of subjects not taking aspirin. Comparison of salicylic acid concentrations in the serum of vegetarians, non-vegetarians, and patients taking low dose aspirin. *J Clin Pathol*. 2001;54(7):553–5.

1311. Knutsen SF. Lifestyle and the use of health services. *Am J Clin Nutr*. 1994;59(5 Suppl):1171S-5S.
1312. McCarty MF. Dietary nitrate and reductive polyphenols may potentiate the vascular benefit and alleviate the ulcerative risk of low-dose aspirin. *Med Hypotheses*. 2013;80(2):186–90.
1313. Scheier L. Salicylic acid: one more reason to eat your fruits and vegetables. *J Am Diet Assoc*. 2001;101(12):1406–8.
1314. Baxter GJ, Graham AB, Lawrence JR, Wiles D, Paterson JR. Salicylic acid in soups prepared from organically and non-organically grown vegetables. *Eur J Nutr*. 2001;40(6):289–92.
1315. Malakar S, Gibson PR, Barrett JS, Muir JG. Naturally occurring dietary salicylates: a closer look at common Australian foods. *J Food Compos Anal*. 2017;57:31–9.
1316. Malakar S, Gibson PR, Barrett JS, Muir JG. Naturally occurring dietary salicylates: a closer look at common Australian foods. *J Food Compos Anal*. 2017;57:31–9.
1317. Paterson JR, Srivastava R, Baxter GJ, Graham AB, Lawrence JR. Salicylic acid content of spices and its implications. *J Agric Food Chem*. 2006;54(8):2891–6.
1318. Kęszycka PK, Szkop M, Gajewska D. Overall content of salicylic acid and salicylates in food available on the European market. *J Agric Food Chem*. 2017;65(50):11085–91.
1319. Gajewska D, Kęszycka PK, Szkop M. Dietary salicylates in herbs and spices. *Food Funct*. 2019;10(11):7037–41.
1320. Paterson JR, Srivastava R, Baxter GJ, Graham AB, Lawrence JR. Salicylic acid content of spices and its implications. *J Agric Food Chem*. 2006;54(8):2891–6.
1321. Malakar S, Gibson PR, Barrett JS, Muir JG. Naturally occurring dietary salicylates: a closer look at common Australian foods. *J Food Compos Anal*. 2017;57:31–9.
1322. Gajewska D, Kęszycka PK, Szkop M. Dietary salicylates in herbs and spices. *Food Funct*. 2019;10(11):7037–41.
1323. Blacklock CJ, Lawrence JR, Wiles D, et al. Salicylic acid in the serum of subjects not taking aspirin. Comparison of salicylic acid concentrations in the serum of vegetarians, non-vegetarians, and patients taking low dose aspirin. *J Clin Pathol*. 2001;54(7):553–5.

1324. Paterson JR, Srivastava R, Baxter GJ, Graham AB, Lawrence JR. Salicylic acid content of spices and its implications. *J Agric Food Chem*. 2006;54(8):2891–6.
1325. Paterson JR, Srivastava R, Baxter GJ, Graham AB, Lawrence JR. Salicylic acid content of spices and its implications. *J Agric Food Chem*. 2006;54(8):2891–6.
1326. Pasche B, Wang M, Pennison M, Jimenez H. Prevention and treatment of cancer with aspirin: where do we stand? *Semin Oncol*. 2014;41(3):397–401.
1327. Baxter GJ, Graham AB, Lawrence JR, Wiles D, Paterson JR. Salicylic acid in soups prepared from organically and non-organically grown vegetables. *Eur J Nutr*. 2001;40(6):289–92.
1328. Duthie GG, Wood AD. Natural salicylates: foods, functions and disease prevention. *Food Funct*. 2011;2(9):515–20.
1329. Pawelec G. Aging as an inflammatory disease and possible reversal strategies. *J Allergy Clin Immunol*. 2020;145(5):1355–6.
1330. Puzianowska-Kuźnicka M, Owczarz M, Wieczorowska-Tobis K, et al. Interleukin-6 and C-reactive protein, successful aging, and mortality: the PolSenior study. *Immun Ageing*. 2016;13:21.
1331. Assmann KE, Adjibade M, Shivappa N, et al. The inflammatory potential of the diet at midlife is associated with later healthy aging in French adults. *J Nutr*. 2018;148(3):437–44.
1332. Pedersen BK. Anti-inflammation—just another word for anti-ageing? *J Physiol*. 2009;587(23):5515.
1333. O'Keefe JH, Bell DSH. Postprandial hyperglycemia/hyperlipidemia (postprandial dysmetabolism) is a cardiovascular risk factor. *Am J Cardiol*. 2007;100(5):899–904.
1334. Vézina C, Kudelski A, Sehgal SN. Rapamycin (AY-22,989), a new antifungal antibiotic. I. Taxonomy of the producing streptomycete and isolation of the active principle. *J Antibiot (Tokyo)*. 1975;28(10):721–6.
1335. Garza-Lombó C, Gonsebatt ME. Mammalian target of rapamycin: its role in early neural development and in adult and aged brain function. *Front Cell Neurosci*. 2016;10:157.
1336. Sabatini DM. Twenty-five years of mTOR: uncovering the link from nutrients to growth. *PNAS*. 2017;114(45):11818–25.

1337. Liu GY, Sabatini DM. mTOR at the nexus of nutrition, growth, ageing and disease. *Nat Rev Mol Cell Biol*. 2020;21(4):183–203.
1338. Blagosklonny MV. TOR-driven aging: speeding car without brakes. *Cell Cycle*. 2009;8(24):4055–9.
1339. Schmeisser K, Parker JA. Pleiotropic effects of mTOR and autophagy during development and aging. *Front Cell Dev Biol*. 2019;7.
1340. Vasunilashorn S, Finch CE, Crimmins EM, et al. Inflammatory gene variants in the Tsimane, an indigenous Bolivian population with a high infectious load. *Biodemography Soc Biol*. 2011;57(1):33–52.
1341. Huebbe P, Schloesser A, Rimbach G. A nutritional perspective on cellular rejuvenation. *Oncotarget*. 2015;6(16):13846–7.
1342. Sabatini DM. Twenty-five years of mTOR: uncovering the link from nutrients to growth. *PNAS*. 2017;114(45):11818–25.
1343. Blagosklonny MV. Does rapamycin slow down time? *Oncotarget*. 2018;9(54):30210–2.
1344. Wei Y, Zhang YJ, Cai Y. Growth or longevity: the TOR's decision on lifespan regulation. *Biogerontology*. 2013;14(4):353–63.
1345. Swindell WR. Meta-analysis of 29 experiments evaluating the effects of rapamycin on life span in the laboratory mouse. *J Gerontol A Biol Sci Med Sci*. 2017;72(8):1024–32.
1346. Blagosklonny MV. Rapamycin for longevity: opinion article. *Aging (Albany NY)*. 2019;11(19):8048–67.
1347. Weichhart T. mTOR as regulator of lifespan, aging, and cellular senescence: a mini-review. *Gerontology*. 2018;64(2):127–34.
1348. Sharp ZD, Strong R. The role of mTOR signaling in controlling mammalian life span: what a fungicide teaches us about longevity. *J Gerontol A Biol Sci Med Sci*. 2010;65A(6):580–9.
1349. Kaeberlein M, Kennedy BK. A midlife longevity drug? *Nature*. 2009;460(7253):331–2.
1350. Blagosklonny MV. Rapamycin for longevity: opinion article. *Aging (Albany NY)*. 2019;11(19):8048–67.
1351. Arriola Apelo SI, Lamming DW. Rapamycin: an inhibiTOR of aging emerges from the soil of Easter Island. *J Gerontol A Biol Sci Med Sci*. 2016;71(7):841–9.
1352. Liu GY, Sabatini DM. mTOR at the nexus of nutrition, growth, ageing and disease. *Nat Rev Mol Cell Biol*. 2020;21(4):183–203.

1353. Weichhart T. mTOR as regulator of lifespan, aging, and cellular senescence: a mini-review. *Gerontology*. 2018;64(2):127–34.
1354. Stallone G, Schena A, Infante B, et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med.* 2005;352(13):1317–23.
1355. Majumder S, Caccamo A, Medina DX, et al. Lifelong rapamycin administration ameliorates age-dependent cognitive deficits by reducing IL-1β and enhancing NMDA signaling. *Aging Cell*. 2012;11(2):326–35.
1356. Wilkinson JE, Burmeister L, Brooks SV, et al. Rapamycin slows aging in mice. *Aging Cell*. 2012;11(4):675–82.
1357. An JY, Kerns KA, Ouellette A, et al. Rapamycin rejuvenates oral health in aging mice. *Elife*. 2020;9:e54318.
1358. Altschuler RA, Kanicki A, Martin C, Kohrman DC, Miller RA. Rapamycin but not acarbose decreases age-related loss of outer hair cells in the mouse cochlea. *Hear Res*. 2018;370:11–5.
1359. Lesniewski LA, Seals DR, Walker AE, et al. Dietary rapamycin supplementation reverses age-related vascular dysfunction and oxidative stress, while modulating nutrient-sensing, cell cycle, and senescence pathways. *Aging Cell.* 2017;16(1):17–26.
1360. Zaseck LW, Miller RA, Brooks SV. Rapamycin attenuates age-associated changes in tibialis anterior tendon viscoelastic properties. *J Gerontol A Biol Sci Med Sci*. 2016;71(7):858–65.
1361. Dai DF, Karunadharma PP, Chiao YA, et al. Altered proteome turnover and remodeling by short-term caloric restriction or rapamycin rejuvenate the aging heart. *Aging Cell*. 2014;13(3):529–39.
1362. Arriola Apelo SI, Pumper CP, Baar EL, Cummings NE, Lamming DW. Intermittent administration of rapamycin extends the life span of female C57BL/6J mice. *J Gerontol A Biol Sci Med Sci*. 2016;71(7):876–81.
1363. Bitto A, Ito TK, Pineda VV, et al. Transient rapamycin treatment can increase lifespan and healthspan in middle-aged mice. *Elife*. 2016;5:e16351.
1364. Urfer SR, Kaeberlein TL, Mailheau S, et al. A randomized controlled trial to establish effects of short-term rapamycin treatment in 24

middle-aged companion dogs. *Geroscience*. 2017;39(2):117–27.
1365. González A, Hall MN, Lin SC, Hardie DG. AMPK and TOR: the Yin and Yang of cellular nutrient sensing and growth control. *Cell Metab*. 2020;31(3):472–92.
1366. Liu GY, Sabatini DM. mTOR at the nexus of nutrition, growth, ageing and disease. *Nat Rev Mol Cell Biol*. 2020;21(4):183–203.
1367. Michels KB, Ekbom A. Caloric restriction and incidence of breast cancer. *JAMA.* 2004;291(10):1226–30.
1368. Wazir U, Newbold RF, Jiang WG, Sharma AK, Mokbel K. Prognostic and therapeutic implications of mTORC1 and Rictor expression in human breast cancer. *Oncol Rep.* 2013;29(5):1969–74.
1369. Arcelus J, Mitchell AJ, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies. *Arch Gen Psychiatry*. 2011;68(7):724–31.
1370. Dar BA, Dar MA, Bashir S. Calorie restriction the fountain of youth. *Food Nutr Sci.* 2012;3(11):1522–6.
1371. Dirks AJ, Leeuwenburgh C. Caloric restriction in humans: potential pitfalls and health concerns. *Mech Ageing Dev*. 2006;127(1):1–7.
1372. Bourzac K. Interventions: live long and prosper. *Nature*. 2012;492(7427):S18–20.
1373. Nakagawa S, Lagisz M, Hector KL, Spencer HG. Comparative and meta-analytic insights into life extension via dietary restriction. *Aging Cell*. 2012;11(3):401–9.
1374. Solon-Biet SM, McMahon AC, Ballard JWO, et al. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. *Cell Metab*. 2014;19(3):418–30.
1375. Ross MH. Length of life and nutrition in the rat. *J Nutr*. 1961;75:197–210.
1376. Liu GY, Sabatini DM. mTOR at the nexus of nutrition, growth, ageing and disease. *Nat Rev Mol Cell Biol*. 2020;21(4):183–203.
1377. Fontana L, Partridge L, Longo VD. Extending healthy life span—from yeast to humans. *Science*. 2010;328(5976):321–6.
1378. Kitada M, Xu J, Ogura Y, Monno I, Koya D. Mechanism of activation of mechanistic target of rapamycin complex 1 by methionine. *Front Cell Dev Biol*. 2020;8:715.

1379. Dumas SN, Lamming DW. Next generation strategies for geroprotection via mTORC1 inhibition. *J Gerontol A Biol Sci Med Sci*. 2020;75(1):14–23.
1380. Norton LE, Layman DK, Bunpo P, Anthony TG, Brana DV, Garlick PJ. The leucine content of a complete meal directs peak activation but not duration of skeletal muscle protein synthesis and mammalian target of rapamycin signaling in rats. *J Nutr*. 2009;139(6):1103–9.
1381. Schmidt JA, Rinaldi S, Scalbert A, et al. Plasma concentrations and intakes of amino acids in male meat-eaters, fish-eaters, vegetarians and vegans: a cross-sectional analysis in the EPIC-Oxford cohort. *Eur J Clin Nutr*. 2016;70(3):306–12.
1382. Jafari S, Hezaveh E, Jalilpiran Y, et al. Plant-based diets and risk of disease mortality: a systematic review and meta-analysis of cohort studies. *Crit Rev Food Sci Nutr*. Published online May 6, 2021:1–13. Accessed June 23, 2021.
1383. Tantamango-Bartley Y, Jaceldo-Siegl K, Fan J, Fraser G. Vegetarian diets and the incidence of cancer in a low-risk population. *Cancer Epidemiol Biomarkers Prev*. 2013;22(2):286–94.
1384. Green CL, Lamming DW. Regulation of metabolic health by essential dietary amino acids. *Mech Ageing Dev*. 2019;177:186–200.
1385. Schmidt JA, Rinaldi S, Scalbert A, et al. Plasma concentrations and intakes of amino acids in male meat-eaters, fish-eaters, vegetarians and vegans: a cross-sectional analysis in the EPIC-Oxford cohort. *Eur J Clin Nutr*. 2016;70(3):306–12.
1386. Willcox BJ, Willcox DC, Todoriki H, et al. Caloric restriction, the traditional Okinawan diet, and healthy aging: the diet of the world's longest-lived people and its potential impact on morbidity and life span. *Ann N Y Acad Sci*. 2007;1114:434–55.
1387. Davinelli S, Willcox DC, Scapagnini G. Extending healthy ageing: nutrient sensitive pathway and centenarian population. *Immun Ageing*. 2012;9:9.
1388. Fraser GE, Shavlik DJ. Ten years of life: is it a matter of choice? *Arch Intern Med*. 2001;161(13):1645–52.
1389. Yasuda M, Tanaka Y, Kume S, et al. Fatty acids are novel nutrient factors to regulate mTORC1 lysosomal localization and apoptosis in podocytes. *Biochim Biophys Acta*. 2014;1842(7):1097–108.

1390. Obersby D, Chappell DC, Dunnett A, Tsiami AA. Plasma total homocysteine status of vegetarians compared with omnivores: a systematic review and meta-analysis. *Br J Nutr*. 2013;109(5):785–94.
1391. Khayati K, Antikainen H, Bonder EM, et al. The amino acid metabolite homocysteine activates mTORC1 to inhibit autophagy and form abnormal proteins in human neurons and mice. *FASEB J*. 2017;31(2):598–609.
1392. Dumas SN, Lamming DW. Next generation strategies for geroprotection via mTORC1 inhibition. *J Gerontol A Biol Sci Med Sci*. 2020;75(1):14–23.
1393. Melnik BC. Dietary intervention in acne: attenuation of increased mTORC1 signaling promoted by Western diet. *Dermatoendocrinol*. 2012;4(1):20–32.
1394. Melnik BC. Linking diet to acne metabolomics, inflammation, and comedogenesis: an update. *Clin Cosmet Investig Dermatol*. 2015;8:371–88.
1395. Moro T, Brightwell CR, Velarde B, et al. Whey protein hydrolysate increases amino acid uptake, mTORC1 signaling, and protein synthesis in skeletal muscle of healthy young men in a randomized crossover trial. *J Nutr*. 2019;149(7):1149–58.
1396. Melnik BC. Milk—a nutrient system of mammalian evolution promoting mTORC1-dependent translation. *Int J Mol Sci*. 2015;16(8):17048–87.
1397. Melnik BC, John SM, Carrera-Bastos P, Cordain L. The impact of cow's milk-mediated mTORC1-signaling in the initiation and progression of prostate cancer. *Nutr Metab (Lond)*. 2012;9(1):74.
1398. Melnik BC. Milk—a nutrient system of mammalian evolution promoting mTORC1-dependent translation. *Int J Mol Sci*. 2015;16(8):17048–87.
1399. Melnik BC. Lifetime impact of cow's milk on overactivation of mTORC1: from fetal to childhood overgrowth, acne, diabetes, cancers, and neurodegeneration. *Biomolecules*. 2021;11(3):404.
1400. Melnik BC, John SM, Schmitz G. Milk is not just food but most likely a genetic transfection system activating mTORC1 signaling for postnatal growth. *Nutr J*. 2013;12:103.

1401. Cordain L, Lindeberg S, Hurtado M, Hill K, Eaton SB, Brand-Miller J. Acne vulgaris: a disease of Western civilization. *Arch Dermatol.* 2002;138(12):1584–90.
1402. Danby FW. Acne and milk, the diet myth, and beyond. *J Am Acad Dermatol*. 2005;52(2):360–2.
1403. Aghasi M, Golzarand M, Shab-Bidar S, Aminianfar A, Omidian M, Taheri F. Dairy intake and acne development: a meta-analysis of observational studies. *Clin Nutr.* 2019;38(3):1067–75.
1404. Melnik BC. Linking diet to acne metabolomics, inflammation, and comedogenesis: an update. *Clin Cosmet Investig Dermatol*. 2015;8:371–88.
1405. Melnik BC. Lifetime impact of cow's milk on overactivation of mTORC1: from fetal to childhood overgrowth, acne, diabetes, cancers, and neurodegeneration. *Biomolecules*. 2021;11(3):404.
1406. Melnik BC. Dietary intervention in acne: attenuation of increased mTORC1 signaling promoted by Western diet. *Dermatoendocrinol*. 2012;4(1):20–32.
1407. Baron JA, Weiderpass E, Newcomb PA, et al. Metabolic disorders and breast cancer risk (United States). *Cancer Causes Control*. 2001;12(10):875–80.
1408. Sutcliffe S, Giovannucci E, Isaacs WB, Willett WC, Platz EA. Acne and risk of prostate cancer. *Int J Cancer*. 2007;121(12):2688–92.
1409. Melnik BC, John SM, Carrera-Bastos P, Cordain L. The impact of cow's milk-mediated mTORC1-signaling in the initiation and progression of prostate cancer. *Nutr Metab (Lond).* 2012;9(1):74.
1410. Sargsyan A, Dubasi HB. Milk consumption and prostate cancer: a systematic review. *World J Mens Health*. 2021;39(3):419–28.
1411. Pettersson A, Kasperzyk JL, Kenfield SA, et al. Milk and dairy consumption among men with prostate cancer and risk of metastases and prostate cancer death. *Cancer Epidemiol Biomarkers Prev*. 2012;21(3):428–36.
1412. Tognon G, Nilsson LM, Shungin D, et al. Nonfermented milk and other dairy products: associations with all-cause mortality. *Am J Clin Nutr*. 2017;105(6):1502–11.
1413. Melnik BC, Schmitz G. Pasteurized non-fermented cow's milk but not fermented milk is a promoter of mTORC1-driven aging and

increased mortality. *Ageing Res Rev*. 2021;67:101270.
1414. Gao X, Jia H, Chen G, Li C, Hao M. Yogurt intake reduces all-cause and cardiovascular disease mortality: a meta-analysis of eight prospective cohort studies. *Chin J Integr Med*. 2020;26(6):462–8.
1415. Sahin K, Orhan C, Tuzcu M, et al. Tomato powder modulates NF-κB, mTOR, and Nrf2 pathways during aging in healthy rats. *J Aging Res*. 2019;2019:1643243.
1416. Takeshima M, Ono M, Higuchi T, Chen C, Hara T, Nakano S. Anti-proliferative and apoptosis-inducing activity of lycopene against three subtypes of human breast cancer cell lines. *Cancer Sci*. 2014;105(3):252–7.
1417. Thomson CA, Ho E, Strom MB. Chemopreventive properties of 3,3'-diindolylmethane in breast cancer: evidence from experimental and human studies. *Nutr Rev*. 2016;74(7):432–43.
1418. Du H, Zhang X, Zeng Y, et al. A novel phytochemical, DIM, inhibits proliferation, migration, invasion and TNF-α induced inflammatory cytokine production of synovial fibroblasts from rheumatoid arthritis patients by targeting MAPK and AKT/mTOR signal pathway. *Front Immunol*. 2019;10:1620.
1419. Zhang Y, Gilmour A, Ahn YH, de la Vega L, Dinkova-Kostova AT. The isothiocyanate sulforaphane inhibits mTOR in an NRF2-independent manner. *Phytomedicine*. 2021;86:153062.
1420. Li N, Wu X, Zhuang W, et al. Green leafy vegetable and lutein intake and multiple health outcomes. *Food Chem*. 2021;360:130145.
1421. Sato A. mTOR, a potential target to treat autism spectrum disorder. *CNS Neurol Disord Drug Targets*. 2016;15(5):533–43.
1422. Matusheski NV, Juvik JA, Jeffery EH. Heating decreases epithiospecifier protein activity and increases sulforaphane formation in broccoli. *Phytochemistry*. 2004;65(9):1273–81.
1423. Singh K, Connors SL, Macklin EA, et al. Sulforaphane treatment of autism spectrum disorder (ASD). *Proc Natl Acad Sci U S A*. 2014;111(43):15550–5.
1424. Wanke V, Cameroni E, Uotila A, et al. Caffeine extends yeast lifespan by targeting TORC1. *Mol Microbiol*. 2008;69(1):277–85.
1425. Takahashi K, Yanai S, Shimokado K, Ishigami A. Coffee consumption in aged mice increases energy production and decreases

hepatic mTOR levels. *Nutrition*. 2017;38:1–8.
1426. Van Aller GS, Carson JD, Tang W, et al. Epigallocatechin gallate (EGCG), a major component of green tea, is a dual phosphoinositide-3-kinase/mTOR inhibitor. *Biochem Biophys Res Commun*. 2011;406(2):194–9.
1427. Elsaie ML, Abdelhamid MF, Elsaaiee LT, Emam HM. The efficacy of topical 2% green tea lotion in mild-to-moderate acne vulgaris. *J Drugs Dermatol*. 2009;8(4):358–64.
1428. Cassidy A, Chung M, Zhao N, et al. Dose–response relation between tea consumption and risk of cardiovascular disease and all-cause mortality: a systematic review and meta-analysis of population-based studies. *Adv Nutr*. 2020;11(4):790–814.
1429. Lamming DW. Inhibition of the mechanistic target of rapamycin (mTOR)–rapamycin and beyond. *Cold Spring Harb Perspect Med*. 2016;6(5).
1430. Kennedy BK, Lamming DW. The mechanistic target of rapamycin: the grand conducTOR of metabolism and aging. *Cell Metab*. 2016;23(6):990–1003.
1431. Morley JE. The mTOR conundrum: essential for muscle function, but dangerous for survival. *J Am Med Dir Assoc*. 2016;17(11):963–6.
1432. Blagosklonny MV. Why men age faster but reproduce longer than women: mTOR and evolutionary perspectives. *Aging (Albany NY)*. 2010;2(5):265–73.
1433. Markofski MM, Dickinson JM, Drummond MJ, et al. Effect of age on basal muscle protein synthesis and mTORC1 signaling in a large cohort of young and older men and women. *Exp Gerontol*. 2015;65:1–7.
1434. Leenders M, Verdijk LB, van der Hoeven L, et al. Prolonged leucine supplementation does not augment muscle mass or affect glycemic control in elderly type 2 diabetic men. *J Nutr*. 2011;141(6):1070–6.
1435. Verhoeven S, Vanschoonbeek K, Verdijk LB, et al. Long-term leucine supplementation does not increase muscle mass or strength in healthy elderly men. *Am J Clin Nutr*. 2009;89(5):1468–75.
1436. Tang H, Shrager JB, Goldman D. Rapamycin protects aging muscle. *Aging (Albany NY)*. 2019;11(16):5868–70.

1437. Liu GY, Sabatini DM. mTOR at the nexus of nutrition, growth, ageing and disease. *Nat Rev Mol Cell Biol*. 2020;21(4):183–203.
1438. Kennedy BK, Lamming DW. The mechanistic target of rapamycin: the grand conducTOR of metabolism and aging. *Cell Metab*. 2016;23(6):990–1003.
1439. Lamming DW, Salmon AB. TORwards a victory over aging. *J Gerontol A Biol Sci Med Sci*. 2020;75(1):1–3.
1440. Caldana C, Martins MCM, Mubeen U, Urrea-Castellanos R. The magic "hammer" of TOR: the multiple faces of a single pathway in the metabolic regulation of plant growth and development. *J Exp Bot*. 2019;70(8):2217–25.
1441. Liu GY, Sabatini DM. mTOR at the nexus of nutrition, growth, ageing and disease. *Nat Rev Mol Cell Biol*. 2020;21(4):183–203.
1442. Kaeberlein M, Galvan V. Rapamycin and Alzheimer's disease: time for a clinical trial? *Sci Transl Med*. 2019;11(476):eaar4289.
1443. Kapahi P, Chen D, Rogers AN, et al. With TOR, less is more: a key role for the conserved nutrient-sensing TOR pathway in aging. *Cell Metab*. 2010;11(6):453–65.
1444. Sansevero TB. *The Profit Machine*. Cultiva Libros; 2009.
1445. Harman D. The biologic clock: the mitochondria? *J Am Geriatr Soc*. 1972;20(4):145–7.
1446. Talaulikar VS, Manyonda IT. Vitamin C as an antioxidant supplement in women's health: a myth in need of urgent burial. *Eur J Obstet Gynecol Reprod Biol*. 2011;157(1):10–3.
1447. Liebman SE, Le TH. Eat your broccoli: oxidative stress, NRF2, and sulforaphane in chronic kidney disease. *Nutrients*. 2021;13(1):266.
1448. Peng C, Wang X, Chen J, et al. Biology of ageing and role of dietary antioxidants. *Biomed Res Int*. 2014;2014:831841.
1449. Maes M, Galecki P, Chang YS, Berk M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(3):676–92.
1450. Peng C, Wang X, Chen J, et al. Biology of ageing and role of dietary antioxidants. *Biomed Res Int*. 2014;2014:831841.

1451. Rinnerthaler M, Bischof J, Streubel MK, Trost A, Richter K. Oxidative stress in aging human skin. *Biomolecules*. 2015;5(2):545–89.
1452. Logan S, Royce GH, Owen D, et al. Accelerated decline in cognition in a mouse model of increased oxidative stress. *GeroScience*. 2019;41(5):591–607.
1453. Hensley K, Floyd RA. Reactive oxygen species and protein oxidation in aging: a look back, a look ahead. *Arch Biochem Biophys*. 2002;397(2):377–83.
1454. Yeung AWK, Tzvetkov NT, El-Tawil OS, Bungău SG, Abdel-Daim MM, Atanasov AG. Antioxidants: scientific literature landscape analysis. *Oxid Med Cell Longev*. 2019;2019:8278454.
1455. Bast A, Haenen GRMM. Ten misconceptions about antioxidants. *Trends Pharmacol Sci*. 2013;34(8):430–6.
1456. Medvedev ZA. An attempt at a rational classification of theories of ageing. *Biol Rev*. 1990;65(3):375–98.
1457. Fusco D, Colloca G, Lo Monaco MR, Cesari M. Effects of antioxidant supplementation on the aging process. *Clin Interv Aging*. 2007;2(3):377–87.
1458. Barja G. Updating the mitochondrial free radical theory of aging: an integrated view, key aspects, and confounding concepts. Antioxid Redox Signal. 2013;19(12):1420–45.
1459. Golubev A, Hanson AD, Gladyshev VN. A tale of two concepts: harmonizing the free radical and antagonistic pleiotropy theories of aging. *Antioxid Redox Signal*. 2018;29(10):1003–17.
1460. Harman D. Aging: a theory based on free radical and radiation chemistry. *J Gerontol*. 1956;11(3):298–300.
1461. Biesalski HK. Free radical theory of aging. *Curr Opin Clin Nutr Metab Care*. 2002;5(1):5–10.
1462. Keane M, Semeiks J, Webb AE, et al. Insights into the evolution of longevity from the bowhead whale genome. *Cell Rep*. 2015;10(1):112–22.
1463. Note: I'm referring to the colloquial usage of "animal." There are sponges and corals technically belonging to the kingdom *Animalia* that can live for thousands of years.

1464. Butler PG, Wanamaker AD Jr, Scourse JD, Richardson CA, Reynolds DJ. Variability of marine climate on the North Icelandic shelf in a 1357-year proxy archive based on growth increments in the bivalve *Arctica islandica*. *Palaeogeogr, Palaeoclimatol, Palaeoecol*. 2013;373:141–51.
1465. Barja G. Updating the mitochondrial free radical theory of aging: an integrated view, key aspects, and confounding concepts. *Antioxid Redox Signal*. 2013;19(12):1420–45.
1466. Barja G. Updating the mitochondrial free radical theory of aging: an integrated view, key aspects, and confounding concepts. *Antioxid Redox Signal*. 2013;19(12):1420–45.
1467. Capt C, Passamonti M, Breton S. The human mitochondrial genome may code for more than 13 proteins. *Mitochondrial DNA Part A*. 2016;27(5):3098–101.
1468. Willyard C. New human gene tally reignites debate. *Nature*. 2018;558(7710):354–5.
1469. Venditti P, Masullo P, Di Meo S. Effect of training on H_2O_2 release by mitochondria from rat skeletal muscle. *Arch Biochem Biophys*. 1999;372(2):315–20.
1470. Barja G. Updating the mitochondrial free radical theory of aging: an integrated view, key aspects, and confounding concepts. *Antioxid Redox Signal*. 2013;19(12):1420–45.
1471. Ruiz MC, Ayala V, Portero-Otín M, Requena JR, Barja G, Pamplona R. Protein methionine content and MDA-lysine adducts are inversely related to maximum life span in the heart of mammals. *Mech Ageing Dev*. 2005;126(10):1106–14.
1472. Gomez J, Sanchez-Roman I, Gomez A, et al. Methionine and homocysteine modulate the rate of ROS generation of isolated mitochondria in vitro. *J Bioenerg Biomembr*. 2011;43(4):377–86.
1473. Barja G. Updating the mitochondrial free radical theory of aging: an integrated view, key aspects, and confounding concepts. *Antioxid Redox Signal*. 2013;19(12):1420–45.
1474. Barja G. The mitochondrial free radical theory of aging. *Prog Mol Biol Transl Sci*. 2014;127:1–27.

1475. Sanz A, Stefanatos RKA. The mitochondrial free radical theory of aging: a critical view. *Curr Aging Sci*. 2008;1(1):10–21.
1476. Sanz A, Caro P, Ayala V, Portero-Otin M, Pamplona R, Barja G. Methionine restriction decreases mitochondrial oxygen radical generation and leak as well as oxidative damage to mitochondrial DNA and proteins. *FASEB J*. 2006;20(8):1064–73.
1477. Barja G. Updating the mitochondrial free radical theory of aging: an integrated view, key aspects, and confounding concepts. *Antioxid Redox Signal*. 2013;19(12):1420–45.
1478. Barja G. The mitochondrial free radical theory of aging. *Prog Mol Biol Transl Sci*. 2014;127:1–27.
1479. López-Torres M, Barja G. Lowered methionine ingestion as responsible for the decrease in rodent mitochondrial oxidative stress in protein and dietary restriction possible implications for humans. *Biochim Biophys Acta*. 2008;1780(11):1337–47.
1480. What we eat in America, NHANES 2017–2018. Agricultural Research Service, United States Department of Agriculture. https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/1718/tables_1–36%20and%2041–56_2017–2018.pdf. Published 2020. Accessed July 6, 2021.
1481. López-Torres M, Barja G. Lowered methionine ingestion as responsible for the decrease in rodent mitochondrial oxidative stress in protein and dietary restriction possible implications for humans. *Biochim Biophys Acta*. 2008;1780(11):1337–47.
1482. Fontana L, Cummings NE, Arriola Apelo SI, et al. Decreased consumption of branched-chain amino acids improves metabolic health. *Cell Rep*. 2016;16(2):520–30.
1483. Barja G. The mitochondrial free radical theory of aging. *Prog Mol Biol Transl Sci*. 2014;127:1–27.
1484. López-Torres M, Barja G. Lowered methionine ingestion as responsible for the decrease in rodent mitochondrial oxidative stress in protein and dietary restriction possible implications for humans. *Biochim Biophys Acta*. 2008;1780(11):1337–47.
1485. Darmadi-Blackberry I, Wahlqvist ML, Kouris-Blazos A, et al. Legumes: the most important dietary predictor of survival in older

people of different ethnicities. *Asia Pac J Clin Nutr*. 2004;13(2):217–20.
1486. Buettner D. The Blue Zones: 9 Lessons for Living Longer from the People Who've Lived the Longest. 2nd ed. National Geographic Books; 2012.
1487. McCarty MF, Barroso-Aranda J, Contreras F. The low-methionine content of vegan diets may make methionine restriction feasible as a life extension strategy. *Med Hypotheses*. 2009;72(2):125–8.
1488. Scudellari M. Myths that will not die. *Nature*. 2015;528(7582):322–5.
1489. Stuart JA, Maddalena LA, Merilovich M, Robb EL. A midlife crisis for the mitochondrial free radical theory of aging. *Longev Healthspan*. 2014;3(1):4.
1490. Golubev A, Hanson AD, Gladyshev VN. A tale of two concepts: harmonizing the free radical and antagonistic pleiotropy theories of aging. *Antioxid Redox Signal*. 2018;29(10):1003–17.
1491. Bjelakovic G, Nikolova D, Gluud C. Antioxidant supplements and mortality. *Curr Opin Clin Nutr Metab Care*. 2014;17(1):40–4.
1492. Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis. *Lancet*. 2004;364(9441):1219–28.
1493. Serafini M, Jakszyn P, Luján-Barroso L, et al. Dietary total antioxidant capacity and gastric cancer risk in the European prospective investigation into cancer and nutrition study. *Int J Cancer*. 2012;131(4):E544–54.
1494. Jacobs DR, Tapsell LC. Food synergy: the key to a healthy diet. *Proc Nutr Soc*. 2013;72(2):200–6.
1495. Cömert ED, Gökmen V. Evolution of food antioxidants as a core topic of food science for a century. *Food Res Int*. 2018;105:76–93.
1496. Barja G. Updating the mitochondrial free radical theory of aging: an integrated view, key aspects, and confounding concepts. *Antioxid Redox Signal*. 2013;19(12):1420–45.
1497. Chial H, Craig J. mtDNA and mitochondrial diseases. *Nature Education*. 2008;1(1):217.
1498. Tubbs A, Nussenzweig A. Endogenous DNA damage as a source of genomic instability in cancer. *Cell*. 2017;168(4):644–56.

1499. Patel J, Baptiste BA, Kim E, Hussain M, Croteau DL, Bohr VA. DNA damage and mitochondria in cancer and aging. *Carcinogenesis*. 2020;41(12):1625–34.
1500. Soares JP, Cortinhas A, Bento T, et al. Aging and DNA damage in humans: a meta-analysis study. *Aging (Albany NY)*. 2014;6(6):432–9.
1501. Belenguer-Varea Á, Tarazona-Santabalbina FJ, Avellana-Zaragoza JA, Martínez-Reig M, Mas-Bargues C, Inglés M. Oxidative stress and exceptional human longevity: systematic review. *Free Radic Biol Med*. 2020;149:51–63.
1502. Patel J, Baptiste BA, Kim E, Hussain M, Croteau DL, Bohr VA. DNA damage and mitochondria in cancer and aging. *Carcinogenesis*. 2020;41(12):1625–34.
1503. Yousefzadeh M, Henpita C, Vyas R, Soto-Palma C, Robbins P, Niedernhofer L. DNA damage—how and why we age? *Elife*. 2021;10:e62852.
1504. Liochev SI. Reflections on the theories of aging, of oxidative stress, and of science in general. Is it time to abandon the free radical (oxidative stress) theory of aging? *Antioxid Redox Signal*. 2015;23(3):187–207.
1505. Belenguer-Varea Á, Tarazona-Santabalbina FJ, Avellana-Zaragoza JA, Martínez-Reig M, Mas-Bargues C, Inglés M. Oxidative stress and exceptional human longevity: systematic review. *Free Radic Biol Med*. 2020;149:51–63.
1506. Liguori I, Russo G, Curcio F, et al. Oxidative stress, aging, and diseases. *Clin Interv Aging*. 2018;13:757–72.
1507. Belenguer-Varea Á, Tarazona-Santabalbina FJ, Avellana-Zaragoza JA, Martínez-Reig M, Mas-Bargues C, Inglés M. Oxidative stress and exceptional human longevity: systematic review. *Free Radic Biol Med*. 2020;149:51–63.
1508. Salmon AB, Richardson A, Pérez VI. Update on the oxidative stress theory of aging: does oxidative stress play a role in aging or healthy aging? *Free Radic Biol Med*. 2010;48(5):642–55.
1509. Edrey YH, Salmon AB. Revisiting an age-old question regarding oxidative stress. *Free Radic Biol Med*. 2014;71:368–78.
1510. Cannon G. Nutritional science for this century. *Public Health Nutr*. 2005;8(4):344–7.

1511. Andrews P. Last common ancestor of apes and humans: morphology and environment. *FPR*. 2020;91(2):122–48.
1512. Milton K. Nutritional characteristics of wild primate foods: do the diets of our closest living relatives have lessons for us? *Nutrition*. 1999;15(6):488–98.
1513. Milton K. Back to basics: why foods of wild primates have relevance for modern human health. *Nutrition*. 2000;16(7–8):480–3.
1514. Milton K. Hunter-gatherer diets: a different perspective. *Am J Clin Nutr*. 2000;71(3):665–7.
1515. Milton K. Micronutrient intakes of wild primates: are humans different? *Comp Biochem Physiol A Mol Integr Physiol*. 2003;136(1):47–59.
1516. Benzie IFF. Evolution of dietary antioxidants. *Comp Biochem Physiol A Mol Integr Physiol*. 2003;136(1):113–26.
1517. Milton K. Nutritional characteristics of wild primate foods: do the diets of our closest living relatives have lessons for us? *Nutrition*. 1999;15(6):488–98.
1518. Benzie IFF. Evolution of dietary antioxidants. *Comp Biochem Physiol A Mol Integr Physiol*. 2003;136(1):113–26.
1519. Milton K. Nutritional characteristics of wild primate foods: do the diets of our closest living relatives have lessons for us? *Nutrition*. 1999;15(6):488–98.
1520. Milton K. Micronutrient intakes of wild primates: are humans different? *Comp Biochem Physiol A Mol Integr Physiol*. 2003;136(1):47–59.
1521. Benzie IFF. Evolution of dietary antioxidants. *Comp Biochem Physiol A Mol Integr Physiol*. 2003;136(1):113–26.
1522. Schuch AP, Moreno NC, Schuch NJ, Menck CFM, Garcia CCM. Sunlight damage to cellular DNA: focus on oxidatively generated lesions. *Free Radic Biol Med*. 2017;107:110–24.
1523. Benzie IFF. Evolution of dietary antioxidants. *Comp Biochem Physiol Part A Mol Integr Physiol*. 2003;136(1):113–26.
1524. Benzie IFF. Evolution of dietary antioxidants. *Comp Biochem Physiol Part A Mol Integr Physiol*. 2003;136(1):113–26.
1525. Coffey DS. Similarities of prostate and breast cancer: evolution, diet, and estrogens. *Urology*. 2001;57(4 Suppl 1):31–8.

1526. Jallinoja P, Niva M, Helakorpi S, Kahma N. Food choices, perceptions of healthiness, and eating motives of self-identified followers of a low-carbohydrate diet. *Food Nutr Res*. 2014;58:23552.
1527. Nestle M. Paleolithic diets: a sceptical view. *Nutr Bull.* 2000;25:43–7.
1528. Vatner SF, Zhang J, Oydanich M, Berkman T, Naftalovich R, Vatner DE. Healthful aging mediated by inhibition of oxidative stress. *Ageing Res Rev*. 2020;64:101194.
1529. Abbasalizad Farhangi M, Vajdi M. Dietary total antioxidant capacity (TAC) significantly reduces the risk of site-specific cancers: an updated systematic review and meta-analysis. *Nutr Cancer*. 2021;73(5):721–39.
1530. Parohan M, Anjom-Shoae J, Nasiri M, Khodadost M, Khatibi SR, Sadeghi O. Dietary total antioxidant capacity and mortality from all causes, cardiovascular disease and cancer: a systematic review and dose-response meta-analysis of prospective cohort studies. *Eur J Nutr*. 2019;58(6):2175–89.
1531. Jayedi A, Rashidy-Pour A, Parohan M, Zargar MS, Shab-Bidar S. Dietary antioxidants, circulating antioxidant concentrations, total antioxidant capacity, and risk of all-cause mortality: a systematic review and dose-response meta-analysis of prospective observational studies. *Adv Nutr*. 2018;9(6):701–16.
1532. Carlsen MH, Halvorsen BL, Holte K, et al. The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. *Nutr J*. 2010;9:3.
1533. Yang M, Chung SJ, Chung CE, et al. Estimation of total antioxidant capacity from diet and supplements in US adults. *Br J Nutr*. 2011;106(2):254–63.
1534. Carlsen MH, Halvorsen BL, Holte K, et al. The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. *Nutr J*. 2010 Jan 22;9:3.
1535. Bastin S, Henken K. Water content of fruits and vegetables. University of Kentucky College of Agriculture Cooperative Extension Service. https://www.academia.edu/5729963/Water_Content_of_Fruits_and_Vegetables. Published December 1997. Accessed November 11, 2021.

1536. Cao G, Prior RL. Comparison of different analytical methods for assessing total antioxidant capacity of human serum. *Clin Chem*. 1998;44(6 Pt 1):1309–15.
1537. Halliwell B. The antioxidant paradox: less paradoxical now? *Br J Clin Pharmacol*. 2013;75(3):637–44.
1538. van Poppel G, Poulsen H, Loft S, Verhagen H. No influence of beta carotene on oxidative DNA damage in male smokers. *J Natl Cancer Inst*. 1995;87(4):310–1.
1539. Priemé H, Loft S, Nyyssönen K, Salonen JT, Poulsen HE. No effect of supplementation with vitamin E, ascorbic acid, or coenzyme Q10 on oxidative DNA damage estimated by 8-oxo-7,8-dihydro-2'-deoxyguanosine excretion in smokers. *Am J Clin Nutr*. 1997;65(2):503–7.
1540. Cao G, Booth SL, Sadowski JA, Prior RL. Increases in human plasma antioxidant capacity after consumption of controlled diets high in fruit and vegetables. *Am J Clin Nutr*. 1998;68(5):1081–7.
1541. Johnson SA, Feresin RG, Navaei N, et al. Effects of daily blueberry consumption on circulating biomarkers of oxidative stress, inflammation, and antioxidant defense in postmenopausal women with pre-and stage 1-hypertension: a randomized controlled trial. *Food Funct*. 2017;8(1):372–80.
1542. Verhagen H, Poulsen HE, Loft S, van Poppel G, Willems MI, van Bladeren PJ. Reduction of oxidative DNA-damage in humans by brussels sprouts. *Carcinogenesis*. 1995;16(4):969–70.
1543. Jayedi A, Rashidy-Pour A, Parohan M, Zargar MS, Shab-Bidar S. Dietary antioxidants, circulating antioxidant concentrations, total antioxidant capacity, and risk of all-cause mortality: a systematic review and dose-response meta-analysis of prospective observational studies. *Adv Nutr*. 2018;9(6):701–16.
1544. Ha K, Kim K, Sakaki JR, Chun OK. Relative validity of dietary total antioxidant capacity for predicting all-cause mortality in comparison to diet quality indexes in US adults. *Nutrients*. 2020;12(5):1210.
1545. Bastide N, Dartois L, Dyevre V, et al. Dietary antioxidant capacity and all-cause and cause-specific mortality in the E3N/EPIC cohort study. *Eur J Nutr*. 2017;56(3):1233–43.

1546. Yang M, Chung SJ, Chung CE, et al. Estimation of total antioxidant capacity from diet and supplements in US adults. *Br J Nutr*. 2011;106(2):254–63.
1547. Bastide N, Dartois L, Dyevre V, et al. Dietary antioxidant capacity and all-cause and cause-specific mortality in the E3N/EPIC cohort study. *Eur J Nutr*. 2017;56(3):1233–43.
1548. Mohanty P, Hamouda W, Garg R, Aljada A, Ghanim H, Dandona P. Glucose challenge stimulates reactive oxygen species (ROS) generation by leucocytes. *J Clin Endocrinol Metab*. 2000;85(8):2970–3.
1549. Prior RL, Gu L, Wu X, et al. Plasma antioxidant capacity changes following a meal as a measure of the ability of a food to alter *in vivo* antioxidant status. *J Am Coll Nutr*. 2007;26(2):170–81.
1550. Darvin ME, Patzelt A, Knorr F, Blume-Peytavi U, Sterry W, Lademann J. One-year study on the variation of carotenoid antioxidant substances in living human skin: influence of dietary supplementation and stress factors. *J Biomed Opt*. 2008;13(4):044028.
1551. Blacker BC, Snyder SM, Eggett DL, Parker TL. Consumption of blueberries with a high-carbohydrate, low-fat breakfast decreases postprandial serum markers of oxidation. *Br J Nutr*. 2013;109(9):1670–7.
1552. Nair AR, Mariappan N, Stull AJ, Francis J. Blueberry supplementation attenuates oxidative stress within monocytes and modulates immune cell levels in adults with metabolic syndrome: a randomized, double-blind, placebo-controlled trial. *Food Funct*. 2017;8(11):4118–28.
1553. Del Bó C, Riso P, Campolo J, et al. A single portion of blueberry (*Vaccinium corymbosum* L) improves protection against DNA damage but not vascular function in healthy male volunteers. *Nutr Res*. 2013;33(3):220–7.
1554. Szeto YT, Chu WK, Benzie IFF. Antioxidants in fruits and vegetables: a study of cellular availability and direct effects on human DNA. *Biosci Biotechnol Biochem*. 2006;70(10):2551–5.
1555. López-Uriarte P, Nogués R, Saez G, et al. Effect of nut consumption on oxidative stress and the endothelial function in metabolic

syndrome. *Clin Nutr*. 2010;29(3):373–80.
1556. Porrini M, Riso P. Lymphocyte lycopene concentration and DNA protection from oxidative damage is increased in women after a short period of tomato consumption. *J Nutr*. 2000;130(2):189–92.
1557. Porrini M, Riso P, Oriani G. Spinach and tomato consumption increases lymphocyte DNA resistance to oxidative stress but this is not related to cell carotenoid concentrations. *Eur J Nutr*. 2002;41(3):95–100.
1558. Frugé AD, Smith KS, Riviere AJ, et al. A dietary intervention high in green leafy vegetables reduces oxidative DNA damage in adults at increased risk of colorectal cancer: biological outcomes of the randomized controlled meat and three greens (M3G) feasibility trial. *Nutrients*. 2021;13(4):1220.
1559. Pool-Zobel BL, Bub A, Müller H, Wollowski I, Rechkemmer G. Consumption of vegetables reduces genetic damage in humans: first results of a human intervention trial with carotenoid-rich foods. *Carcinogenesis*. 1997;18(9):1847–50.
1560. Hoelzl C, Glatt H, Meinl W, et al. Consumption of Brussels sprouts protects peripheral human lymphocytes against 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and oxidative DNA-damage: results of a controlled human intervention trial. *Mol Nutr Food Res*. 2008;52(3):330–41.
1561. Fogarty MC, Hughes CM, Burke G, Brown JC, Davison GW. Acute and chronic watercress supplementation attenuates exercise-induced peripheral mononuclear cell DNA damage and lipid peroxidation. *Br J Nutr*. 2013;109(2):293–301.
1562. Han KC, Wong WC, Benzie IFF. Genoprotective effects of green tea (*Camellia sinensis*) in human subjects: results of a controlled supplementation trial. *Br J Nutr*. 2011;105(2):171–9.
1563. Pool-Zobel BL, Bub A, Müller H, Wollowski I, Rechkemmer G. Consumption of vegetables reduces genetic damage in humans: first results of a human intervention trial with carotenoid-rich foods. *Carcinogenesis*. 1997;18(9):1847–50.
1564. Szeto YT, To TL, Pak SC, Kalle W. A study of DNA protective effect of orange juice supplementation. *Appl Physiol Nutr Metab*. 2013;38(5):533–6.

1565. Guarnieri S, Riso P, Porrini M. Orange juice *vs* vitamin C: effect on hydrogen peroxide-induced DNA damage in mononuclear blood cells. *Br J Nutr*. 2007;97(4):639–43.
1566. Pool-Zobel BL, Bub A, Müller H, Wollowski I, Rechkemmer G. Consumption of vegetables reduces genetic damage in humans: first results of a human intervention trial with carotenoid-rich foods. *Carcinogenesis*. 1997;18(9):1847–50.
1567. Collins BH, Horská A, Hotten PM, Riddoch C, Collins AR. Kiwifruit protects against oxidative DNA damage in human cells and *in vitro*. *Nutr Cancer*. 2001;39(1):148–53.
1568. Collins AR, Harrington V, Drew J, Melvin R. Nutritional modulation of DNA repair in a human intervention study. *Carcinogenesis*. 2003;24(3):511–5.
1569. Collins AR, Harrington V, Drew J, Melvin R. Nutritional modulation of DNA repair in a human intervention study. *Carcinogenesis*. 2003;24(3):511–5.
1570. Astley SB, Elliott RM, Archer DB, Southon S. Evidence that dietary supplementation with carotenoids and carotenoid-rich foods modulates the DNA damage: repair balance in human lymphocytes. *Br J Nutr*. 2004;91(1):63–72.
1571. Ho CK, Choi SW, Siu PM, Benzie IFF. Effects of single dose and regular intake of green tea (*Camellia sinensis*) on DNA damage, DNA repair, and heme oxygenase-1 expression in a randomized controlled human supplementation study. *Mol Nutr Food Res*. 2014;58(6):1379–83.
1572. Collins AR, Azqueta A, Langie SAS. Effects of micronutrients on DNA repair. *Eur J Nutr*. 2012;51(3):261–79.
1573. Astley SB, Elliott RM, Archer DB, Southon S. Evidence that dietary supplementation with carotenoids and carotenoid-rich foods modulates the DNA damage:repair balance in human lymphocytes. *Br J Nutr*. 2004;91(1):63–72.
1574. Vayndorf EM, Lee SS, Liu RH. Whole apple extracts increase lifespan, healthspan and resistance to stress in *Caenorhabditis elegans*. *J Funct Foods*. 2013;5(3):1236–43.
1575. Wang J, Deng N, Wang H, et al. Effects of orange extracts on longevity, healthspan, and stress resistance in *Caenorhabditis*

elegans. *Molecules*. 2020;25(2):351.
1576. Wang E, Wink M. Chlorophyll enhances oxidative stress tolerance in *Caenorhabditis elegans* and extends its lifespan. *PeerJ*. 2016;4:e1879.
1577. Salehi B, Azzini E, Zucca P, et al. Plant-derived bioactives and oxidative stress-related disorders: a key trend towards healthy aging and longevity promotion. *Appl Sci*. 2020;10(3):947.
1578. Saul N, Pietsch K, Stürzenbaum SR, Menzel R, Steinberg CEW. Diversity of polyphenol action in *Caenorhabditis elegans*: between toxicity and longevity. *J Nat Prod*. 2011;74(8):1713–20.
1579. Ferk F, Chakraborty A, Jäger W, et al. Potent protection of gallic acid against DNA oxidation: results of human and animal experiments. *Mutat Res*. 2011;715(1–2):61–71.
1580. Ferk F, Kundi M, Brath H, et al. Gallic acid improves health-associated biochemical parameters and prevents oxidative damage of DNA in type 2 diabetes patients: results of a placebo-controlled pilot study. *Mol Nutr Food Res*. 2018;62(4).
1581. Vayndorf EM, Lee SS, Liu RH. Whole apple extracts increase lifespan, healthspan and resistance to stress in *Caenorhabditis elegans*. *J Funct Foods*. 2013;5(3):1236–43.
1582. Kampkötter A, Timpel C, Zurawski RF, et al. Increase of stress resistance and lifespan of *Caenorhabditis elegans* by quercetin. *Comp Biochem Physiol B Biochem Mol Biol*. 2008;149(2):314–23.
1583. Shimizu C, Wakita Y, Inoue T, et al. Effects of lifelong intake of lemon polyphenols on aging and intestinal microbiome in the senescence-accelerated mouse prone 1 (SAMP1). *Sci Rep*. 2019;9(1):3671.
1584. Rawal S, Singh P, Gupta A, Mohanty S. Dietary intake of *Curcuma longa* and *Emblica officinalis* increases life span in *Drosophila melanogaster*. *Biomed Res Int*. 2014;2014:910290.
1585. Chattopadhyay D, Thirumurugan K. Longevity promoting efficacies of different plant extracts in lower model organisms. *Mech Ageing Dev*. 2018;171:47–57.
1586. Bahadorani S, Hilliker AJ. Cocoa confers life span extension in *Drosophila melanogaster*. *Nutr Res*. 2008;28(6):377–82.

1587. Rawal S, Singh P, Gupta A, Mohanty S. Dietary intake of *Curcuma longa* and *Emblica officinalis* increases life span in *Drosophila melanogaster*. *Biomed Res Int*. 2014;2014:910290.
1588. Parohan M, Anjom-Shoae J, Nasiri M, Khodadost M, Khatibi SR, Sadeghi O. Dietary total antioxidant capacity and mortality from all causes, cardiovascular disease and cancer: a systematic review and dose-response meta-analysis of prospective cohort studies. *Eur J Nutr*. 2019;58(6):2175–89.
1589. Percival SS, Vanden Heuvel JP, Nieves CJ, Montero C, Migliaccio AJ, Meadors J. Bioavailability of herbs and spices in humans as determined by *ex vivo* inflammatory suppression and DNA strand breaks. *J Am Coll Nutr*. 2012;31(4):288–94.
1590. Kapoor MP, Suzuki K, Derek T, Ozeki M, Okubo T. Clinical evaluation of Emblica Officinalis Gatertn (Amla) in healthy human subjects: health benefits and safety results from a randomized, double-blind, crossover placebo-controlled study. *Contemp Clin Trials Commun*. 2020;17:100499.
1591. Carlsen MH, Halvorsen BL, Holte K, et al. The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. *Nutr J.* 2010;9:3.
1592. Carlsen MH, Halvorsen BL, Holte K, et al. The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. *Nutr J.* 2010;9:3.
1593. Zhu C, Yan H, Zheng Y, Santos HO, Macit MS, Zhao K. Impact of cinnamon supplementation on cardiometabolic biomarkers of inflammation and oxidative stress: a systematic review and meta-analysis of randomized controlled trials. *Complement Ther Med*. 2020;53:102517.
1594. Ninfali P, Mea G, Giorgini S, Rocchi M, Bacchiocca M. Antioxidant capacity of vegetables, spices and dressings relevant to nutrition. *Br J Nutr*. 2005;93(2):257–66.
1595. Morvaridzadeh M, Sadeghi E, Agah S, et al. Effect of ginger (*Zingiber officinale*) supplementation on oxidative stress parameters: a systematic review and meta-analysis. *J Food Biochem*. 2021;45(2):e13612.

1596. Askari M, Mozaffari H, Darooghegi Mofrad M, et al. Effects of garlic supplementation on oxidative stress and antioxidative capacity biomarkers: a systematic review and meta-analysis of randomized controlled trials. *Phytother Res*. 2021;35(6):3032–45.
1597. Carlsen MH, Halvorsen BL, Holte K, et al. The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. *Nutr J.* 2010;9:3.
1598. Mehrabani S, Arab A, Mohammadi H, Amani R. The effect of cocoa consumption on markers of oxidative stress: a systematic review and meta-analysis of interventional studies. *Complement Ther Med*. 2020;48:102240.
1599. Grassi D, Desideri G, Necozione S, et al. Cocoa consumption dose-dependently improves flow-mediated dilation and arterial stiffness decreasing blood pressure in healthy individuals. *J Hypertens*. 2015;33(2):294–303.
1600. Taubert D, Berkels R, Roesen R, Klaus W. Chocolate and blood pressure in elderly individuals with isolated systolic hypertension. *JAMA*. 2003;290(8):1029–30.
1601. Carnevale R, Loffredo L, Pignatelli P, et al. Dark chocolate inhibits platelet isoprostanes via NOX2 down-regulation in smokers. *J Thromb Haemost*. 2012;10(1):125–32.
1602. Parsaeyan N, Mozaffari-Khosravi H, Absalan A, Mozayan MR. Beneficial effects of cocoa on lipid peroxidation and inflammatory markers in type 2 diabetic patients and investigation of probable interactions of cocoa active ingredients with prostaglandin synthase-2 (PTGS-2/COX-2) using virtual analysis. *J Diabetes Metab Disord*. 2014;13(1):30.
1603. Onuegbu AJ, Olisekodiaka JM, Irogue SE, et al. Consumption of soymilk reduces lipid peroxidation but may lower micronutrient status in apparently healthy individuals. *J Med Food*. 2018;21(5):506–10.
1604. Ballard KD, Mah E, Guo Y, Pei R, Volek JS, Bruno RS. Low-fat milk ingestion prevents postprandial hyperglycemia-mediated impairments in vascular endothelial function in obese individuals with metabolic syndrome. *J Nutr*. 2013;143(10):1602–10.

1605. Dickinson KM, Clifton PM, Keogh JB. Endothelial function is impaired after a high-salt meal in healthy subjects. *Am J Clin Nutr*. 2011;93(3):500–5.
1606. Jablonski KL, Racine ML, Geolfos CJ, et al. Dietary sodium restriction reverses vascular endothelial dysfunction in middle-aged/older adults with moderately elevated systolic blood pressure. *J Am Coll Cardiol*. 2013;61(3):335–43.
1607. McCord JM. Analysis of superoxide dismutase activity. *Curr Protoc Toxicol*. 2001;Chapter 7:Unit 7.3.
1608. Chai SC, Davis K, Zhang Z, Zha L, Kirschner KF. Effects of tart cherry juice on biomarkers of inflammation and oxidative stress in older adults. *Nutrients*. 2019;11(2):228.
1609. Dourado GKZS, Cesar TB. Investigation of cytokines, oxidative stress, metabolic, and inflammatory biomarkers after orange juice consumption by normal and overweight subjects. *Food Nutr Res*. 2015;59(1):28147.
1610. Shema-Didi L, Sela S, Ore L, et al. One year of pomegranate juice intake decreases oxidative stress, inflammation, and incidence of infections in hemodialysis patients: a randomized placebo-controlled trial. *Free Radic Biol Med*. 2012;53(2):297–304.
1611. Ghavipour M, Sotoudeh G, Ghorbani M. Tomato juice consumption improves blood antioxidative biomarkers in overweight and obese females. *Clin Nutr*. 2015;34(5):805–9.
1612. Shyam R, Singh SN, Vats P, et al. Wheat grass supplementation decreases oxidative stress in healthy subjects: a comparative study with spirulina. *J Altern Complement Med*. 2007;13(8):789–91.
1613. Basu A, Betts NM, Ortiz J, Simmons B, Wu M, Lyons TJ. Low-calorie cranberry juice decreases lipid oxidation and increases plasma antioxidant capacity in women with metabolic syndrome. *Nutr Res*. 2011;31(3):190–6.
1614. de Lima Tavares Toscano L, Silva AS, de França ACL, et al. A single dose of purple grape juice improves physical performance and antioxidant activity in runners: a randomized, crossover, double-blind, placebo study. *Eur J Nutr*. 2020;59(7):2997–3007.
1615. Cao G, Russell RM, Lischner N, Prior RL. Serum antioxidant capacity is increased by consumption of strawberries, spinach, red

wine or vitamin C in elderly women. *J Nutr*. 1998;128(12):2383–90.
1616. Ursini F, Zamburlini A, Cazzolato G, Maiorino M, Bon GB, Sevanian A. Postprandial plasma lipid hydroperoxides: a possible link between diet and atherosclerosis. *Free Radic Biol Med*. 1998;25(2):250–2.
1617. Caccetta RAA, Burke V, Mori TA, Beilin LJ, Puddey IB, Croft KD. Red wine polyphenols, in the absence of alcohol, reduce lipid peroxidative stress in smoking subjects. *Free Radic Biol Med*. 2001;30(6):636–42.
1618. Meagher EA, Barry OP, Burke A, et al. Alcohol-induced generation of lipid peroxidation products in humans. *J Clin Invest*. 1999;104(6):805–13.
1619. Xue KX, Wang S, Ma GJ, et al. Micronucleus formation in peripheral-blood lymphocytes from smokers and the influence of alcohol- and tea-drinking habits. *Int J Cancer*. 1992;50(5):702–5.
1620. Bloomer RJ, Trepanowski JF, Farney TM. Influence of acute coffee consumption on postprandial oxidative stress. *Nutr Metab Insights*. 2013;6:35–42.
1621. Takahashi M, Miyashita M, Suzuki K, et al. Acute ingestion of catechin-rich green tea improves postprandial glucose status and increases serum thioredoxin concentrations in postmenopausal women. *Br J Nutr*. 2014;112(9):1542–50.
1622. Leenen R, Roodenburg AJ, Tijburg LB, Wiseman SA. A single dose of tea with or without milk increases plasma antioxidant activity in humans. *Eur J Clin Nutr*. 2000;54(1):87–92.
1623. Rashidinejad A, Birch EJ, Sun-Waterhouse D, Everett DW. Addition of milk to tea infusions: helpful or harmful? Evidence from in vitro and in vivo studies on antioxidant properties. *Crit Rev Food Sci Nutr*. 2017;57(15):3188–96.
1624. Ho CK, Choi SW, Siu PM, Benzie IFF. Effects of single dose and regular intake of green tea (*Camellia sinensis*) on DNA damage, DNA repair, and heme oxygenase-1 expression in a randomized controlled human supplementation study. *Mol Nutr Food Res*. 2014;58(6):1379–83.
1625. Han KC, Wong WC, Benzie IFF. Genoprotective effects of green tea (*Camellia sinensis*) in human subjects: results of a controlled supplementation trial. *Br J Nutr*. 2011;105(2):171–9.

1626. Dias TR, Alves MG, Tomás GD, Socorro S, Silva BM, Oliveira PF. White tea as a promising antioxidant medium additive for sperm storage at room temperature: a comparative study with green tea. *J Agric Food Chem*. 2014;62(3):608–17.
1627. Choi SW, Yeung VTF, Collins AR, Benzie IFF. Redox-linked effects of green tea on DNA damage and repair, and influence of microsatellite polymorphism in *HMOX-1*: results of a human intervention trial. *Mutagenesis*. 2015;30(1):129–37.
1628. Leaf DA, Kleinman MT, Hamilton M, Deitrick RW. The exercise-induced oxidative stress paradox: the effects of physical exercise training. *Am J Med Sci*. 1999;317(5):295–300.
1629. Mastaloudis A, Yu TW, O'Donnell RP, Frei B, Dashwood RH, Traber MG. Endurance exercise results in DNA damage as detected by the comet assay. *Free Radic Biol Med*. 2004;36(8):966–75.
1630. Vollaard NBJ, Shearman JP, Cooper CE. Exercise-induced oxidative stress: myths, realities and physiological relevance. *Sports Med*. 2005;35(12):1045–62.
1631. Mastaloudis A, Yu TW, O'Donnell RP, Frei B, Dashwood RH, Traber MG. Endurance exercise results in DNA damage as detected by the comet assay. *Free Radic Biol Med*. 2004;36(8):966–75.
1632. Fisher-Wellman K, Bloomer RJ. Acute exercise and oxidative stress: a 30 year history. *Dyn Med*. 2009;8:1.
1633. Ristow M, Zarse K, Oberbach A, et al. Antioxidants prevent health-promoting effects of physical exercise in humans. *Proc Natl Acad Sci U S A*. 2009;106(21):8665–70.
1634. Braakhuis AJ. Effect of vitamin C supplements on physical performance. *Curr Sports Med Rep*. 2012;11(4):180–4.
1635. Kashi DS, Shabir A, Da Boit M, Bailey SJ, Higgins MF. The efficacy of administering fruit-derived polyphenols to improve health biomarkers, exercise performance and related physiological responses. *Nutrients*. 2019;11(10):E2389.
1636. Van der Avoort CMT, Van Loon LJC, Hopman MTE, Verdijk LB. Increasing vegetable intake to obtain the health promoting and ergogenic effects of dietary nitrate. *Eur J Clin Nutr*. 2018;72(11):1485–9.

1637. Trapp D, Knez W, Sinclair W. Could a vegetarian diet reduce exercise-induced oxidative stress? A review of the literature. *J Sports Sci*. 2010;28(12):1261–8.
1638. Lyall KA, Hurst SM, Cooney J, et al. Short-term blackcurrant extract consumption modulates exercise-induced oxidative stress and lipopolysaccharide-stimulated inflammatory responses. *Am J Physiol Regul Integr Comp Physiol*. 2009;297(1):R70–81.
1639. Funes L, Carrera-Quintanar L, Cerdán-Calero M, et al. Effect of lemon verbena supplementation on muscular damage markers, proinflammatory cytokines release and neutrophils' oxidative stress in chronic exercise. *Eur J Appl Physiol*. 2011;111(4):695–705.
1640. Ghezzi P, Jaquet V, Marcucci F, Schmidt HHHW. The oxidative stress theory of disease: levels of evidence and epistemological aspects. *Br J Pharmacol*. 2017;174(12):1784–96.
1641. Scudellari M. The science myths that will not die. *Nature*. 2015;528(7582):322–5.
1642. Peng C, Wang X, Chen J, et al. Biology of ageing and role of dietary antioxidants. *Biomed Res Int*. 2014;2014:831841.
1643. Milisav I, Ribarič S, Poljsak B. Antioxidant vitamins and ageing. *Subcell Biochem*. 2018;90:1–23.
1644. Smejkal GB, Kakumanu S. Enzymes and their turnover numbers. *Expert Rev Proteom*. 2019;16(7):543–4.
1645. Raghunath A, Sundarraj K, Nagarajan R, et al. Antioxidant response elements: discovery, classes, regulation and potential applications. *Redox Biol*. 2018;17:297–314.
1646. Zang H, Mathew RO, Cui T. The dark side of Nrf2 in the heart. *Front Physiol*. 2020;11:722.
1647. Brandes MS, Gray NE. NRF2 as a therapeutic target in neurodegenerative diseases. *ASN Neuro*. 2020;12:1759091419899782.
1648. Sharma V, Kaur A, Singh TG. Counteracting role of nuclear factor erythroid 2-related factor 2 pathway in Alzheimer's disease. *Biomed Pharmacother*. 2020;129:110373.
1649. Yuan H, Xu Y, Luo Y, Wang NX, Xiao JH. Role of Nrf2 in cell senescence regulation. *Mol Cell Biochem*. 2021;476(1):247–59.

1650. Raghunath A, Sundarraj K, Nagarajan R, et al. Antioxidant response elements: discovery, classes, regulation and potential applications. Redox Biol. 2018;17:297–314.
1651. Raghunath A, Sundarraj K, Nagarajan R, et al. Antioxidant response elements: discovery, classes, regulation and potential applications. *Redox Biol*. 2018;17:297–314.
1652. Ferguson LR, Schlothauer RC. The potential role of nutritional genomics tools in validating high health foods for cancer control: broccoli as example. *Mol Nutr Food Res*. 2012;56(1):126–46.
1653. Sun Y, Yang T, Leak RK, Chen J, Zhang F. Preventive and protective roles of dietary Nrf2 activators against central nervous system diseases. *CNS Neurol Disord Drug Targets*. 2017;16(3):326–38.
1654. Yang L, Palliyaguru DL, Kensler TW. Frugal chemoprevention: targeting Nrf2 with foods rich in sulforaphane. *Semin Oncol*. 2016;43(1):146–53.
1655. Qu Z, Sun J, Zhang W, Yu J, Zhuang C. Transcription factor NRF2 as a promising therapeutic target for Alzheimer's disease. *Free Radic Biol Med*. 2020;159:87–102.
1656. Lewis KN, Mele J, Hayes JD, Buffenstein R. Nrf2, a guardian of healthspan and gatekeeper of species longevity. *Integr Comp Biol*. 2010;50(5):829–43.
1657. Tullet JMA, Hertweck M, An JH, et al. Direct inhibition of the longevity-promoting factor SKN-1 by insulin-like signaling in *C. elegans*. *Cell*. 2008;132(6):1025–38.
1658. Sykiotis GP, Bohmann D. Keap1/Nrf2 signaling regulates oxidative stress tolerance and lifespan in *Drosophila*. *Dev Cell*. 2008;14(1):76–85.
1659. Lewis KN, Wason E, Edrey YH, Kristan DM, Nevo E, Buffenstein R. Regulation of Nrf2 signaling and longevity in naturally long-lived rodents. *Proc Natl Acad Sci U S A*. 2015;112(12):3722–7.
1660. Yu C, Li Y, Holmes A, et al. RNA sequencing reveals differential expression of mitochondrial and oxidation reduction genes in the long-lived naked mole-rat when compared to mice. *PLoS ONE*. 2011;6(11):e26729.
1661. Lewis KN, Wason E, Edrey YH, Kristan DM, Nevo E, Buffenstein R. Regulation of Nrf2 signaling and longevity in naturally long-lived

rodents. *Proc Natl Acad Sci U S A*. 2015;112(12):3722–7.
1662. Andziak B, O'Connor TP, Buffenstein R. Antioxidants do not explain the disparate longevity between mice and the longest-living rodent, the naked mole-rat. *Mech Ageing Dev*. 2005;126(11):1206–12.
1663. Lewis KN, Wason E, Edrey YH, Kristan DM, Nevo E, Buffenstein R. Regulation of Nrf2 signaling and longevity in naturally long-lived rodents. *Proc Natl Acad Sci U S A*. 2015;112(12):3722–7.
1664. Yuan H, Xu Y, Luo Y, Wang NX, Xiao JH. Role of Nrf2 in cell senescence regulation. *Mol Cell Biochem*. 2021;476(1):247–59.
1665. Zhou L, Zhang H, Davies KJA, Forman HJ. Aging-related decline in the induction of Nrf2-regulated antioxidant genes in human bronchial epithelial cells. *Redox Biol*. 2018;14:35–40.
1666. Mallard AR, Spathis JG, Coombes JS. Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and exercise. *Free Radic Biol Med*. 2020;160:471–9.
1667. Zhang DD, Chapman E. The role of natural products in revealing NRF2 function. *Nat Prod Rep*. 2020;37(6):797–826.
1668. Su X, Jiang X, Meng L, Dong X, Shen Y, Xin Y. Anticancer activity of sulforaphane: the epigenetic mechanisms and the Nrf2 signaling pathway. *Oxid Med Cell Longev*. 2018;2018:5438179.
1669. Bose C, Alves I, Singh P, et al. Sulforaphane prevents age-associated cardiac and muscular dysfunction through Nrf2 signaling. *Aging Cell*. 2020;19(11):e13261.
1670. Kubo E, Chhunchha B, Singh P, Sasaki H, Singh DP. Sulforaphane reactivates cellular antioxidant defense by inducing Nrf2/ARE/Prdx6 activity during aging and oxidative stress. *Sci Rep*. 2017;7:14130.
1671. Yuan H, Xu Y, Luo Y, Wang NX, Xiao JH. Role of Nrf2 in cell senescence regulation. *Mol Cell Biochem*. 2021;476(1):247–59.
1672. Riso P, Martini D, Møller P, et al. DNA damage and repair activity after broccoli intake in young healthy smokers. *Mutagenesis*. 2010;25(6):595–602.
1673. Hoelzl C, Glatt H, Meinl W, et al. Consumption of Brussels sprouts protects peripheral human lymphocytes against 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and oxidative DNA-damage: results of a controlled human intervention trial. *Mol Nutr Food Res*. 2008;52(3):330–41.

1674. Egner PA, Chen JG, Zarth AT, et al. Rapid and sustainable detoxication of airborne pollutants by broccoli sprout beverage: results of a randomized clinical trial in China. *Cancer Prev Res*. 2014;7(8):813–23.
1675. Heber D, Li Z, Garcia-Lloret M, et al. Sulforaphane-rich broccoli sprout extract attenuates nasal allergic response to diesel exhaust particles. *Food Funct*. 2014;5(1):35–41.
1676. Eagles SK, Gross AS, McLachlan AJ. The effects of cruciferous vegetable-enriched diets on drug metabolism: a systematic review and meta-analysis of dietary intervention trials in humans. *Clin Pharmacol Ther*. 2020;108(2):212–27.
1677. Knatko EV, Ibbotson SH, Zhang Y, et al. Nrf2 activation protects against solar-simulated ultraviolet radiation in mice and humans. *Cancer Prev Res (Phila)*. 2015;8(6):475–86.
1678. Houghton CA, Fassett RG, Coombes JS. Sulforaphane and other nutrigenomic Nrf2 activators: can the clinician's expectation be matched by the reality? *Oxid Med Cell Longev*. 2016;2016:7857186.
1679. Aune D, Giovannucci E, Boffetta P, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality—a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol.* 2017;46(3):1029–56.
1680. Mori N, Shimazu T, Charvat H, et al. Cruciferous vegetable intake and mortality in middle-aged adults: a prospective cohort study. *Clin Nutr*. 2019;38(2):631–43.
1681. Grünwald S, Stellzig J, Adam IV, et al. Longevity in the red flour beetle *Tribolium castaneum* is enhanced by broccoli and depends on *nrf-2*, *jnk-1* and *foxo-1* homologous genes. *Genes Nutr*. 2013;8(5):439–48.
1682. Hanschen FS. Domestic boiling and salad preparation habits affect glucosinolate degradation in red cabbage (*Brassica oleracea* var. *capitata* f. *rubra*). *Food Chem*. 2020;321:126694.
1683. Hernández-Ruiz Á, García-Villanova B, Guerra-Hernández E, Amiano P, Ruiz-Canela M, Molina-Montes E. A review of *a priori* defined oxidative balance scores relative to their components and impact on health outcomes. *Nutrients*. 2019;11(4):774.

1684. Holland RD, Gehring T, Taylor J, Lake BG, Gooderham NJ, Turesky RJ. Formation of a mutagenic heterocyclic aromatic amine from creatinine in urine of meat eaters and vegetarians. *Chem Res Toxicol*. 2005;18(3):579–90.
1685. Carvalho AM, Miranda AM, Santos FA, Loureiro APM, Fisberg RM, Marchioni DM. High intake of heterocyclic amines from meat is associated with oxidative stress. *Br J Nutr*. 2015;113(8):1301–7.
1686. Macho-González A, Garcimartín A, López-Oliva ME, et al. Can meat and meat-products induce oxidative stress? *Antioxidants (Basel)*. 2020;9(7):638.
1687. Kanner J, Lapidot T. The stomach as a bioreactor: dietary lipid peroxidation in the gastric fluid and the effects of plant-derived antioxidants. *Free Radic Biol Med*. 2001;31(11):1388–95.
1688. Mohamed B, Mohamed I. The effects of residual blood of carcasses on poultry technological quality. *Food Nutri Sci*. 2012;03(10):1382–6.
1689. Alvarado CZ, Richards MP, O'Keefe SF, Wang H. The effect of blood removal on oxidation and shelf life of broiler breast meat. *Poult Sci*. 2007;86(1):156–61.
1690. Cohn JS. Oxidized fat in the diet, postprandial lipaemia and cardiovascular disease. *Curr Opin Lipidol*. 2002;13(1):19–24.
1691. Gorelik S, Kanner J, Schurr D, Kohen R. A rational approach to prevent postprandial modification of LDL by dietary polyphenols. *J Funct Foods*. 2013;5(1):163–9.
1692. Jafari S, Hezaveh E, Jalilpiran Y, et al. Plant-based diets and risk of disease mortality: a systematic review and meta-analysis of cohort studies. *Crit Rev Food Sci Nutr*. https://www.tandfonline.com/doi/full/10.1080/10408398.2021.1918628. Published May 6, 2021. Accessed July 10, 2021.
1693. Cohn JS. Oxidized fat in the diet, postprandial lipaemia and cardiovascular disease. *Curr Opin Lipidol*. 2002;13(1):19–24.
1694. Edalati S, Bagherzadeh F, Asghari Jafarabadi M, Ebrahimi-Mamaghani M. Higher ultra-processed food intake is associated with higher DNA damage in healthy adolescents. *Br J Nutr*. 2021;125(5):568–76.

1695. Macho-González A, Garcimartín A, López-Oliva ME, et al. Can meat and meat-products induce oxidative stress? *Antioxidants (Basel)*. 2020;9(7):638.
1696. Aleksandrova K, Koelman L, Rodrigues CE. Dietary patterns and biomarkers of oxidative stress and inflammation: a systematic review of observational and intervention studies. *Redox Biol*. 2021;42:101869.
1697. Benzie IFF, Wachtel-Galor S. Vegetarian diets and public health: biomarker and redox connections. *Antioxid Redox Signal*. 2010;13(10):1575–91.
1698. Burri BJ. Antioxidant status in vegetarians versus omnivores: a mechanism for longer life? *Nutrition*. 2000;16(2):149–50.
1699. Krajčovičová-Kudláčková M, Šimončič R, Béderová A, Klvanová J, Brtková A, Grančičová E. Lipid and antioxidant blood levels in vegetarians. *Nahrung*. 1996;40(1):17–20.
1700. Kováčiková Z, Čerhata D, Kadrabová J, Madarič A, Ginter E. Antioxidant status in vegetarians and nonvegetarians in Bratislava region (Slovakia). Z Ernahrungswiss. 1998;37(2):178–82.
1701. Nagyová A, Kudláčková M, Grančičová E, Magálová T. LDL oxidizability and antioxidative status of plasma in vegetarians. Ann Nutr Metab. 1998;42(6):328–32.
1702. Boancă MM, Colosi HA, Crăciun EC. The impact of the lacto-ovo vegetarian diet on the erythrocyte superoxide dismutase activity: a study in the Romanian population. Eur J Clin Nutr. 2014;68(2):184–8.
1703. Krajčovičová-Kudláčková M, Valachovičová M, Pauková V, Dušinská M. Effects of diet and age on oxidative damage products in healthy subjects. *Physiol Res*. 2008;57(4):647–51.
1704. Somannavar MS, Kodliwadmath MV. Correlation between oxidative stress and antioxidant defence in South Indian urban vegetarians and non-vegetarians. *Eur Rev Med Pharmacol Sci*. 2012;16(3):351–4.
1705. Manjari V, Suresh Y, Sailaja Devi MM, Das UN. Oxidant stress, anti-oxidants and essential fatty acids in South Indian vegetarians and non-vegetarians. *Prostaglandins Leukot Essent Fatty Acids*. 2001;64(1):53–9.

1706. Kim MK, Cho SW, Park YK. Long-term vegetarians have low oxidative stress, body fat, and cholesterol levels. *Nutr Res Pract*. 2012;6(2):155–61.
1707. Szeto YT, Kwok TCY, Benzie IFF. Effects of a long-term vegetarian diet on biomarkers of antioxidant status and cardiovascular disease risk. *Nutrition*. 2004;20(10):863–6.
1708. Gajski G, Gerić M, Vučić Lovrenčić M, et al. Analysis of health-related biomarkers between vegetarians and non-vegetarians: a multi-biomarker approach. J Funct Foods. 2018;48:643–53.
1709. Poornima K, Cariappa M, Asha K, Kedilaya HP, Nandini M. Oxidant and antioxidant status in vegetarians and fish eaters. Indian J Clin Biochem. 2003;18(2):197–205.
1710. Krajčovičová-Kudláčková M, Šimončič R, Babinská K, Béderová A. Levels of lipid peroxidation and antioxidants in vegetarians. Eur *J Epidemiol*. 1995;11(2):207–11.
1711. Nadimi H, Yousefinejad A, Djazayery A, Hosseini M, Hosseini S. Association of vegan diet with RMR, body composition and oxidative stress. *Acta Sci Pol Technol Aliment.* 2013;12(3):311–8.
1712. Herrmann W, Schorr H, Purschwitz K, Rassoul F, Richter V. Total homocysteine, vitamin B_{12}, and total antioxidant status in vegetarians. *Clin Chem*. 2001;47(6):1094–101.
1713. van de Lagemaat EE, de Groot LCPGM, van den Heuvel EGHM. Vitamin B_{12} in relation to oxidative stress: a systematic review. *Nutrients*. 2019;11(2):E482.
1714. Pawlak R, Lester SE, Babatunde T. The prevalence of cobalamin deficiency among vegetarians assessed by serum vitamin B12: a review of literature. *Eur J Clin Nutr*. 2014;68(5):541–8.
1715. Poli G, Biasi F, Leonarduzzi G. Oxysterols in the pathogenesis of major chronic diseases. *Redox Biol*. 2013;1:125–30.
1716. Wellington CL, Frikke-Schmidt R. Relation between plasma and brain lipids. *Curr Opin Lipidol*. 2016;27(3):225–32.
1717. Poli G, Biasi F, Leonarduzzi G. Oxysterols in the pathogenesis of major chronic diseases. *Redox Biol*. 2013;1:125–30.
1718. Gamba P, Testa G, Gargiulo S, Staurenghi E, Poli G, Leonarduzzi G. Oxidized cholesterol as the driving force behind the development of

Alzheimer's disease. *Front Aging Neurosci*. 2015;7.
1719. Otaegui-Arrazola A, Menéndez-Carreño M, Ansorena D, Astiasarán I. Oxysterols: a world to explore. *Food Chem Toxicol*. 2010;48(12):3289–303.
1720. Iuliano L, Micheletta F, Natoli S, et al. Measurement of oxysterols and α-tocopherol in plasma and tissue samples as indices of oxidant stress status. *Anal Biochem*. 2003;312(2):217–23.
1721. Zarrouk A, Vejux A, Mackrill J, et al. Involvement of oxysterols in age-related diseases and ageing processes. *Ageing Res Rev*. 2014;18:148–62.
1722. Otaegui-Arrazola A, Menéndez-Carreño M, Ansorena D, Astiasarán I. Oxysterols: a world to explore. *Food Chem Toxicol*. 2010;48(12):3289–303.
1723. Zarrouk A, Vejux A, Mackrill J, et al. Involvement of oxysterols in age-related diseases and ageing processes. *Ageing Res Rev*. 2014;18:148–62.
1724. Lordan S, Mackrill JJ, O'Brien NM. Oxysterols and mechanisms of apoptotic signaling: implications in the pathology of degenerative diseases. *J Nutr Biochem*. 2009;20(5):321–36.
1725. Si R, Qu K, Jiang Z, Yang X, Gao P. Egg consumption and breast cancer risk: a meta-analysis. *Breast Cancer*. 2014;21(3):251–61.
1726. Li C, Yang L, Zhang D, Jiang W. Systematic review and meta-analysis suggest that dietary cholesterol intake increases risk of breast cancer. *Nutr Res*. 2016;36(7):627–35.
1727. Asghari A, Umetani M. Obesity and cancer: 27-hydroxycholesterol, the missing link. *Int J Mol Sci*. 2020;21(14):4822.
1728. Nelson ER, Chang C, McDonnell DP. Cholesterol and breast cancer pathophysiology. *Trends Endocrinol & Metab*. 2014;25(12):649–55.
1729. Kaiser J. Cholesterol forges link between obesity and breast cancer. *Science*. 2013;342(6162):1028.
1730. Staprans I, Pan XM, Rapp JH, Feingold KR. Oxidized cholesterol in the diet is a source of oxidized lipoproteins in human serum. *J Lipid Res*. 2003;44(4):705–15.
1731. Emanuel HA, Hassel CA, Addis PB, Bergmann SD, Zavoral JH. Plasma cholesterol oxidation products (oxysterols) in human subjects fed a meal rich in oxysterols. *J Food Sci*. 1991;56(3):843–7.

1732. Natella F, Macone A, Ramberti A, et al. Red wine prevents the postprandial increase in plasma cholesterol oxidation products: a pilot study. *Br J Nutr*. 2011;105(12):1718–23.
1733. Lordan S, Mackrill JJ, O'Brien NM. Oxysterols and mechanisms of apoptotic signaling: implications in the pathology of degenerative diseases. *J Nutr Biochem*. 2009;20(5):321–36.
1734. Emanuel HA, Hassel CA, Addis PB, Bergmann SD, Zavoral JH. Plasma cholesterol oxidation products (oxysterols) in human subjects fed a meal rich in oxysterols. *J Food Sci*. 1991;56(3):843–7.
1735. Khan MI, Min JS, Lee SO, et al. Cooking, storage, and reheating effect on the formation of cholesterol oxidation products in processed meat products. *Lipids Health Dis*. 2015;14:89.
1736. Min JS, Lee SO, Khan MI, et al. Monitoring the formation of cholesterol oxidation products in model systems using response surface methodology. *Lipids Health Dis*. 2015;14:77.
1737. Hur SJ, Park GB, Joo ST. Formation of cholesterol oxidation products (COPs) in animal products. *Food Control*. 2007;18(8):939–47.
1738. Echarte M, Ansorena D, Astiasarán I. Consequences of microwave heating and frying on the lipid fraction of chicken and beef patties. *J Agric Food Chem*. 2003;51(20):5941–5.
1739. Hur SJ, Park GB, Joo ST. Formation of cholesterol oxidation products (COPs) in animal products. *Food Control*. 2007;18(8):939–47.
1740. Maldonado-Pereira L, Schweiss M, Barnaba C, Medina-Meza IG. The role of cholesterol oxidation products in food toxicity. *Food Chem Toxicol*. 2018;118:908–39.
1741. Savage GP, Dutta PC, Rodriguez-Estrada MT. Cholesterol oxides: their occurrence and methods to prevent their generation in foods. *Asia Pac J Clin Nutr*. 2002;11(1):72–8.
1742. Savage GP, Dutta PC, Rodriguez-Estrada MT. Cholesterol oxides: their occurrence and methods to prevent their generation in foods. *Asia Pac J Clin Nutr*. 2002;11(1):72–8.
1743. Otaegui-Arrazola A, Menéndez-Carreño M, Ansorena D, Astiasarán I. Oxysterols: a world to explore. *Food Chem Toxicol*. 2010;48(12):3289–303.

1744. Savage GP, Dutta PC, Rodriguez-Estrada MT. Cholesterol oxides: their occurrence and methods to prevent their generation in foods. *Asia Pac J Clin Nutr*. 2002;11(1):72–8.
1745. Jacobson MS. Cholesterol oxides in Indian ghee: possible cause of unexplained high risk of atherosclerosis in Indian immigrant populations. *Lancet*. 1987;2(8560):656–8.
1746. Raheja BS. Ghee, cholesterol, and heart disease. *Lancet*. 1987;2(8568):1144–5.
1747. Connor JM. *Global Price Fixing*. 2nd ed. Springer-Verlag; 2008.
1748. Bjelakovic G, Nikolova D, Gluud C. Antioxidant supplements to prevent mortality. *JAMA*. 2013;310(11):1178–9.
1749. Sadowska-Bartosz I, Bartosz G. Effect of antioxidants supplementation on aging and longevity. *Biomed Res Int*. 2014;2014:404680.
1750. Bast A, Haenen GRMM. Ten misconceptions about antioxidants. *Trends Pharmacol Sci*. 2013;34(8):430–6.
1751. Vajdi M, Abbasalizad Farhangi M. Alpha-lipoic acid supplementation significantly reduces the risk of obesity in an updated systematic review and dose response meta-analysis of randomised placebo-controlled clinical trials. *Int J Clin Pract*. 2020;74(6):e13493.
1752. de Barcelos IP, Haas RH. CoQ10 and aging. *Biology (Basel)*. 2019;8(2):28.
1753. Raizner AE, Quiñones MA. Coenzyme Q_{10} for patients with cardiovascular disease: JAAC Focus Seminar. *J Am Coll Cardiol*. 2021;77(5):609–19.
1754. Arenas-Jal M, Suñé-Negre JM, García-Montoya E. Coenzyme Q10 supplementation: efficacy, safety, and formulation challenges. *Compr Rev Food Sci Food Saf*. 2020;19(2):574–94.
1755. Nagase M, Yamamoto Y, Matsumoto N, Arai Y, Hirose N. Increased oxidative stress and coenzyme Q10 deficiency in centenarians. *J Clin Biochem Nutr*. 2018;63(2):129–36.
1756. Varela-López A, Giampieri F, Battino M, Quiles JL. Coenzyme Q and its role in the dietary therapy against aging. *Molecules*. 2016;21(3):373.

1757. Asencio C, Rodríguez-Aguilera JC, Ruiz-Ferrer M, Vela J, Navas P. Silencing of ubiquinone biosynthesis genes extends life span in *Caenorhabditis elegans*. *FASEB J*. 2003;17(9):1135–7.
1758. Díaz-Casado ME, Quiles JL, Barriocanal-Casado E, et al. The paradox of coenzyme Q_{10} in aging. *Nutrients*. 2019;11(9):E2221.
1759. Fan L, Feng Y, Chen GC, Qin LQ, Fu CL, Chen LH. Effects of coenzyme Q10 supplementation on inflammatory markers: a systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res*. 2017;119:128–36.
1760. Akbari A, Mobini GR, Agah S, et al. Coenzyme Q10 supplementation and oxidative stress parameters: a systematic review and meta-analysis of clinical trials. *Eur J Clin Pharmacol*. 2020;76(11):1483–99.
1761. Jafari M, Mousavi SM, Asgharzadeh A, Yazdani N. Coenzyme Q10 in the treatment of heart failure: a systematic review of systematic reviews. *Indian Heart J*. 2018;70(Suppl 1):S111–7.
1762. Sazali S, Badrin S, Norhayati MN, Idris NS. Coenzyme Q10 supplementation for prophylaxis in adult patients with migraine—a meta-analysis. *BMJ Open*. 2021;11(1):e039358.
1763. Arenas-Jal M, Suñé-Negre JM, García-Montoya E. Coenzyme Q10 supplementation: efficacy, safety, and formulation challenges. *Compr Rev Food Sci Food Saf*. 2020;19(2):574–94.
1764. Qu J, Ma L, Zhang J, Jockusch S, Washington I. Dietary chlorophyll metabolites catalyze the photoreduction of plasma ubiquinone. *Photochem Photobiol.* 2013;89(2):310–3.
1765. Littarru GP, Langsjoen P. Coenzyme Q_{10} and statins: biochemical and clinical implications. *Mitochondrion*. 2007;7S:S168–74.
1766. Lee TK, Johnke RM, Allison RR, O'Brien KF, Dobbs LJ. Radioprotective potential of ginseng. *Mutagenesis*. 2005;20(4):237–43.
1767. Fan S, Zhang Z, Su H, et al. Panax ginseng clinical trials: current status and future perspectives. *Biomed Pharmacother*. 2020;132:110832.
1768. Shergis JL, Zhang AL, Zhou W, Xue CC. *Panax ginseng* in randomised controlled trials: a systematic review. *Phytother Res*.

2013;27(7):949–65.
1769. Gui QF, Xu ZR, Xu KY, Yang YM. The efficacy of ginseng-related therapies in type 2 diabetes mellitus: an updated systematic review and meta-analysis. *Medicine*. 2016;95(6):e2584.
1770. Szeto YT, Sin YSP, Pak SC, Kalle W. American ginseng tea protects cellular DNA within 2 h from consumption: results of a pilot study in healthy human volunteers. *Int J Food Sci Nutr*. 2015;66(7):815–8.
1771. Szeto YT, Lee LKY. Rapid but mild genoprotective effect on lymphocytic DNA with *Panax notoginseng* extract supplementation. *J Intercult Ethnopharmacol*. 2014;3(4):155–8.
1772. Szeto YT, Ko AW. Acute genoprotective effects on lymphocytic DNA with ginseng extract supplementation. *J Aging Res Clin Practice.* 2013;2(2):174–7.
1773. Kim HG, Yoo SR, Park HJ, et al. Antioxidant effects of *Panax ginseng* C.A. Meyer in healthy subjects: a randomized, placebo-controlled clinical trial. *Food Chem Toxicol*. 2011;49(9):2229–35.
1774. Dickman JR, Koenig RT, Ji LL. American ginseng supplementation induces an oxidative stress in postmenopausal women. *J Am Coll Nutr*. 2009;28(2):219–28.
1775. Flurkey K, Astle CM, Harrison DE. Life extension by diet restriction and *N*-acetyl-$_{L}$-cysteine in genetically heterogeneous mice. *J Gerontol A Biol Sci Med Sci*. 2010;65(12):1275–84.
1776. Oh SI, Park JK, Park SK. Lifespan extension and increased resistance to environmental stressors by N-Acetyl-L-Cysteine in *Caenorhabditis elegans*. *Clinics*. 2015;70(5):380–6.
1777. Niraula P, Kim MS. *N*-Acetylcysteine extends lifespan of *Drosophila* via modulating ROS scavenger gene expression. *Biogerontology*. 2019;20(4):533–43.
1778. Zoidis E, Seremelis I, Kontopoulos N, Danezis GP. Selenium-dependent antioxidant enzymes: actions and properties of selenoproteins. *Antioxidants (Basel)*. 2018;7(5):66.
1779. Schiavon M, Nardi S, dalla Vecchia F, Ertani A. Selenium biofortification in the 21st century: status and challenges for healthy human nutrition. *Plant Soil*. 2020;453(1–2):245–70.

1780. Duarte GBS, Reis BZ, Rogero MM, et al. Consumption of Brazil nuts with high selenium levels increased inflammation biomarkers in obese women: a randomized controlled trial. *Nutrition*. 2019;63–64:162–8.
1781. Xiang S, Dai Z, Man C, Fan Y. Circulating selenium and cardiovascular or all-cause mortality in the general population: a meta-analysis. *Biol Trace Elem Res*. 2020;195(1):55–62.
1782. Bleys J, Navas-Acien A, Guallar E. Serum selenium levels and all-cause, cancer, and cardiovascular mortality among US adults. *Arch Intern Med*. 2008;168(4):404–10.
1783. Rayman MP, Winther KH, Pastor-Barriuso R, et al. Effect of long-term selenium supplementation on mortality: results from a multiple-dose, randomised controlled trial. *Free Radic Biol Med*. 2018;127:46–54.
1784. Faghihi T, Radfar M, Barmal M, et al. A randomized, placebo-controlled trial of selenium supplementation in patients with type 2 diabetes: effects on glucose homeostasis, oxidative stress, and lipid profile. *Am J Ther*. 2014;21(6):491–5.
1785. Stranges S, Marshall JR, Natarajan R, et al. Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. *Ann Intern Med*. 2007;147(4):217–23.
1786. Talaulikar VS, Manyonda IT. Vitamin C as an antioxidant supplement in women's health: a myth in need of urgent burial. *Eur J Obstet Gynecol Reprod Biol*. 2011;157(1):10–3.
1787. Camarena V, Wang G. The epigenetic role of vitamin C in health and disease. *Cell Mol Life Sci*. 2016;73(8):1645–58.
1788. Schaus R. The ascorbic acid content of human pituitary, cerebral cortex, heart, and skeletal muscle and its relation to age. *Am J Clin Nutr*. 1957;5(1):39–41.
1789. Granger M, Eck P. Dietary vitamin C in human health. *Adv Food Nutr Res*. 2018;83:281–310.
1790. Duarte TL, Lunec J. Review: When is an antioxidant not an antioxidant? A review of novel actions and reactions of vitamin C. *Free Radic Res*. 2005;39(7):671–86.
1791. Childs A, Jacobs C, Kaminski T, Halliwell B, Leeuwenburgh C. Supplementation with vitamin C and N-acetyl-cysteine increases

oxidative stress in humans after an acute muscle injury induced by eccentric exercise. *Free Radic Biol Med*. 2001;31(6):745–53.

1792. Mendes-da-Silva RF, Lopes-de-Morais AAC, Bandim-da-Silva ME, et al. Prooxidant *versus* antioxidant brain action of ascorbic acid in well-nourished and malnourished rats as a function of dose: a cortical spreading depression and malondialdehyde analysis. *Neuropharmacology*. 2014;86:155–60.

1793. Pallauf K, Bendall JK, Scheiermann C, et al. Vitamin C and lifespan in model organisms. *Food Chem Toxicol*. 2013;58:255–63.

1794. Brauchla M, Dekker MJ, Rehm CD. Trends in vitamin C consumption in the United States: 1999–2018. *Nutrients*. 2021;13(2):420.

1795. Thomas LDK, Elinder CG, Tiselius HG, Wolk A, Åkesson A. Ascorbic acid supplements and kidney stone incidence among men: a prospective study. *JAMA Intern Med*. 2013;173(5):386–8.

1796. Fletcher RH. The risk of taking ascorbic acid. *JAMA Intern Med*. 2013;173(5):388.

1797. Cavuoto P, Fenech MF. A review of methionine dependency and the role of methionine restriction in cancer growth control and life-span extension. *Cancer Treat Rev*. 2012;38(6):726–36.

1798. Toledo C, Saltsman K. Genetics by the numbers. Inside Life Science. National Institute of General Medical Sciences. https://www.nigms.nih.gov/education/Inside-Life-Science/Pages/genetics-by-the-numbers.aspx. Published June 12, 2012. Accessed June 28, 2021.

1799. Zhang F, Wang S, Gan L, et al. Protective effects and mechanisms of sirtuins in the nervous system. *Prog Neurobiol.* 2011;95(3):373–95.

1800. Zhao L, Cao J, Hu K, et al. Sirtuins and their biological relevance in aging and age-related diseases. *Aging Dis*. 2020;11(4):927–45.

1801. Grabowska W, Sikora E, Bielak-Zmijewska A. Sirtuins, a promising target in slowing down the ageing process. *Biogerontology*. 2017;18(4):447–76.

1802. Kaeberlein M, McVey M, Guarente L. The *SIR2/3/4* complex and *SIR2* alone promote longevity in *Saccharomyces cerevisiae* by two different mechanisms. *Genes Dev*. 1999;13(19):2570–80.

1803. Zhao L, Cao J, Hu K, et al. Sirtuins and their biological relevance in aging and age-related diseases. *Aging Dis*. 2020;11(4):927–45.
1804. Satoh A, Brace CS, Rensing N, et al. Sirt1 extends life span and delays aging in mice through the regulation of Nk2 homeobox 1 in the DMH and LH. *Cell Metab*. 2013;18(3):416–30.
1805. Kanfi Y, Naiman S, Amir G, et al. The sirtuin SIRT6 regulates lifespan in male mice. *Nature*. 2012;483(7388):218–21.
1806. Brenner C. Sirtuins are not conserved longevity genes. *Life Metabolism*. Published online September 22, 2022. https://academic.oup.com/lifemeta/advance-article/doi/10.1093/lifemeta/loac025/6711379. Accessed December 27, 2022.
1807. Giblin W, Skinner ME, Lombard DB. Sirtuins: guardians of mammalian healthspan. *Trends Genet*. 2014;30(7):271–86.
1808. Wang RH, Sengupta K, Li C, et al. Impaired DNA damage response, genome instability, and tumorigenesis in SIRT1 mutant mice. *Cancer Cell*. 2008;14(4):312–23.
1809. Lee SH, Lee JH, Lee HY, Min KJ. Sirtuin signaling in cellular senescence and aging. *BMB Rep*. 2019;52(1):24–34.
1810. Wątroba M, Szukiewicz D. The role of sirtuins in aging and age-related diseases. *Adv Med Sci*. 2016;61(1):52–62.
1811. Palacios JA, Herranz D, De Bonis ML, Velasco S, Serrano M, Blasco MA. SIRT1 contributes to telomere maintenance and augments global homologous recombination. *J Cell Biol*. 2010;191(7):1299–313.
1812. Morris BJ. Seven sirtuins for seven deadly diseases of aging. *Free Radic Biol Med*. 2013;56:133–71.
1813. Giblin W, Skinner ME, Lombard DB. Sirtuins: guardians of mammalian healthspan. *Trends Genet*. 2014;30(7):271–86.
1814. Flachsbart F, Croucher PJP, Nikolaus S, et al. Sirtuin 1 *(SIRT1)* sequence variation is not associated with exceptional human longevity. *Exp Gerontol*. 2006;41(1):98–102.
1815. Houtkooper RH, Pirinen E, Auwerx J. Sirtuins as regulators of metabolism and healthspan. *Nat Rev Mol Cell Biol*. 2012;13(4):225–38.
1816. Cantó C, Gerhart-Hines Z, Feige JN, et al. AMPK regulates energy expenditure by modulating NAD^+ metabolism and SIRT1 activity.

Nature. 2009;458(7241):1056–60.
1817. Xu W, Deng YY, Yang L, et al. Metformin ameliorates the proinflammatory state in patients with carotid artery atherosclerosis through sirtuin 1 induction. *Transl Res*. 2015;166(5):451–8.
1818. Dang W. The controversial world of sirtuins. *Drug Discov Today Technol*. 2014;12:e9–17.
1819. Guerra B, Guadalupe-Grau A, Fuentes T, et al. SIRT1, AMP-activated protein kinase phosphorylation and downstream kinases in response to a single bout of sprint exercise: influence of glucose ingestion. *Eur J Appl Physiol*. 2010;109(4):731–43.
1820. Guerra B, Guadalupe-Grau A, Fuentes T, et al. SIRT1, AMP-activated protein kinase phosphorylation and downstream kinases in response to a single bout of sprint exercise: influence of glucose ingestion. *Eur J Appl Physiol*. 2010;109(4):731–43.
1821. Asghari S, Asghari-Jafarabadi M, Somi MH, Ghavami SM, Rafraf M. Comparison of calorie-restricted diet and resveratrol supplementation on anthropometric indices, metabolic parameters, and serum sirtuin-1 levels in patients with nonalcoholic fatty liver disease: a randomized controlled clinical trial. *J Am Coll Nutr*. 2018;37(3):223–33.
1822. Crujeiras AB, Parra D, Goyenechea E, Martínez JA. Sirtuin gene expression in human mononuclear cells is modulated by caloric restriction. *Eur J Clin Invest*. 2008;38(9):672–8.
1823. Draznin B, Wang C, Adochio R, Leitner JW, Cornier MA. Effect of dietary macronutrient composition on AMPK and SIRT1 expression and activity in human skeletal muscle. *Horm Metab Res*. 2012;44(9):650–5.
1824. Lilja S, Stoll C, Krammer U, et al. Five days periodic fasting elevates levels of longevity related *Christensenella* and sirtuin expression in humans. *Int J Mol Sci*. 2021;22(5):2331.
1825. Heilbronn LK, Civitarese AE, Bogacka I, Smith SR, Hulver M, Ravussin E. Glucose tolerance and skeletal muscle gene expression in response to alternate day fasting. *Obes Res*. 2005;13(3):574–81.
1826. Mansur AP, Roggerio A, Goes MFS, et al. Serum concentrations and gene expression of sirtuin 1 in healthy and slightly overweight subjects after caloric restriction or resveratrol supplementation: a randomized trial. *Int J Cardiol*. 2017;227:788–94.

1827. Civitarese AE, Carling S, Heilbronn LK, et al. Calorie restriction increases muscle mitochondrial biogenesis in healthy humans. *PLoS Med*. 2007;4(3):e76.
1828. Cantó C, Gerhart-Hines Z, Feige JN, et al. AMPK regulates energy expenditure by modulating NAD^+ metabolism and SIRT1 activity. *Nature*. 2009;458(7241):1056–60.
1829. Giblin W, Skinner ME, Lombard DB. Sirtuins: guardians of mammalian healthspan. *Trends Genet*. 2014;30(7):271–86.
1830. Wątroba M, Szukiewicz D. The role of sirtuins in aging and age-related diseases. *Adv Med Sci*. 2016;61(1):52–62.
1831. Giblin W, Skinner ME, Lombard DB. Sirtuins: guardians of mammalian healthspan. *Trends Genet*. 2014;30(7):271–86.
1832. Smoliga JM, Blanchard O. Enhancing the delivery of resveratrol in humans: if low bioavailability is the problem, what is the solution? *Molecules*. 2014;19(11):17154–72.
1833. Pezzuto JM. Resveratrol: twenty years of growth, development and controversy. *Biomol Ther (Seoul)*. 2019;27(1):1–14.
1834. Singh CK, Liu X, Ahmad N. Resveratrol, in its natural combination in whole grape, for health promotion and disease management. *Ann N Y Acad Sci*. 2015;1348(1):150–60.
1835. Visioli F, Panaite SA, Tomé-Carneiro J. Wine's phenolic compounds and health: a Pythagorean view. *Molecules*. 2020;25(18):4105.
1836. Burr ML. Explaining the French paradox. *J R Soc Health*. 1995;115(4):217–9.
1837. Vang O. What is new for resveratrol? Is a new set of recommendations necessary? *Ann N Y Acad Sci*. 2013;1290:1–11.
1838. Resveratrol. National Library of Medicine. https://pubmed.ncbi.nlm.nih.gov/?term=resveratrol. Accessed January 18, 2023.
1839. Hector KL, Lagisz M, Nakagawa S. The effect of resveratrol on longevity across species: a meta-analysis. *Biol Lett*. 2012;8(5):790–3.
1840. Rascón B, Hubbard BP, Sinclair DA, Amdam GV. The lifespan extension effects of resveratrol are conserved in the honey bee and may be driven by a mechanism related to caloric restriction. *Aging (Albany NY)*. 2012;4(7):499–508.

1841. Hector KL, Lagisz M, Nakagawa S. The effect of resveratrol on longevity across species: a meta-analysis. *Biol Lett*. 2012;8(5):790–3.
1842. Kim E, Ansell CM, Dudycha JL. Resveratrol and food effects on lifespan and reproduction in the model crustacean Daphnia. *J Exp Zool A Ecol Genet Physiol*. 2014;321(1):48–56.
1843. Hector KL, Lagisz M, Nakagawa S. The effect of resveratrol on longevity across species: a meta-analysis. *Biol Lett*. 2012;8(5):790–3.
1844. Pacholec M, Bleasdale JE, Chrunyk B, et al. SRT1720, SRT2183, SRT1460, and resveratrol are not direct activators of SIRT1. *J Biol Chem*. 2010;285(11):8340–51.
1845. Cottart CH, Nivet-Antoine V, Beaudeux JL. Is resveratrol an imposter? *Mol Nutr Food Res*. 2015;59(1):7.
1846. Tang PCT, Ng YF, Ho S, Gyda M, Chan SW. Resveratrol and cardiovascular health—promising therapeutic or hopeless illusion? *Pharmacol Res*. 2014;90:88–115.
1847. Visioli F. The resveratrol fiasco. *Pharmacol Res*. 2014;90:87.
1848. Roehr B. Cardiovascular researcher fabricated data in studies of red wine. *BMJ*. 2012;344:e406.
1849. Visioli F. The resveratrol fiasco. *Pharmacol Res*. 2014;90:87.
1850. Resveratrol clinical trial, humans from 2014/12/1–3000/12/12. National Library of Medicine. https://pubmed.ncbi.nlm.nih.gov/?term=resveratrol&filter=pubt.clinicaltrial&filter=dates.2014%2F12%2F1–3000%2F12%2F12&filter=hum_ani.humans. Accessed January 18, 2023.
1851. Rabassa M, Zamora-Ros R, Urpi-Sarda M, et al. Association of habitual dietary resveratrol exposure with the development of frailty in older age: the Invecchiare in Chianti study. *Am J Clin Nutr*. 2015;102(6):1534–42.
1852. Semba RD, Ferrucci L, Bartali B, et al. Resveratrol levels and all-cause mortality in older community-dwelling adults. *JAMA Intern Med*. 2014;174(7):1077–84.
1853. Omidian M, Abdolahi M, Daneshzad E, et al. The effects of resveratrol on oxidative stress markers: a systematic review and meta-analysis of randomized clinical trials. *Endocr Metab Immune Disord Drug Targets*. 2020;20(5):718–27.

1854. Koushki M, Lakzaei M, Khodabandehloo H, Hosseini H, Meshkani R, Panahi G. Therapeutic effect of resveratrol supplementation on oxidative stress: a systematic review and meta-analysis of randomised controlled trials. *Postgrad Med J*. 2020;96(1134):197–205.
1855. Heger A, Ferk F, Nersesyan A, et al. Intake of a resveratrol-containing dietary supplement has no impact on DNA stability in healthy subjects. *Mutat Res*. 2012;749(1–2):82–6.
1856. Zeraattalab-Motlagh S, Jayedi A, Shab-Bidar S. The effects of resveratrol supplementation in patients with type 2 diabetes, metabolic syndrome, and nonalcoholic fatty liver disease: an umbrella review of meta-analyses of randomized controlled trials. *Am J Clin Nutr*. 2021;114(5):1675–85.
1857. Zhang T, He Q, Liu Y, Chen Z, Hu H. Efficacy and safety of resveratrol supplements on blood lipid and blood glucose control in patients with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Evid Based Complement Alternat Med*. 2021;2021:5644171.
1858. Zeraattalab-Motlagh S, Jayedi A, Shab-Bidar S. The effects of resveratrol supplementation in patients with type 2 diabetes, metabolic syndrome, and nonalcoholic fatty liver disease: an umbrella review of meta-analyses of randomized controlled trials. *Am J Clin Nutr*. 2021;114(5):1675–8.
1859. Bashmakov YK, Assaad-Khalil SH, Abou Seif M, et al. Resveratrol promotes foot ulcer size reduction in type 2 diabetes patients. *ISRN Endocrinol*. 2014;2014:816307.
1860. Moxey PW, Gogalniceanu P, Hinchliffe RJ, et al. Lower extremity amputations—a review of global variability in incidence. *Diabet Med*. 2011;28(10):1144–53.
1861. Bhattarai G, Poudel SB, Kook SH, Lee JC. Resveratrol prevents alveolar bone loss in an experimental rat model of periodontitis. *Acta Biomater*. 2016;29:398–408.
1862. Zhen L, Fan DS, Zhang Y, Cao XM, Wang LM. Resveratrol ameliorates experimental periodontitis in diabetic mice through negative regulation of TLR4 signaling. *Acta Pharmacol Sin*. 2015;36(2):221–8.

1863. Javid AZ, Hormoznejad R, Yousefimanesh HA, Haghighi-Zadeh MH, Zakerkish M. Impact of resveratrol supplementation on inflammatory, antioxidant, and periodontal markers in type 2 diabetic patients with chronic periodontitis. *Diabetes Metab Syndr*. 2019;13(4):2769–74.
1864. Samsamikor M, Daryani NE, Asl PR, Hekmatdoost A. Resveratrol supplementation and oxidative/anti-oxidative status in patients with ulcerative colitis: a randomized, double-blind, placebo-controlled pilot study. *Arch Med Res*. 2016;47(4):304–9.
1865. Samsami-Kor M, Daryani NE, Asl PR, Hekmatdoost A. Anti-inflammatory effects of resveratrol in patients with ulcerative colitis: a randomized, double-blind, placebo-controlled pilot study. *Arch Med Res*. 2015;46(4):280–5.
1866. Hussain SA, Marouf BH, Ali ZS, Ahmmad RS. Efficacy and safety of co-administration of resveratrol with meloxicam in patients with knee osteoarthritis: a pilot interventional study. *Clin Interv Aging*. 2018;13:1621–30.
1867. Qasem RJ. The estrogenic activity of resveratrol: a comprehensive review of *in vitro* and *in vivo* evidence and the potential for endocrine disruption. *Crit Rev Toxicol*. 2020;50(5):439–62.
1868. Dzator JSA, Howe PRC, Coupland KG, Wong RHX. A randomised, double-blind, placebo-controlled crossover trial of resveratrol supplementation for prophylaxis of hormonal migraine. *Nutrients*. 2022;14(9):1763.
1869. Mansour A, Samadi M, Sanginabadi M, et al. Effect of resveratrol on menstrual cyclicity, hyperandrogenism and metabolic profile in women with PCOS. *Clin Nutr*. 2021;40(6):4106–12.
1870. Zaw JJT, Howe PRC, Wong RHX. Long-term resveratrol supplementation improves pain perception, menopausal symptoms, and overall well-being in postmenopausal women: findings from a 24-month randomized, controlled, crossover trial. *Menopause*. 2020;28(1):40–9.
1871. Li Q, Yang G, Xu H, Tang S, Lee WYW. Effects of resveratrol supplementation on bone quality: a systematic review and meta-analysis of randomized controlled trials. *BMC Complement Med Ther*. 2021;21(1):214.

1872. Johnson JJ, Nihal M, Siddiqui IA, et al. Enhancing the bioavailability of resveratrol by combining it with piperine. *Mol Nutr Food Res*. 2011;55(8):1169–76.
1873. Smoliga JM, Blanchard O. Enhancing the delivery of resveratrol in humans: if low bioavailability is the problem, what is the solution? *Molecules*. 2014;19(11):17154–72.
1874. Gliemann L. What are the chances that resveratrol will be the drug of tomorrow? *Pharmacol Res*. 2018;129:139–40.
1875. Semba RD, Ferrucci L, Bartali B, et al. Resveratrol levels and all-cause mortality in older community-dwelling adults. *JAMA Intern Med*. 2014;174(7):1077–84.
1876. Wahab A, Gao K, Jia C, et al. Significance of resveratrol in clinical management of chronic diseases. *Molecules*. 2017;22(8):1329.
1877. Scribbans TD, Ma JK, Edgett BA, et al. Resveratrol supplementation does not augment performance adaptations or fibre-type-specific responses to high-intensity interval training in humans. *Appl Physiol Nutr Metab*. 2014;39(11):1305–13.
1878. Gliemann L, Schmidt JF, Olesen J, et al. Resveratrol blunts the positive effects of exercise training on cardiovascular health in aged men. *J Physiol*. 2013;591(Pt 20):5047–59.
1879. Meng X, Zhou J, Zhao CN, Gan RY, Li HB. Health benefits and molecular mechanisms of resveratrol: a narrative review. *Foods*. 2020;9(3):340.
1880. Dybkowska E, Sadowska A, Świderski F, Rakowska R, Wysocka K. The occurrence of resveratrol in foodstuffs and its potential for supporting cancer prevention and treatment. A review. *Rocz Panstw Zakl Hig*. 2018;69(1):5–14.
1881. Morris BJ. Seven sirtuins for seven deadly diseases of aging. *Free Radic Biol Med*. 2013;56:133–71.
1882. Lagouge M, Argmann C, Gerhart-Hines Z, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1α. *Cell*. 2006;127(6):1109–22.
1883. Timmers S, Konings E, Bilet L, et al. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. *Cell Metab*. 2011;14(5):612–22.

1884. Tang PCT, Ng YF, Ho S, Gyda M, Chan SW. Resveratrol and cardiovascular health—promising therapeutic or hopeless illusion? *Pharmacol Res*. 2014;90:88–115.
1885. Gliemann L, Olesen J, Biensø RS, et al. Reply from Lasse Gliemann, Jesper Olesen, Rasmus Sjørup Biensø, Stefan Peter Mortensen, Michael Nyberg, Jens Bangsbo, Henriette Pilegaard and Ylva Hellsten. *J Physiol*. 2014;592(Pt 3):553.
1886. Zhao L, Cao J, Hu K, et al. Sirtuins and their biological relevance in aging and age-related diseases. *Aging Dis*. 2020;11(4):927–45.
1887. Li D, Cui Y, Wang X, Liu F, Li X. Apple polyphenol extract alleviates lipid accumulation in free-fatty-acid-exposed HepG2 cells via activating autophagy mediated by SIRT1/AMPK signaling. *Phytother Res*. 2021;35(3):1416–31.
1888. Gayer BA, Avendano EE, Edelson E, Nirmala N, Johnson EJ, Raman G. Effects of intake of apples, pears, or their products on cardiometabolic risk factors and clinical outcomes: a systematic review and meta-analysis. *Curr Dev Nutr*. 2019;3(10):nzz109.
1889. Hodgson JM, Prince RL, Woodman RJ, et al. Apple intake is inversely associated with all-cause and disease-specific mortality in elderly women. *Br J Nutr*. 2016;115(5):860–7.
1890. Spiegelhalter D. Using speed of ageing and “microlives” to communicate the effects of lifetime habits and environment. *BMJ*. 2012;345:e8223.
1891. Xiang L, Sun K, Lu J, et al. Anti-aging effects of phloridzin, an apple polyphenol, on yeast *via* the SOD and Sir2 genes. *Biosci Biotechnol Biochem*. 2011;75(5):854–8.
1892. Peng C, Chan HYE, Huang Y, Yu H, Chen ZY. Apple polyphenols extend the mean lifespan of *Drosophila melanogaster*. *J Agric Food Chem*. 2011;59(5):2097–106.
1893. Shaposhnikov M, Latkin D, Plyusnina E, et al. The effects of pectins on life span and stress resistance in *Drosophila melanogaster*. *Biogerontology*. 2014;15(2):113–27.
1894. Palermo V, Mattivi F, Silvestri R, La Regina G, Falcone C, Mazzoni C. Apple can act as anti-aging on yeast cells. *Oxid Med Cell Longev*. 2012;2012:491759.

1895. Vayndorf EM, Lee SS, Liu RH. Whole apple extracts increase lifespan, healthspan and resistance to stress in *Caenorhabditis elegans*. *J Funct Foods*. 2013;5(3):1236–43.
1896. Sunagawa T, Shimizu T, Kanda T, Tagashira M, Sami M, Shirasawa T. Procyanidins from apples (*Malus pumila* Mill.) extend the lifespan of *Caenorhabditis elegans*. *Planta Med*. 2011;77(2):122–7.
1897. Song B, Wang H, Xia W, Zheng B, Li T, Liu RH. Combination of apple peel and blueberry extracts synergistically induced lifespan extension *via* DAF-16 in *Caenorhabditis elegans*. *Food Funct*. 2020;11(7):6170–85.
1898. Pallauf K, Giller K, Huebbe P, Rimbach G. Nutrition and healthy ageing: calorie restriction or polyphenol-rich "MediterrAsian" diet? *Oxid Med Cell Longev*. 2013;2013:707421.
1899. Wu X, Cao N, Fenech M, Wang X. Role of sirtuins in maintenance of genomic stability: relevance to cancer and healthy aging. *DNA Cell Biol*. 2016;35(10):542–75.
1900. Khazdouz M, Daryani NE, Alborzi F, et al. Effect of selenium supplementation on expression of SIRT1 and PGC-1α genes in ulcerative colitis patients: a double blind randomized clinical trial. *Clin Nutr Res*. 2020;9(4):284–95.
1901. Stranges S, Marshall JR, Natarajan R, et al. Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. *Ann Intern Med*. 2007;147(4):217–23.
1902. Fusi J, Bianchi S, Daniele S, et al. An in vitro comparative study of the antioxidant activity and SIRT1 modulation of natural compounds. *Biomed Pharmacother*. 2018;101:805–19.
1903. Yang Y, Duan W, Lin Y, et al. SIRT1 activation by curcumin pretreatment attenuates mitochondrial oxidative damage induced by myocardial ischemia reperfusion injury. *Free Radic Biol Med*. 2013;65:667–79.
1904. Heshmati J, Golab F, Morvaridzadeh M, et al. The effects of curcumin supplementation on oxidative stress, Sirtuin-1 and peroxisome proliferator activated receptor γ coactivator 1α gene expression in polycystic ovarian syndrome (PCOS) patients: a randomized placebo-controlled clinical trial. *Diabetes Metab Syndr*. 2020;14(2):77–82.

1905. Daneshi-Maskooni M, Keshavarz SA, Qorbani M, et al. Green cardamom supplementation improves serum irisin, glucose indices, and lipid profiles in overweight or obese non-alcoholic fatty liver disease patients: a double-blind randomized placebo-controlled clinical trial. *BMC Complement Altern Med*. 2019;19(1):59.
1906. Daneshi-Maskooni M, Keshavarz SA, Qorbani M, et al. Green cardamom increases Sirtuin-1 and reduces inflammation in overweight or obese patients with non-alcoholic fatty liver disease: a double-blind randomized placebo-controlled clinical trial. *Nutr Metab (Lond)*. 2018;15:63.
1907. Zhong Y, Chen AF, Zhao J, Gu YJ, Fu GX. Serum levels of cathepsin D, sirtuin1, and endothelial nitric oxide synthase are correlatively reduced in elderly healthy people. *Aging Clin Exp Res*. 2016;28(4):641–5.
1908. Kumar R, Mohan N, Upadhyay AD, et al. Identification of serum sirtuins as novel noninvasive protein markers for frailty. *Aging Cell*. 2014;13(6):975–80.
1909. Kumar R, Chaterjee P, Sharma PK, et al. Sirtuin1: a promising serum protein marker for early detection of Alzheimer's disease. *PLoS One*. 2013;8(4):e61560.
1910. Yanagisawa S, Papaioannou AI, Papaporfyriou A, et al. Decreased serum sirtuin-1 in COPD. *Chest*. 2017;152(2):343–52.
1911. Kazemi S, Yaghooblou F, Siassi F, et al. Cardamom supplementation improves inflammatory and oxidative stress biomarkers in hyperlipidemic, overweight, and obese pre-diabetic women: a randomized double-blind clinical trial. *J Sci Food Agric*. 2017;97(15):5296–301.
1912. Shekarchizadeh-Esfahani P, Arab A, Ghaedi E, Hadi A, Jalili C. Effects of cardamom supplementation on lipid profile: a systematic review and meta-analysis of randomized controlled clinical trials. *Phytother Res*. 2020;34(3):475–85.
1913. Daneshi-Maskooni M, Keshavarz SA, Qorbani M, et al. Green cardamom supplementation improves serum irisin, glucose indices, and lipid profiles in overweight or obese non-alcoholic fatty liver disease patients: a double-blind randomized placebo-controlled clinical trial. *BMC Complement Altern Med*. 2019;19(1):59.

1914. Rajendrasozhan S, Yang SR, Kinnula VL, Rahman I. SIRT1, an antiinflammatory and antiaging protein, is decreased in lungs of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2008;177(8):861–70.
1915. Caito S, Rajendrasozhan S, Cook S, et al. SIRT1 is a redox-sensitive deacetylase that is post-translationally modified by oxidants and carbonyl stress. *FASEB J*. 2010;24(9):3145–59.
1916. Cai W, Uribarri J, Zhu L, et al. Oral glycotoxins are a modifiable cause of dementia and the metabolic syndrome in mice and humans. *Proc Natl Acad Sci U S A*. 2014;111(13):4940–5.
1917. Rizzi L, Roriz-Cruz M. Sirtuin 1 and Alzheimer's disease: an up-to-date review. *Neuropeptides*. 2018;71:54–60.
1918. Cai W, Uribarri J, Zhu L, et al. Oral glycotoxins are a modifiable cause of dementia and the metabolic syndrome in mice and humans. *Proc Natl Acad Sci U S A*. 2014;111(13):4940–5.
1919. Potthast AB, Nebl J, Wasserfurth P, et al. Impact of nutrition on short-term exercise-induced sirtuin regulation: vegans differ from omnivores and lacto-ovo vegetarians. *Nutrients*. 2020;12(4):1004.
1920. Brenner C. Sirtuins are not conserved longevity genes. *Life Metabolism*. Published online September 22, 2022. https://academic.oup.com/lifemeta/advance-article/doi/10.1093/lifemeta/loac025/6711379. Accessed December 27, 2022.
1921. Boccardi V, Mecocci P. Telomerase activation and human health-span: an open issue. *Aging Clin Exp Res*. 2018;30(2):221–3.
1922. Shay JW, Wright WE. Telomeres and telomerase: three decades of progress. *Nat Rev Genet*. 2019;20(5):299–309.
1923. Herrmann W, Herrmann M. The importance of telomere shortening for atherosclerosis and mortality. *J Cardiovasc Dev Dis*. 2020;7(3):29.
1924. Serrano M, Blasco MA. Cancer and ageing: convergent and divergent mechanisms. *Nat Rev Mol Cell Biol*. 2007;8(9):715–22.
1925. Bonafè M, Sabbatinelli J, Olivieri F. Exploiting the telomere machinery to put the brakes on inflamm-aging. *Ageing Res Rev*. 2020;59:101027.

1926. Stone RC, Horvath K, Kark JD, Susser E, Tishkoff SA, Aviv A. Telomere length and the cancer–atherosclerosis trade-off. *PLoS Genet*. 2016;12(7):e1006144.
1927. Shay JW, Wright WE. Telomeres and telomerase: three decades of progress. *Nat Rev Genet*. 2019;20(5):299–309.
1928. Saretzki G. Telomeres, telomerase and ageing. *Subcell Biochem*. 2018;90:221–308.
1929. Rizvi S, Raza ST, Mahdi F. Telomere length variations in aging and age-related diseases. *Curr Aging Sci*. 2014;7(3):161–7.
1930. Wang J, Liu Y, Xia Q, et al. Potential roles of telomeres and telomerase in neurodegenerative diseases. *Int J Biol Macromol*. 2020;163:1060–78.
1931. Leung CW, Laraia BA, Needham BL, et al. Soda and cell aging: associations between sugar-sweetened beverage consumption and leukocyte telomere length in healthy adults from the National Health and Nutrition Examination Surveys. *Am J Public Health*. 2014;104(12):2425–31.
1932. Huang Z, Liu C, Ruan Y, et al. Dynamics of leukocyte telomere length in adults aged 50 and older: a longitudinal population-based cohort study. *GeroScience*. 2021;43(2):645–54.
1933. Prieto-Oliveira P. Telomerase activation in the treatment of aging or degenerative diseases: a systematic review. *Mol Cell Biochem*. 2021;476(2):599–607.
1934. Zhou J, Wang J, Shen Y, et al. The association between telomere length and frailty: a systematic review and meta-analysis. *Exp Gerontol*. 2018;106:16–20.
1935. Cohen S, Janicki-Deverts D, Turner RB, et al. Association between telomere length and experimentally induced upper respiratory viral infection in healthy adults. *JAMA*. 2013;309(7):699–705.
1936. Zhan Y, Clements MS, Roberts RO, et al. Association of telomere length with general cognitive trajectories: a meta-analysis of four prospective cohort studies. *Neurobiol Aging*. 2018;69:111–6.
1937. Smith L, Luchini C, Demurtas J, et al. Telomere length and health outcomes: an umbrella review of systematic reviews and meta-analyses of observational studies. *Ageing Res Rev*. 2019;51:1–10.

1938. Herrmann W, Herrmann M. The importance of telomere shortening for atherosclerosis and mortality. *J Cardiovasc Dev Dis*. 2020;7(3):29.
1939. Zhan Y, Liu XR, Reynolds CA, Pedersen NL, Hägg S, Clements MS. Leukocyte telomere length and all-cause mortality: a between-within twin study with time-dependent effects using generalized survival models. *Am J Epidemiol.* 2018;187(10):2186–91.
1940. Christensen K, Thinggaard M, McGue M, et al. Perceived age as clinically useful biomarker of ageing: cohort study. *BMJ*. 2009;339:b5262.
1941. Christensen K, Thinggaard M, McGue M, et al. Perceived age as clinically useful biomarker of ageing: cohort study. *BMJ*. 2009;339:b5262.
1942. Zhan Y, Hägg S. Association between genetically predicted telomere length and facial skin aging in the UK Biobank: a Mendelian randomization study. *GeroScience*. 2021;43(3):1519–25.
1943. Astuti Y, Wardhana A, Watkins J, Wulaningsih W. Cigarette smoking and telomere length: a systematic review of 84 studies and meta-analysis. *Environ Res*. 2017;158:480–9.
1944. Aviv A, Shay JW. Reflections on telomere dynamics and ageing-related diseases in humans. *Philos Trans R Soc Lond B Biol Sci*. 2018;373(1741):20160436.
1945. Whittemore K, Vera E, Martínez-Nevado E, Sanpera C, Blasco MA. Telomere shortening rate predicts species life span. *Proc Natl Acad Sci U S A*. 2019;116(30):15122–7.
1946. Fick LJ, Fick GH, Li Z, et al. Telomere length correlates with life span of dog breeds. *Cell Rep*. 2012;2(6):1530–6.
1947. Muñoz-Lorente MA, Cano-Martin AC, Blasco MA. Mice with hyper-long telomeres show less metabolic aging and longer lifespans. *Nat Commun*. 2019;10(1):4723.
1948. Blackburn EH, Epel ES, Lin J. Human telomere biology: a contributory and interactive factor in aging, disease risks, and protection. *Science*. 2015;350(6265):1193–8.
1949. Zhu Y, Liu X, Ding X, Wang F, Geng X. Telomere and its role in the aging pathways: telomere shortening, cell senescence and mitochondria dysfunction. *Biogerontology*. 2019;20(1):1–16.

1950. Blackburn EH, Epel ES, Lin J. Human telomere biology: a contributory and interactive factor in aging, disease risks, and protection. *Science*. 2015;350(6265):1193–8.
1951. Tsuji A, Ishiko A, Takasaki T, Ikeda N. Estimating age of humans based on telomere shortening. *Forensic Sci Int*. 2002;126(3):197–9.
1952. Huang Z, Liu C, Ruan Y, et al. Dynamics of leukocyte telomere length in adults aged 50 and older: a longitudinal population-based cohort study. *GeroScience*. 2021;43(2):645–54.
1953. Blackburn EH. Telomeres and telomerase: the means to the end (Nobel lecture). *Angew Chemie Int Ed Engl*. 2010;49(41):7405–21.
1954. Laberthonnière C, Magdinier F, Robin JD. Bring it to an end: does telomeres size matter? *Cells*. 2019;8(1):30.
1955. Saretzki G. Telomeres, telomerase and ageing. *Subcell Biochem*. 2018;90:221–308.
1956. Boccardi V, Mecocci P. Telomerase activation and human health-span: an open issue. *Aging Clin Exp Res*. 2018;30(2):221–3.
1957. Flanary BE, Kletetschka G. Analysis of telomere length and telomerase activity in tree species of various life-spans, and with age in the bristlecone pine Pinus longaeva. *Biogerontology*. 2005;6(2):101–11.
1958. Wright WE, Piatyszek MA, Rainey WE, Byrd W, Shay JW. Telomerase activity in human germline and embryonic tissues and cells. *Dev Genet.* 1996;18(2):173–9.
1959. Shay JW, Bacchetti S. A survey of telomerase activity in human cancer. *Eur J Cancer*. 1997;33(5):787–91.
1960. Lulkiewicz M, Bajsert J, Kopczynski P, Barczak W, Rubis B. Telomere length: how the length makes a difference. *Mol Biol Rep*. 2020;47(9):7181–8.
1961. Huang Z, Liu C, Ruan Y, et al. Dynamics of leukocyte telomere length in adults aged 50 and older: a longitudinal population-based cohort study. *GeroScience*. 2021;43(2):645–54.
1962. Chen W, Kimura M, Kim S, et al. Longitudinal versus cross-sectional evaluations of leukocyte telomere length dynamics: age-dependent telomere shortening is the rule. *J Gerontol A Biol Sci Med Sci.* 2011;66(3):312–9.

1963. Epel ES, Merkin SS, Cawthon R, et al. The rate of leukocyte telomere shortening predicts mortality from cardiovascular disease in elderly men. *Aging (Albany NY)*. 2008;1(1):81–8.
1964. Tedone E, Arosio B, Gussago C, et al. Leukocyte telomere length and prevalence of age-related diseases in semisupercentenarians, centenarians and centenarians' offspring. *Exp Gerontol*. 2014;58:90–5.
1965. Tedone E, Huang E, O'Hara R, et al. Telomere length and telomerase activity in T cells are biomarkers of high-performing centenarians. *Aging Cell*. 2019;18(1):e12859.
1966. Kamal S, Junaid M, Ejaz A, Bibi I, Akash MSH, Rehman K. The secrets of telomerase: retrospective analysis and future prospects. *Life Sci*. 2020;257:118115.
1967. Boccardi V, Paolisso G. Telomerase activation: a potential key modulator for human healthspan and longevity. *Ageing Res Rev*. 2014;15:1–5.
1968. Bär C, Blasco MA. Telomeres and telomerase as therapeutic targets to prevent and treat age-related diseases. *F1000Res*. 2016;5:89.
1969. Tomás-Loba A, Flores I, Fernández-Marcos PJ, et al. Telomerase reverse transcriptase delays aging in cancer-resistant mice. *Cell*. 2008;135(4):609–22.
1970. Bernardes de Jesus B, Vera E, Schneeberger K, et al. Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer. *EMBO Mol Med*. 2012;4(8):691–704.
1971. Bär C, Bernardes de Jesus B, Serrano R, et al. Telomerase expression confers cardioprotection in the adult mouse heart after acute myocardial infarction. *Nat Commun*. 2014;5:5863.
1972. Rudolph KL, Chang S, Millard M, Schreiber-Agus N, DePinho RA. Inhibition of experimental liver cirrhosis in mice by telomerase gene delivery. *Science*. 2000;287(5456):1253–8.
1973. Bär C, Bernardes de Jesus B, Serrano R, et al. Telomerase expression confers cardioprotection in the adult mouse heart after acute myocardial infarction. *Nat Commun*. 2014;5:5863.
1974. Bernardes de Jesus B, Vera E, Schneeberger K, et al. Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer. *EMBO Mol Med*. 2012;4(8):691–704.

1975. Eitan E, Tichon A, Gazit A, Gitler D, Slavin S, Priel E. Novel telomerase-increasing compound in mouse brain delays the onset of amyotrophic lateral sclerosis. *EMBO Mol Med*. 2012;4(4):313–29.
1976. Gilson E, Ségal-Bendirdjian E. The telomere story or the triumph of an open-minded research. *Biochimie*. 2010;92(4):321–6.
1977. Suram A, Herbig U. The replicometer is broken: telomeres activate cellular senescence in response to genotoxic stresses. *Aging Cell*. 2014;13(5):780–6.
1978. Shay JW, Wright WE. Telomeres and telomerase: three decades of progress. *Nat Rev Genet*. 2019;20(5):299–309.
1979. Hornsby PJ. Telomerase and the aging process. *Exp Gerontol*. 2007;42(7):575–81.
1980. Bodnar AG, Ouellette M, Frolkis M, et al. Extension of life-span by introduction of telomerase into normal human cells. *Science*. 1998;279(5349):349–52.
1981. Bernardes de Jesus B, Vera E, Schneeberger K, et al. Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer. *EMBO Mol Med*. 2012;4(8):691–704.
1982. Huang Z, Liu C, Ruan Y, et al. Dynamics of leukocyte telomere length in adults aged 50 and older: a longitudinal population-based cohort study. *GeroScience*. 2021;43(2):645–54.
1983. Broer L, Codd V, Nyholt DR, et al. Meta-analysis of telomere length in 19713 subjects reveals high heritability, stronger maternal inheritance and a paternal age effect. *Eur J Hum Genet*. 2013;21(10):1163–8.
1984. Maugeri A, Barchitta M, Magnano San Lio R, et al. The effect of alcohol on telomere length: a systematic review of epidemiological evidence and a pilot study during pregnancy. *Int J Environ Res Public Health*. 2021;18(9):5038.
1985. Ip P, Chung BHY, Ho FKW, et al. Prenatal tobacco exposure shortens telomere length in children. *Nicotine Tob Res*. 2017;19(1):111–8.
1986. Zhao B, Vo HQ, Johnston FH, Negishi K. Air pollution and telomere length: a systematic review of 12,058 subjects. *Cardiovasc Diagn Ther*. 2018;8(4):480–92.
1987. Aviv A, Shay JW. Reflections on telomere dynamics and ageing-related diseases in humans. *Philos Trans R Soc Lond B Biol Sci*.

2018;373(1741):20160436.
1988. Galiè S, Canudas S, Muralidharan J, García-Gavilán J, Bulló M, Salas-Salvadó J. Impact of nutrition on telomere health: systematic review of observational cohort studies and randomized clinical trials. *Adv Nutr*. 2020;11(3):576–601.
1989. Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. *Lancet.* 1990;336(8708):129–33.
1990. Ornish D, Weidner G, Fair WR, et al. Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol*. 2005;174(3):1065–70.
1991. U.S. National Library of Medicine. Can lifestyle changes reverse early-stage Alzheimer's disease. ClincalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04606420. Updated October 28, 2020. Accessed July 17, 2021.
1992. Ornish D, Lin J, Daubenmier J, et al. Increased telomerase activity and comprehensive lifestyle changes: a pilot study. *Lancet Oncol*. 2008;9(11):1048–57.
1993. Ornish D, Lin J, Daubenmier J, et al. Increased telomerase activity and comprehensive lifestyle changes: a pilot study. *Lancet Oncol*. 2008;9(11):1048–57.
1994. Skordalakes E. Telomerase and the benefits of healthy living. *Lancet Oncol*. 2008;9(11):1023–4.
1995. Ornish D, Lin J, Chan JM, et al. Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. *Lancet Oncol*. 2013;14(11):1112–20.
1996. Blackburn EH, Epel ES. Too toxic to ignore. *Nature*. 2012;490(7419):169–71.
1997. Epel ES, Lin J, Dhabhar FS, et al. Dynamics of telomerase activity in response to acute psychological stress. *Brain Behav Immun*. 2010;24(4):531–9.
1998. Damjanovic AK, Yang Y, Glaser R, et al. Accelerated telomere erosion is associated with a declining immune function of caregivers of Alzheimer's disease patients. *J Immunol*. 2007;179(6):4249–54.

1999. Schutte NS, Malouff JM, Keng SL. Meditation and telomere length: a meta-analysis. *Psychol Health*. 2020;35(8):901–15.
2000. Cherkas LF, Hunkin JL, Kato BS, et al. The association between physical activity in leisure time and leukocyte telomere length. *Arch Intern Med*. 2008;168(2):154–8.
2001. Tucker LA. Walking and biologic ageing: evidence based on NHANES telomere data. *J Sports Sci*. 2020;38(9):1026–35.
2002. Lin X, Zhou J, Dong B. Effect of different levels of exercise on telomere length: A systematic review and meta-analysis. *J Rehabil Med*. 2019;51(7):473–8.
2003. Mundstock E, Zatti H, Louzada FM, et al. Effects of physical activity in telomere length: Systematic review and meta-analysis. *Ageing Res Rev*. 2015;22:72–80.
2004. Abrahin O, Cortinhas-Alves EA, Vieira RP, Guerreiro JF. Elite athletes have longer telomeres than sedentary subjects: a meta-analysis. *Exp Gerontol*. 2019;119:138–45.
2005. Aguiar SS, Sousa CV, Santos PA, et al. Master athletes have longer telomeres than age-matched non-athletes. A systematic review, meta-analysis and discussion of possible mechanisms. *Exp Gerontol*. 2021;146:111212.
2006. Denham J, Nelson CP, O'Brien BJ, et al. Longer leukocyte telomeres are associated with ultra-endurance exercise independent of cardiovascular risk factors. *PLoS One*. 2013;8(7):e69377.
2007. Werner C, Fürster T, Widmann T, et al. Physical exercise prevents cellular senescence in circulating leukocytes and in the vessel wall. *Circulation*. 2009;120(24):2438–47.
2008. Friedenreich CM, Wang Q, Ting NS, et al. Effect of a 12-month exercise intervention on leukocyte telomere length: results from the ALPHA Trial. *Cancer Epidemiol*. 2018;56:67–74.
2009. Sjögren P, Fisher R, Kallings L, Svenson U, Roos G, Hellénius ML. Stand up for health—avoiding sedentary behaviour might lengthen your telomeres: secondary outcomes from a physical activity RCT in older people. *Br J Sports Med*. 2014;48(19):1407–9.
2010. Mason C, Risques RA, Xiao L, et al. Independent and combined effects of dietary weight loss and exercise on leukocyte telomere

length in postmenopausal women. *Obesity (Silver Spring)*. 2013;21(12):E549–54.

2011. Werner CM, Hecksteden A, Morsch A, et al. Differential effects of endurance, interval, and resistance training on telomerase activity and telomere length in a randomized, controlled study. *Eur Heart J*. 2019;40(1):34–46.

2012. Werner CM, Hecksteden A, Morsch A, et al. Differential effects of endurance, interval, and resistance training on telomerase activity and telomere length in a randomized, controlled study. *Eur Heart J*. 2019;40(1):34–46.

2013. To-Miles FYL, Backman CL. What telomeres say about activity and health: a rapid review. *Can J Occup Ther*. 2016;83(3):143–53.

2014. Mason C, Risques RA, Xiao L, et al. Independent and combined effects of dietary weight loss and exercise on leukocyte telomere length in postmenopausal women. *Obesity (Silver Spring)*. 2013;21(12):E549–54.

2015. Himbert C, Thompson H, Ulrich CM. Effects of intentional weight loss on markers of oxidative stress, DNA repair and telomere length —a systematic review. *Obes Facts*. 2017;10(6):648–65.

2016. Ornish D, Lin J, Daubenmier J, et al. Increased telomerase activity and comprehensive lifestyle changes: a pilot study. *Lancet Oncol*. 2008;9(11):1048–57.

2017. Ornish D, Lin J, Chan JM, et al. Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. *Lancet Oncol*. 2013;14(11):1112–20.

2018. Lulkiewicz M, Bajsert J, Kopczynski P, Barczak W, Rubis B. Telomere length: how the length makes a difference. *Mol Biol Rep*. 2020;47(9):7181–8.

2019. Prieto-Oliveira P. Telomerase activation in the treatment of aging or degenerative diseases: a systematic review. *Mol Cell Biochem*. 2021;476(2):599–607.

2020. De Meyer T, Bekaert S, De Buyzere ML, et al. Leukocyte telomere length and diet in the apparently healthy, middle-aged Asklepios population. *Sci Rep*. 2018;8(1):6540.

2021. Tucker LA. Milk fat intake and telomere length in U.S. women and men: the role of the milk fat fraction. *Oxid Med Cell Longev.* 2019;2019:1574021.
2022. Marin C, Delgado-Lista J, Ramirez R, et al. Mediterranean diet reduces senescence-associated stress in endothelial cells. *Age (Dordr)*. 2012;34(6):1309–16.
2023. Alonso-Pedrero L, Ojeda-Rodríguez A, Martínez-González MA, Zalba G, Bes-Rastrollo M, Marti A. Ultra-processed food consumption and the risk of short telomeres in an elderly population of the Seguimiento Universidad de Navarra (SUN) Project. *Am J Clin Nutr*. 2020;111(6):1259–66.
2024. Askari M, Heshmati J, Shahinfar H, Tripathi N, Daneshzad E. Ultra-processed food and the risk of overweight and obesity: a systematic review and meta-analysis of observational studies. *Int J Obes (Lond).* 2020;44(10):2080–91.
2025. Pagliai G, Dinu M, Madarena MP, Bonaccio M, Iacoviello L, Sofi F. Consumption of ultra-processed foods and health status: a systematic review and meta-analysis. *Br J Nutr*. 2021;125(3):308–18.
2026. Strandberg TE, Strandberg AY, Saijonmaa O, Tilvis RS, Pitkälä KH, Fyhrquist F. Association between alcohol consumption in healthy midlife and telomere length in older men. The Helsinki Businessmen Study. *Eur J Epidemiol*. 2012;27(10):815–22.
2027. Maugeri A, Barchitta M, Magnano San Lio R, et al. The effect of alcohol on telomere length: a systematic review of epidemiological evidence and a pilot study during pregnancy. *Int J Environ Res Public Health*. 2021;18(9):5038.
2028. Huang Y, Cao D, Chen Z, et al. Red and processed meat consumption and cancer outcomes: umbrella review. *Food Chem*. 2021;356:129697.
2029. Fretts AM, Howard BV, Siscovick DS, et al. Processed meat, but not unprocessed red meat, is inversely associated with leukocyte telomere length in the Strong Heart Family Study. *J Nutr*. 2016;146(10):2013–8.
2030. De Meyer T, Bekaert S, De Buyzere ML, et al. Leukocyte telomere length and diet in the apparently healthy, middle-aged Asklepios population. *Sci Rep*. 2018;8(1):6540.

2031. Nettleton JA, Diez-Roux A, Jenny NS, Fitzpatrick AL, Jacobs DR Jr. Dietary patterns, food groups, and telomere length in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Clin Nutr*. 2008;88(5):1405–12.
2032. Galiè S, Canudas S, Muralidharan J, García-Gavilán J, Bulló M, Salas-Salvadó J. Impact of nutrition on telomere health: systematic review of observational cohort studies and randomized clinical trials. *Adv Nutr*. 2020;11(3):576–601.
2033. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8):1689–96.
2034. Farzaneh-Far R, Lin J, Epel ES, Harris WS, Blackburn EH, Whooley MA. Association of marine omega-3 fatty acid levels with telomeric aging in patients with coronary heart disease. *JAMA*. 2010;303(3):250.
2035. Pawełczyk T, Grancow-Grabka M, Trafalska E, Szemraj J, Żurner N, Pawełczyk A. Telomerase level increase is related to n-3 polyunsaturated fatty acid efficacy in first episode schizophrenia: secondary outcome analysis of the OFFER randomized clinical trial. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;83:142–8.
2036. O'Callaghan N, Parletta N, Milte CM, Benassi-Evans B, Fenech M, Howe PRC. Telomere shortening in elderly individuals with mild cognitive impairment may be attenuated with ω-3 fatty acid supplementation: a randomized controlled pilot study. *Nutrition*. 2014;30(4):489–91.
2037. Holub A, Mousa S, Abdolahi A, et al. The effects of aspirin and N-3 fatty acids on telomerase activity in adults with diabetes mellitus. *Nutr Metab Cardiovasc Dis*. 2020;30(10):1795–9.
2038. Kiecolt-Glaser JK, Epel ES, Belury MA, et al. Omega-3 fatty acids, oxidative stress, and leukocyte telomere length: a randomized controlled trial. *Brain Behav Immun*. 2013;28:16–24.
2039. Barden A, O'Callaghan N, Burke V, et al. *n*–3 fatty acid supplementation and leukocyte telomere length in patients with chronic kidney disease. *Nutrients*. 2016;8(3):175.
2040. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary

inflammatory index. *Public Health Nutr*. 2014;17(8):1689–96.
2041. Pitkänen N, Pahkala K, Rovio SP, et al. Effects of randomized controlled infancy-onset dietary intervention on leukocyte telomere length—the Special Turku Coronary Risk Factor Intervention Project (STRIP). *Nutrients*. 2021;13(2):318.
2042. Marin C, Delgado-Lista J, Ramirez R, et al. Mediterranean diet reduces senescence-associated stress in endothelial cells. *Age (Dordr)*. 2012;34(6):1309–16.
2043. Canudas S, Becerra-Tomás N, Hernández-Alonso P, et al. Mediterranean diet and telomere length: a systematic review and meta-analysis. *Adv Nutr*. 2020;11(6):1544–54.
2044. Tucker LA. Milk fat intake and telomere length in U.S. women and men: the role of the milk fat fraction. *Oxid Med Cell Longev.* 2019;2019:e1574021.
2045. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8):1689–96.
2046. Tucker LA. Dietary fiber and telomere length in 5674 U.S. adults: an NHANES study of biological aging. *Nutrients*. 2018;10(4):400.
2047. Fretts AM, Howard BV, Siscovick DS, et al. Processed meat, but not unprocessed red meat, is inversely associated with leukocyte telomere length in the Strong Heart Family Study. *J Nutr*. 2016;146(10):2013–8.
2048. Leung CW, Laraia BA, Needham BL, et al. Soda and cell aging: associations between sugar-sweetened beverage consumption and leukocyte telomere length in healthy adults from the National Health and Nutrition Examination Surveys. *Am J Public Health*. 2014;104(12):2425–31.
2049. Valdes AM, Andrew T, Gardner JP, et al. Obesity, cigarette smoking, and telomere length in women. *Lancet*. 2005;366(9486):662–4.
2050. Institute of Medicine. Dietary Reference Intakes: Proposed Definition of Dietary Fiber. National Academies Press; 2001.
2051. Xu Q, Parks CG, DeRoo LA, Cawthon RM, Sandler DP, Chen H. Multivitamin use and telomere length in women. *Am J Clin Nutr*. 2009;89(6):1857–63.

2052. Min KB, Min JY. Association between leukocyte telomere length and serum carotenoid in US adults. *Eur J Nutr*. 2017;56(3):1045–52.
2053. Liu JJ, Crous-Bou M, Giovannucci E, De Vivo I. Coffee consumption is positively associated with longer leukocyte telomere length in the Nurses' Health Study. *J Nutr*. 2016;146(7):1373–8.
2054. Tucker LA. Caffeine consumption and telomere length in men and women of the National Health and Nutrition Examination Survey (NHANES). *Nutr Metab (Lond)*. 2017;14(1):10.
2055. Freitas-Simoes TM, Ros E, Sala-Vila A. Telomere length as a biomarker of accelerated aging: is it influenced by dietary intake? *Curr Opin Clin Nutr Metab Care*. 2018;21(6):430–6.
2056. Chan R, Woo J, Suen E, Leung J, Tang N. Chinese tea consumption is associated with longer telomere length in elderly Chinese men. *Br J Nutr*. 2010;103(1):107–13.
2057. Sheng R, Gu ZL, Xie ML. Epigallocatechin gallate, the major component of polyphenols in green tea, inhibits telomere attrition mediated cardiomyocyte apoptosis in cardiac hypertrophy. *Int J Cardiol*. 2013;162(3):199–209.
2058. Rusak G, Komes D, Likić S, Horžić D, Kovač M. Phenolic content and antioxidative capacity of green and white tea extracts depending on extraction conditions and the solvent used. *Food Chem*. 2008;110(4):852–8.
2059. Hovanloo F, Fallah Huseini H, Hedayati M, Teimourian M. Effects of aerobic training combined with green tea extract on leukocyte telomere length, quality of life and body composition in elderly women. *J Med Plants.* 2016;15(59):47–57.
2060. Tran HTT, Schreiner M, Schlotz N, Lamy E. Short-term dietary intervention with cooked but not raw *Brassica* leafy vegetables increases telomerase activity in CD8+ lymphocytes in a randomized human trial. *Nutrients*. 2019;11(4):786.
2061. Sarma DN, Barrett ML, Chavez ML, et al. Safety of green tea extracts: a systematic review by the US Pharmacopeia. *Drug Saf.* 2008;31(6):469–84.
2062. Yu Z, Samavat H, Dostal AM, et al. Effect of green tea supplements on liver enzyme elevation: results from a randomized intervention

study in the United States. *Cancer Prev Res (Phila).* 2017;10(10):571–9.
2063. Hu J, Webster D, Cao J, Shao A. The safety of green tea and green tea extract consumption in adults—results of a systematic review. *Regul Toxicol Pharmacol.* 2018;95:412–33.
2064. O'Callaghan N, Parletta N, Milte CM, Benassi-Evans B, Fenech M, Howe PRC. Telomere shortening in elderly individuals with mild cognitive impairment may be attenuated with ω-3 fatty acid supplementation: a randomized controlled pilot study. *Nutrition*. 2014;30(4):489–91.
2065. Holub A, Mousa S, Abdolahi A, et al. The effects of aspirin and N-3 fatty acids on telomerase activity in adults with diabetes mellitus. *Nutr Metab Cardiovasc Dis*. 2020;30(10):1795–9.
2066. Kiecolt-Glaser JK, Epel ES, Belury MA, et al. Omega-3 fatty acids, oxidative stress, and leukocyte telomere length: a randomized controlled trial. *Brain Behav Immun*. 2013;28:16–24.
2067. Barden A, O'Callaghan N, Burke V, et al. *n*–3 fatty acid supplementation and leukocyte telomere length in patients with chronic kidney disease. *Nutrients*. 2016;8(3):175.
2068. García-Calzón S, Martínez-González MA, Razquin C, et al. Mediterranean diet and telomere length in high cardiovascular risk subjects from the PREDIMED-NAVARRA study. *Clin Nutr*. 2016;35(6):1399–405.
2069. Pusceddu I, Herrmann M, Kirsch SH, et al. Prospective study of telomere length and LINE-1 methylation in peripheral blood cells: the role of B vitamins supplementation. *Eur J Nutr*. 2016;55(5):1863–73.
2070. Sharif R, Thomas P, Zalewski P, Fenech M. Zinc supplementation influences genomic stability biomarkers, antioxidant activity, and zinc transporter genes in an elderly Australian population with low zinc status. *Mol Nutr Food Res*. 2015;59(6):1200–12.
2071. Zarei M, Zarezadeh M, Hamedi Kalajahi F, Javanbakht MH. The relationship between vitamin D and telomere/telomerase: a comprehensive review. *J Frailty Aging*. 2021;10(1):2–9.
2072. Zhu H, Guo D, Li K, et al. Increased telomerase activity and vitamin D supplementation in overweight African Americans. *Int J Obes (Lond)*. 2012;36(6):805–9.

2073. Yang T, Wang H, Xiong Y, et al. Vitamin D supplementation improves cognitive function through reducing oxidative stress regulated by telomere length in older adults with mild cognitive impairment: a 12-month randomized controlled trial. *J Alzheimers Dis*. 2020;78(4):1509–18.
2074. Guo Z, Lou Y, Kong M, Luo Q, Liu Z, Wu J. A systematic review of phytochemistry, pharmacology and pharmacokinetics on *Astragali* radix: implications for *Astragali* radix as a personalized medicine. *Int J Mol Sci*. 2019;20(6):1463.
2075. Liu P, Zhao H, Luo Y. Anti-aging implications of *Astragalus membranaceus* (Huangqi): a well-known Chinese tonic. *Aging Dis*. 2017;8(6):868–86.
2076. Fauce SR, Jamieson BD, Chin AC, et al. Telomerase-based pharmacologic enhancement of antiviral function of human $CD8^+$ T lymphocytes. *J Immunol*. 2008;181(10):7400–6.
2077. Dow CT, Harley CB. Evaluation of an oral telomerase activator for early age-related macular degeneration—a pilot study. *Clin Ophthalmol*. 2016;10:243–9.
2078. United States of America before the Federal Trade Commission in the matter of Telomerase Activation Sciences, Inc., and Noel Thomas Patton. Docket No. C-4644. FTC.gov. https://www.ftc.gov/system/files/documents/cases/142_3103_-_telomerase_complaint_final.pdf. Updated April 19, 2018. Accessed December10, 2021.
2079. Tsoukalas D, Fragkiadaki P, Docea AO, et al. Discovery of potent telomerase activators: unfolding new therapeutic and anti-aging perspectives. *Mol Med Rep*. 2019;20(4):3701–8.
2080. Tsoukalas D, Fragkiadaki P, Docea AO, et al. Discovery of potent telomerase activators: unfolding new therapeutic and anti-aging perspectives. *Mol Med Rep*. 2019;20(4):3701–8.
2081. Chandrika UG, Kumara PAASP. Gotu kola (*Centella asiatica*): nutritional properties and plausible health benefits. *Adv Food Nutr Res*. 2015;76:125–57.
2082. Tsoukalas D, Fragkiadaki P, Docea AO, et al. Discovery of potent telomerase activators: unfolding new therapeutic and anti-aging perspectives. *Mol Med Rep*. 2019;20(4):3701–8.

2083. Puttarak P, Dilokthornsakul P, Saokaew S, et al. Effects of *Centella asiatica* (L.) Urb. on cognitive function and mood related outcomes: a systematic review and meta-analysis. *Sci Rep*. 2017;7(1):10646.
2084. Larrick JW, Mendelsohn AR. Telomerase redux: ready for prime time? *Rejuvenation Res*. 2015;18(2):185–7.
2085. Shammas MA. Telomeres, lifestyle, cancer, and aging. *Curr Opin Clin Nutr Metab Care*. 2011;14(1):28–34.
2086. Prieto-Oliveira P. Telomerase activation in the treatment of aging or degenerative diseases: a systematic review. *Mol Cell Biochem*. 2021;476(2):599–607.
2087. Artandi SE, Depinho RA. Telomeres and telomerase in cancer. *Carcinogenesis*. 2010;31(1):9–18.
2088. Ornish D, Weidner G, Fair WR, et al. Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol*. 2005;174(3):1065–70.
2089. Skordalakes E. Telomerase and the benefits of healthy living. *Lancet Oncol*. 2008;9(11):1023–4.
2090. Huzen J, Wong LS, van Veldhuisen DJ, et al. Telomere length loss due to smoking and metabolic traits. *J Intern Med*. 2014;275(2):155–63.
2091. García-Calzón S, Moleres A, Martínez-González MA, et al. Dietary total antioxidant capacity is associated with leukocyte telomere length in a children and adolescent population. *Clin Nutr*. 2015;34(4):694–9.
2092. Leung CW, Laraia BA, Needham BL, et al. Soda and cell aging: associations between sugar-sweetened beverage consumption and leukocyte telomere length in healthy adults from the National Health and Nutrition Examination Surveys. *Am J Public Health*. 2014;104(12):2425–31.
2093. Nettleton JA, Diez-Roux A, Jenny NS, Fitzpatrick AL, Jacobs DR. Dietary patterns, food groups, and telomere length in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Clin Nutr*. 2008;88(5):1405–12.
2094. Gu Y, Honig LS, Schupf N, et al. Mediterranean diet and leukocyte telomere length in a multi-ethnic elderly population. *Age* (Dordr). 2015;37(2):9758.

2095. Hou L, Savage SA, Blaser MJ, et al. Telomere length in peripheral leukocyte DNA and gastric cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2009;18(11):3103–9.
2096. Gu Y, Honig LS, Schupf N, et al. Mediterranean diet and leukocyte telomere length in a multi-ethnic elderly population. *Age* (Dordr). 2015;37(2):9758.
2097. García-Calzón S, Moleres A, Martínez-González MA, et al. Dietary total antioxidant capacity is associated with leukocyte telomere length in a children and adolescent population. *Clin Nutr*. 2015;34(4):694–9.
2098. Zainabadi K. A brief history of modern aging research. *Exp Gerontol*. 2018;104:35–42.
2099. Zainabadi K. A brief history of modern aging research. *Exp Gerontol*. 2018;104:35–42.
2100. Strong R, Miller RA, Antebi A, et al. Longer lifespan in male mice treated with a weakly estrogenic agonist, an antioxidant, an α-glucosidase inhibitor or a Nrf2-inducer. *Aging Cell*. 2016;15(5):872–84.

II. The Optimal Anti-Aging Regimen

2101. Gebreslassie M, Sampaio F, Nystrand C, Ssegonja R, Feldman I. Economic evaluations of public health interventions for physical activity and healthy diet: a systematic review. *Prev Med*. 2020;136:106100.

2102. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2095–128.

2103. Mokdad AH, Ballestros K, Echko M, et al. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319(14):1444–72.

2104. Afshin A, Sur PJ, Fay KA, et al. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2019;393(10184):1958–72.

2105. Gebreslassie M, Sampaio F, Nystrand C, Ssegonja R, Feldman I. Economic evaluations of public health interventions for physical activity and healthy diet: a systematic review. *Prev Med*. 2020;136:106100.

2106. Das P, Samarasekera U. The story of GBD 2010: a “super-human” effort. *Lancet*. 2012;380(9859):2067–70.

2107. Mokdad AH, Ballestros K, Echko M, et al. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319(14):1444–72.

2108. Dato S, Bellizzi D, Rose G, Passarino G. The impact of nutrients on the aging rate: a complex interaction of demographic, environmental and genetic factors. *Mech Ageing Dev*. 2016;154:49–61.

2109. Campisi J, Kapahi P, Lithgow GJ, Melov S, Newman JC, Verdin E. From discoveries in ageing research to therapeutics for healthy ageing. *Nature*. 2019;571(7764):183–92.

2110. Govindaraju T, Sahle BW, McCaffrey TA, McNeil JJ, Owen AJ. Dietary patterns and quality of life in older adults: a systematic

review. *Nutrients*. 2018;10(8):971.
2111. Milte CM, McNaughton SA. Dietary patterns and successful ageing: a systematic review. *Eur J Nutr*. 2016;55(2):423–50.
2112. Reedy J, Krebs-Smith SM, Miller PE, et al. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. *J Nutr*. 2014;144(6):881–9.
2113. McCullough ML. Diet patterns and mortality: common threads and consistent results. *J Nutr*. 2014;144(6):795–6.
2114. Reedy J, Krebs-Smith SM, Miller PE, et al. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. *J Nutr*. 2014;144(6):881–9.
2115. Afshin A, Sur PJ, Fay KA, et al. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2019;393(10184):1958–72.
2116. Yip CSC, Chan W, Fielding R. The associations of fruit and vegetable intakes with burden of diseases: a systematic review of meta-analyses. *J Acad Nutr Diet*. 2019;119(3):464–81.
2117. Fisher D. Study finds no link between secondhand smoke and cancer. *Forbes*. https://www.forbes.com/sites/danielfisher/2013/12/12/study-finds-no-link-between-secondhand-smoke-and-cancer/?sh=77c79a2565d4. Published December 12, 2013. Accessed December 12, 2021.
2118. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. *BMJ*. 1997;315(7114):980–8.
2119. Gori GB, Mantel N. Mainstream and environmental tobacco smoke. *Regul Toxicol Pharmacol*. 1991;14(1):88–105.
2120. Barnes DE, Bero LA. Why review articles on the health effects of passive smoking reach different conclusions. *JAMA*. 1998;279(19):1566–70.
2121. Drope J, Chapman S. Tobacco industry efforts at discrediting scientific knowledge of environmental tobacco smoke: a review of internal industry documents. *J Epidemiol Community Health*. 2001;55(8):588–94.
2122. Barnes DE, Bero LA. Why review articles on the health effects of passive smoking reach different conclusions. *JAMA*.

1998;279(19):1566–70.
2123. Fardet A, Boirie Y. Associations between food and beverage groups and major diet-related chronic diseases: an exhaustive review of pooled/meta-analyses and systematic reviews. *Nutr Rev*. 2014;72(12):741–62.
2124. Fardet A, Boirie Y. Associations between food and beverage groups and major diet-related chronic diseases: an exhaustive review of pooled/meta-analyses and systematic reviews. *Nutr Rev*. 2014;72(12):741–62.
2125. Abdelhamid AS, Brown TJ, Brainard JS, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2018;7:CD003177.
2126. Gonzales JF, Barnard ND, Jenkins DJA, et al. Applying the precautionary principle to nutrition and cancer. *J Am Coll Nutr*. 2014;33(3):239–46.
2127. Lane KE, Wilson M, Hellon TG, Davies IG. Bioavailability and conversion of plant based sources of omega-3 fatty acids—a scoping review to update supplementation options for vegetarians and vegans. *Crit Rev Food Sci Nutr*. 2022;62(18):4982–97.
2128. Fardet A, Boirie Y. Associations between food and beverage groups and major diet-related chronic diseases: an exhaustive review of pooled/meta-analyses and systematic reviews. *Nutr Rev*. 2014;72(12):741–62.
2129. Yip CSC, Lam W, Fielding R. A summary of meat intakes and health burdens. *Eur J Clin Nutr*. 2018;72(1):18–29.
2130. Spiegelhalter D. Microlives. Understanding Uncertainty. http://understandinguncertainty.org/microlives. Published November 22, 2011. Accessed August 30, 2021.
2131. Spiegelhalter D. Using speed of ageing and “microlives” to communicate the effects of lifetime habits and environment. *BMJ*. 2012;345:e8223.
2132. Spiegelhalter D. Using speed of ageing and “microlives” to communicate the effects of lifetime habits and environment. *BMJ*. 2012;345:e8223.
2133. Zhuang P, Wu F, Mao L, et al. Egg and cholesterol consumption and mortality from cardiovascular and different causes in the United

States: a population-based cohort study. *PLoS Med*. 2021;18(2):e1003508.

2134. Zeraatkar D, Han MA, Guyatt GH, et al. Red and processed meat consumption and risk for all-cause mortality and cardiometabolic outcomes: a systematic review and meta-analysis of cohort studies. *Ann Intern Med*. 2019;171(10):703–10.

2135. Heard CL, Rakow T, Spiegelhalter D. Comparing comprehension and perception for alternative speed-of-ageing and standard hazard ratio formats. *Appl Cognit Psychol.* 2018;32(1):81–93.

2136. Heard CL, Rakow T, Spiegelhalter D. Comparing comprehension and perception for alternative speed-of-ageing and standard hazard ratio formats. *Appl Cognit Psychol.* 2018;32(1):81–93.

2137. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans; Volume 114: Red Meat and Processed Meat*. IARC Press; 2018. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono114.pdf. Accessed December 19, 2021.

2138. Chaffetz J. Letter on behalf of the U.S. House of Representatives Committee on Oversight and Government Reform of the 114th Congress to Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health. September 26, 2016.

2139. Boobis AR, Cohen SM, Dellarco VL, et al. Classification schemes for carcinogenicity based on hazard-identification have become outmoded and serve neither science nor society. *Regul Toxicol Pharmacol*. 2016;82:158–66.

2140. Wild CP. Letter to Dr. Francis S. Collins re: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. October 5, 2016. https://monographs.iarc.who.int/ENG/News/LetterFromDrWild-to-DrCollins.pdf. Accessed December 19, 2021.

2141. International Agency for Research on Cancer. World Health Organization. Q&A on the carcinogenicity of the consumption of red meat and processed meat. 2015. https://www.iarc.who.int/wp-content/uploads/2018/11/Monographs-QA_Vol114.pdf. Accessed December 28, 2022.

2142. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans; Volume 114: Red Meat and Processed Meat*. IARC Press; 2018. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono114.pdf. Accessed December 19, 2021.
2143. Office on Smoking and Health (US). The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Centers for Disease Control and Prevention (US); 2006.
2144. Modica C, Lewis JH, Bay C. Colorectal cancer: applying the value transformation framework to increase the percent of patients receiving screening in federally qualified health centers. *Prev Med Rep*. 2019;15:100894.
2145. Kim H, Caulfield LE, Rebholz CM. Healthy plant-based diets are associated with lower risk of all-cause mortality in US adults. *J Nutr*. 2018;148(4):624–31.
2146. Bamia C, Trichopoulos D, Ferrari P, et al. Dietary patterns and survival of older Europeans: the EPIC–Elderly Study (European Prospective Investigation into Cancer and Nutrition). *Public Health Nutr*. 2007;10(6):590–8.
2147. Kahleova H, Levin S, Barnard ND. Plant-based diets for healthy aging. *J Am Coll Nutr*. 2021;40(5):478–9.
2148. Ekmekcioglu C. Nutrition and longevity—from mechanisms to uncertainties. *Crit Rev Food Sci Nutr*. 2020;60(18):3063–82.
2149. Everitt AV, Hilmer SN, Brand-Miller JC, et al. Dietary approaches that delay age-related diseases. *Clin Interv Aging*. 2006;1(1):11–31.
2150. Kahleova H, Levin S, Barnard ND. Plant-based diets for healthy aging. *J Am Coll Nutr*. 2021;40(5):478–9.
2151. O'Hara JK. The $11 trillion reward: how simple dietary changes can save lives and money, and how we get there. UCSusa.org. https://www.ucsusa.org/sites/default/files/2019–09/11-trillion-reward.pdf. Published August 2013. Accessed December 15, 2021.
2152. Cross AJ, Pollock JRA, Bingham SA. Haem, not protein or inorganic iron, is responsible for endogenous intestinal *N*-nitrosation arising from red meat. *Cancer Res*. 2003;63(10):2358–60.

2153. Tucker KL, Hallfrisch J, Qiao N, Muller D, Andres R, Fleg JL. The combination of high fruit and vegetable and low saturated fat intakes is more protective against mortality in aging men than is either alone: the Baltimore Longitudinal Study of Aging. *J Nutr*. 2005;135(3):556–61.
2154. Jenkins DJ, Kendall CW. The Garden of Eden: plant-based diets, the genetic drive to store fat and conserve cholesterol, and implications for epidemiology in the 21st century. *Epidemiology*. 2006;17(2):128–30.
2155. Eaton SB, Konner M. Paleolithic nutrition. A consideration of its nature and current implications. *N Engl J Med*. 1985;312(5):283–9.
2156. Anderson JW, Konz EC, Jenkins DJ. Health advantages and disadvantages of weight-reducing diets: a computer analysis and critical review. *J Am Coll Nutr*. 2000;19(5):578–90.
2157. Hladik CM, Pasquet P. The human adaptations to meat eating: a reappraisal. *Hum Evol*. 2002;17(3–4):199–206.
2158. Milton K. Micronutrient intakes of wild primates: are humans different? *Comp Biochem Physiol A Mol Integr Physiol*. 2003;136(1):47–59.
2159. Jenkins DJA, Kendall CWC, Marchie A, et al. The Garden of Eden—plant based diets, the genetic drive to conserve cholesterol and its implications for heart disease in the 21st century. *Comp Biochem Physiol A Mol Integr Physiol*. 2003;136(1):141–51.
2160. Larsen SC, Ängquist L, Sørensen TI, Heitmann BL. 24h urinary sodium excretion and subsequent change in weight, waist circumference and body composition. *PLoS ONE*. 2013;8(7):e69689.
2161. Roberts WC. High salt intake, its origins, its economic impact, and its effect on blood pressure. *Am J Cardiol*. 2001;88(11):1338–46.
2162. Yin X, Tian M, Neal B. Sodium reduction: how big might the risks and benefits be? *Heart Lung Circ*. 2021;30(2):180–5.
2163. Afshin A, Sur PJ, Fay KA, et al. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2019;393(10184):1958–72.
2164. MacGregor GA, Markandu ND, Best FE, et al. Double-blind randomised crossover trial of moderate sodium restriction in essential hypertension. *Lancet*. 1982;1(8268):351–5.

2165. Rudelt A, French S, Harnack L. Fourteen-year trends in sodium content of menu offerings at eight leading fast-food restaurants in the USA. *Public Nutr*. 2014;17(8):1682–8.
2166. Suckling RJ, He FJ, Markandu ND, MacGregor GA. Dietary salt influences postprandial plasma sodium concentration and systolic blood pressure. *Kidney Int*. 2012;81(4):407–11.
2167. Chobufo MD, Gayam V, Soluny J, et al. Prevalence and control rates of hypertension in the USA: 2017–2018. *Int J Cardiol Hypertens*. 2020;6:100044.
2168. Celermajer DS, Neal B. Excessive sodium intake and cardiovascular disease: a-salting our vessels. *J Am Coll Cardiol*. 2013;61(3):344–5.
2169. Mancilha-Carvalho J de J, de Souza e Silva NA. The Yanomami Indians in the INTERSALT Study. *Arq Bras Cardiol*. 2003;80(3):289–300.
2170. Roberts WC. High salt intake, its origins, its economic impact, and its effect on blood pressure. *Am J Cardiol*. 2001;88(11):1338–46.
2171. Cappuccio FP, Capewell S, Lincoln P, McPherson K. Policy options to reduce population salt intake. *BMJ*. 2011;343:d4995.
2172. Toldrá F, Barat JM. Strategies for salt reduction in foods. *Recent Pat Food Nutr Agric*. 2012;4(1):19–25.
2173. Appel LJ, Anderson CA. Compelling evidence for public health action to reduce salt intake. *N Engl J Med*. 2010;362(7):650–2.
2174. Drewnowski A, Rehm CD. Sodium intakes of US children and adults from foods and beverages by location of origin and by specific food source. *Nutrients*. 2013;5(6):1840–55.
2175. Buying this chicken? You could pay up to $1.70 for broth. *Consum Rep*. June 2008;7.
2176. Select Committee on Nutrition and Human Needs. *Dietary Goals for the United States—Supplemental Views*. U.S. Government Printing Office; 1977.
2177. Foscolou A, Critselis E, Tyrovolas S, et al. The association of sodium intake with successful aging, in 3,349 middle-aged and older adults: results from the ATTICA and MEDIS cross-sectional epidemiological studies. *Nutr Healthy Aging*. 2020;5(4):287–96.
2178. Madiloggovit J, Chotechuang N, Trachootham D. Impact of self-tongue brushing on taste perception in Thai older adults: a pilot study.

Geriatr Nurs. 2016;37(2):128–36.
2179. Quirynen M, Avontroodt P, Soers C, Zhao H, Pauwels M, van Steenberghe D. Impact of tongue cleansers on microbial load and taste. *J Clin Periodontol*. 2004;31(7):506–10.
2180. Madiloggovit J, Chotechuang N, Trachootham D. Impact of self-tongue brushing on taste perception in Thai older adults: a pilot study. *Geriatr Nurs*. 2016;37(2):128–36.
2181. Sigurdsson EL. Salt: a taste of death? *Scand J Prim Health Care*. 2014;32(2):53–4.
2182. Maleki A, Soltanian AR, Zeraati F, Sheikh V, Poorolajal J. The flavor and acceptability of six different potassium-enriched (sodium reduced) iodized salts: a single-blind, randomized, crossover design. *Clin Hypertens*. 2016;22(1):18.
2183. Whelton PK, Appel LJ, Sacco RL, et al. Sodium, blood pressure, and cardiovascular disease: further evidence supporting the American Heart Association sodium reduction recommendations. *Circulation*. 2012;126(24):2880–9.
2184. Cogswell ME, Zhang Z, Carriquiry AL, et al. Sodium and potassium intakes among US adults: NHANES 2003–2008. *Am J Clin Nutr*. 2012;96(3):647–57.
2185. Sebastian A, Cordain L, Frassetto L, Banerjee T, Morris RC. Postulating the major environmental condition resulting in the expression of essential hypertension and its associated cardiovascular diseases: dietary imprudence in daily selection of foods in respect of their potassium and sodium content resulting in oxidative stress-induced dysfunction of the vascular endothelium, vascular smooth muscle, and perivascular tissues. *Med Hypotheses*. 2018;119:110–9.
2186. Palmer BF, Clegg DJ. Achieving the benefits of a high-potassium, paleolithic diet, without the toxicity. *Mayo Clin Proc*. 2016;91(4):496–508.
2187. Jew S, AbuMweis SS, Jones PJH. Evolution of the human diet: linking our ancestral diet to modern functional foods as a means of chronic disease prevention. *J Med Food*. 2009;12(5):925–34.
2188. Drewnowski A, Maillot M, Rehm C. Reducing the sodium-potassium ratio in the US diet: a challenge for public health. *Am J Clin Nutr*. 2012;96(2):439–44.

2189. van Buren L, Dötsch-Klerk M, Seewi G, Newson RS. Dietary impact of adding potassium chloride to foods as a sodium reduction technique. *Nutrients*. 2016;8(4):235.
2190. Jafarnejad S, Mirzaei H, Clark CCT, Taghizadeh M, Ebrahimzadeh A. The hypotensive effect of salt substitutes in stage 2 hypertension: a systematic review and meta-analysis. *BMC Cardiovasc Disord*. 2020;20(1):98.
2191. Chang HY, Hu YW, Yue CSJ, et al. Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. Am J Clin Nutr. 2006;83(6):1289–96.
2192. Lambert K, Conley M, Dumont R, et al. Letter to the editor on "Potential use of salt substitutes to reduce blood pressure." *J Clin Hypertens*. 2019;21(10):1609–10.
2193. Farrand C, MacGregor G, Campbell NRC, Webster J. Potential use of salt substitutes to reduce blood pressure. *J Clin Hypertens*. 2019;21(3):350–4.
2194. Greer RC, Marklund M, Anderson CAM, et al. Potassium-enriched salt substitutes as a means to lower blood pressure: benefits and risks. *Hypertension*. 2020;75(2):266–74.
2195. Greer RC, Marklund M, Anderson CAM, et al. Potassium-enriched salt substitutes as a means to lower blood pressure: benefits and risks. *Hypertension*. 2020;75(2):266–74.
2196. Greer RC, Marklund M, Anderson CAM, et al. Potassium-enriched salt substitutes as a means to lower blood pressure: benefits and risks. *Hypertension*. 2020;75(2):266–74.
2197. Mokdad AH, Ballestros K, Echko M, et al. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319(14):1444–72.
2198. Mokdad AH, Ballestros K, Echko M, et al. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319(14):1444–72.
2199. Reedy J, Krebs-Smith SM, Miller PE, et al. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. *J Nutr*. 2014;144(6):881–9.
2200. Devries S, Willett W, Bonow RO. Nutrition education in medical school, residency training, and practice. *JAMA*. 2019;321(14):1351–

2.
2201. Freeman KJ, Grega ML, Friedman SM, et al. Lifestyle medicine reimbursement: a proposal for policy priorities informed by a cross-sectional survey of lifestyle medicine practitioners. *Int J Environ Res Public Health*. 2021;18(21):11632.
2202. Brody H. Pharmaceutical industry financial support for medical education: benefit, or undue influence? *J Law Med Ethics*. 2009;37(3):451–60.
2203. Proctor RN. The history of the discovery of the cigarette–lung cancer link: evidentiary traditions, corporate denial, global toll. *Tob Control*. 2012;21(2):87–91.
2204. Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, CDC. Tobacco use—United States, 1900–1999. *JAMA*. 1999;282(23):2202–4.
2205. Editorial. The advertising of cigarettes. *JAMA*. 1948;138(9):652–3.
2206. Editorial. The advertising of cigarettes. *JAMA*. 1948;138(9):652–3.
2207. Proctor RN. The history of the discovery of the cigarette–lung cancer link: evidentiary traditions, corporate denial, global toll. *Tob Control*. 2012;21(2):87–91.
2208. Gugiu PC, Gugiu MR. Levels of evidence: a reply to Berger and Knoll. *Eval Health Prof*. 2011;34(1):127–30.
2209. Chopra M, Darnton-Hill I. Tobacco and obesity epidemics: not so different after all? *BMJ*. 2004;328(7455):1558–60.
2210. Industries. OpenSecrets.org. https://www.opensecrets.org/federal-lobbying/industries. Published July 23, 2021. Accessed August 31, 2021.
2211. Maplight, Feed the Truth. Draining the Big Food swamp. FeedtheTruth.org. https://feedthetruth.org/wp-content/uploads/2021/08/FTT-DrainingTheSwamp-ExecSummary-FINAL.pdf. Published February 25, 2021. Accessed January 6, 2022.
2212. Sarna L, Bialous SA, Nandy K, Antonio ALM, Yang Q. Changes in smoking prevalences among health care professionals from 2003 to 2010–2011. *JAMA*. 2014;311(2):197–9.
2213. Jindeel A. Health care providers who smoke. *Am J Nurs*. 2010;110(6):11.

2214. Aggarwal M, Singh Ospina N, Kazory A, et al. The mismatch of nutrition and lifestyle beliefs and actions among physicians: a wake-up call. *Am J Lifestyle Med*. 2020;14(3):304–15.
2215. Bertozzi B, Tosti V, Fontana L. Beyond calories: an integrated approach to promote health, longevity and well-being. *Gerontology*. 2017;63(1):13–9.
2216. Fadnes LT, Økland JM, Haaland ØA, Johansson KA. Estimating impact of food choices on life expectancy: a modeling study. *PLoS Med*. 2022;19(2):e1003889.
2217. Hooper L, Bunn D, Jimoh FO, Fairweather-Tait SJ. Water-loss dehydration and aging. *Mech Ageing Dev*. 2014;136–7:50–8.
2218. Kenney WL, Chiu P. Influence of age on thirst and fluid intake. *Med Sci Sports Exerc*. 2001;33(9):1524–32.
2219. Lorenzo I, Serra-Prat M, Yébenes JC. The role of water homeostasis in muscle function and frailty: a review. *Nutrients*. 2019;11(8):E1857.
2220. Hooper L, Bunn D, Jimoh FO, Fairweather-Tait SJ. Water-loss dehydration and aging. *Mech Ageing Dev*. 2014;136–7:50–8.
2221. Popkin BM, Armstrong LE, Bray GM, Caballero B, Frei B, Willett WC. A new proposed guidance system for beverage consumption in the United States. *Am J Clin Nutr.* 2006;83(3):529–42.
2222. Walsh NP, Fortes MB, Purslow C, Esmaeelpour M. Author response: is whole body hydration an important consideration in dry eye? *Invest Ophthalmol Vis Sci.* 2013;54(3):1713–4.
2223. Chan J, Knutsen SF, Blix GG, Lee JW, Fraser GE. Water, other fluids, and fatal coronary heart disease: the Adventist Health Study. *Am J Epidemiol.* 2002;155(9):827–33.
2224. Cui R, Iso H, Eshak ES, Maruyama K, Tamakoshi A, JACC Study Group. Water intake from foods and beverages and risk of mortality from CVD: the Japan Collaborative Cohort (JACC) Study. *Public Health Nutr*. 2018;21(16):3011–7.
2225. Stookey JD, Kavouras SA, Suh H, Lang F. Underhydration is associated with obesity, chronic diseases, and death within 3 to 6 years in the U.S. population aged 51–70 years. *Nutrients*. 2020;12(4):E905.
2226. Lim WH, Wong G, Lewis JR, et al. Total volume and composition of fluid intake and mortality in older women: a cohort study. *BMJ Open*.

2017;7(3):e011720.
2227. Kant AK, Graubard BI. A prospective study of water intake and subsequent risk of all-cause mortality in a national cohort. *Am J Clin Nutr*. 2017;105(1):212–20.
2228. Leurs LJ, Schouten LJ, Goldbohm RA, van den Brandt PA. Total fluid and specific beverage intake and mortality due to IHD and stroke in the Netherlands Cohort Study. *Br J Nutr*. 2010;104(8):1212–21.
2229. Loomba RS, Aggarwal S, Arora RR. Raw water consumption does not affect all-cause or cardiovascular mortality: a secondary analysis. *Am J Ther*. 2016;23(6):e1287–92.
2230. Hooper L, Bunn D, Jimoh FO, Fairweather-Tait SJ. Water-loss dehydration and aging. *Mech Ageing Dev*. 2014;136–7:50–8.
2231. Masot O, Miranda J, Santamaría AL, Paraiso Pueyo E, Pascual A, Botigué T. Fluid intake recommendation considering the physiological adaptations of adults over 65 years: a critical review. *Nutrients*. 2020;12(11):E3383.
2232. McKenzie AL, Muñoz CX, Armstrong LE. Accuracy of urine color to detect equal to or greater than 2% body mass loss in men. *J Athl Train.* 2015;50(12):1306–9.
2233. McKenzie AL, Armstrong LE. Monitoring body water balance in pregnant and nursing women: the validity of urine color. *Ann Nutr Metab.* 2017;70 Suppl 1:18–22.
2234. Perrier ET, Johnson EC, McKenzie AL, Ellis LA, Armstrong LE. Urine colour change as an indicator of change in daily water intake: a quantitative analysis. *Eur J Nutr.* 2016;55(5):1943–9.
2235. Kostelnik SB, Davy KP, Hedrick VE, Thomas DT, Davy BM. The validity of urine color as a hydration biomarker within the general adult population and athletes: a systematic review. *J Am Coll Nutr*. 2021;40(2):172–9.
2236. Hooper L, Abdelhamid A, Attreed NJ, et al. Clinical symptoms, signs and tests for identification of impending and current water-loss dehydration in older people. *Cochrane Database Syst Rev*. 2015; (4):CD009647.
2237. Benelam B, Wyness L. Hydration and health: a review. *Nutr Bull.* 2010;35:3–25.

2238. Vivanti AP. Origins for the estimations of water requirements in adults. *Eur J Clin Nutr.* 2012;66(12):1282–9.
2239. Benelam B, Wyness L. Hydration and health: a review. *Nutr Bull.* 2010;35:3–25.
2240. Masot O, Miranda J, Santamaría AL, Paraiso Pueyo E, Pascual A, Botigué T. Fluid intake recommendation considering the physiological adaptations of adults over 65 years: a critical review. *Nutrients*. 2020;12(11):E3383.
2241. Hoffman MD, Bross TL, Hamilton RT. Are we being drowned by overhydration advice on the Internet? *Phys Sportsmed*. 2016;44(4):343–8.
2242. Onufrak SJ, Park S, Sharkey JR, Sherry B. The relationship of perceptions of tap water safety with intake of sugar-sweetened beverages and plain water among US adults. *Public Health Nutr*. 2014;17(1):179–85.
2243. Saleh MA, Abdel-Rahman FH, Woodard BB, et al. Chemical, microbial and physical evaluation of commercial bottled waters in greater Houston area of Texas. *J Environ Sci Health A Tox Hazard Subst Environ Eng*. 2008;43(4):335–47.
2244. Fardet A, Boirie Y. Associations between food and beverage groups and major diet-related chronic diseases: an exhaustive review of pooled/meta-analyses and systematic reviews. *Nutr Rev*. 2014;72(12):741–62.
2245. Øverby NC, Lillegaard ITL, Johansson L, Andersen LF. High intake of added sugar among Norwegian children and adolescents. *Public Health Nutr*. 2004;7(2):285–93.
2246. Chikritzhs T, Stockwell T, Naimi T, Andreasson S, Dangardt F, Liang W. Has the leaning tower of presumed health benefits from 'moderate' alcohol use finally collapsed? *Addiction*. 2015;110(5):726–7.
2247. Fillmore KM, Stockwell T, Chikritzhs T, Bostrom A, Kerr W. Moderate alcohol use and reduced mortality risk: systematic error in prospective studies and new hypotheses. *Ann Epidemiol*. 2007;17(5 Suppl):S16–23.
2248. Johnson T, Gerson L, Hershcovici T, Stave C, Fass R. Systematic review: the effects of carbonated beverages on gastro-oesophageal

reflux disease. *Aliment Pharmacol Ther*. 2010;31(6):607–14.
2249. Lesser LI, Ebbeling CB, Goozner M, Wypij D, Ludwig DS. Relationship between funding source and conclusion among nutrition-related scientific articles. *PLoS Med*. 2007;4(1):e5.
2250. Quik M. Smoking, nicotine and Parkinson's disease. *Trends Neurosci*. 2004;27(9):561–8.
2251. Searles Nielsen S, Gallagher LG, Lundin JI, et al. Environmental tobacco smoke and Parkinson's disease. *Mov Disord*. 2012;27(2):293–6.
2252. U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General.* Centers for Disease Control and Prevention; 2014.
2253. Nielsen SS, Franklin GM, Longstreth WT, Swanson PD, Checkoway H. Nicotine from edible *Solanaceae* and risk of Parkinson disease. *Ann Neurol*. 2013;74(3):472–7.
2254. Aune D, Rosenblatt DAN, Chan DSM, et al. Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies. *Am J Clin Nutr*. 2015;101(1):87–117.
2255. Vasconcelos A, Santos T, Ravasco P, Neves PM. Dairy products: is there an impact on promotion of prostate cancer? A review of the literature. *Front Nutr*. 2019;6:62.
2256. Aune D, Lau R, Chan DSM, et al. Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. *Ann Oncol*. 2012;23(1):37–45.
2257. Veettil SK, Ching SM, Lim KG, Saokaew S, Phisalprapa P, Chaiyakunapruk N. Effects of calcium on the incidence of recurrent colorectal adenomas: a systematic review with meta-analysis and trial sequential analysis of randomized controlled trials. *Medicine*. 2017;96(32):e7661.
2258. Gonzales JF, Barnard ND, Jenkins DJA, et al. Applying the precautionary principle to nutrition and cancer. *J Am Coll Nutr*. 2014;33(3):239–46.
2259. Bridges, M. Moo-ove over, cow's milk: the rise of plant-based dairy alternatives. *Pract Gastroenterol*. 2018;42(1):20–7.
2260. Boland, MA. Milk processors are going bankrupt as Americans ditch dairy. Bloomberg. https://www.bloomberg.com/news/articles/2020–

01–10/distaste-for-dairy-sends-milk-processors-to-bankruptcy-court. Published January 10, 2020. Accessed January 6, 2022.
2261. Silva ARA, Silva MMN, Ribeiro BD. Health issues and technological aspects of plant-based alternative milk. *Food Res Int*. 2020;131:108972.
2262. Jacobs ET, Foote JA, Kohler LN, Skiba MB, Thomson CA. Re-examination of dairy as a single commodity in US dietary guidance. *Nutr Rev*. 2020;78(3):225–34.
2263. Vanga SK, Raghavan V. How well do plant based alternatives fare nutritionally compared to cow's milk? *J Food Sci Technol.* 2018;55(1):10–20.
2264. Storhaug CL, Fosse SK, Fadnes LT. Country, regional, and global estimates for lactose malabsorption in adults: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2017;2(10):738–46.
2265. National Institute of Child Health and Human Development. Lactose intolerance: information for health care providers. U.S. Dept. of Health and Human Services, National Institutes of Health. http://purl.access.gpo.gov/GPO/LPS80173. Published January 2006. Accessed January 6, 2022.
2266. Bertron P, Barnard ND, Mills M. Racial bias in federal nutrition policy, part I: the public health implications of variations in lactase persistence. *J Natl Med Assoc.* 1999;91(3):151–7.
2267. Jacobs ET, Foote JA, Kohler LN, Skiba MB, Thomson CA. Re-examination of dairy as a single commodity in US dietary guidance. *Nutr Rev*. 2020;78(3):225–34.
2268. Jacobs ET, Foote JA, Kohler LN, Skiba MB, Thomson CA. Re-examination of dairy as a single commodity in US dietary guidance. *Nutr Rev*. 2020;78(3):225–34.
2269. Godlee F, Malone R, Timmis A, et al. Journal policy on research funded by the tobacco industry. *Thorax*. 2013;68(12):1090–1.
2270. Yi M, Wu X, Zhuang W, et al. Tea consumption and health outcomes: umbrella review of meta-analyses of observational studies in humans. *Mol Nutr Food Res*. 2019;63(16):e1900389.
2271. Zhang L, Jie G, Zhang J, Zhao B. Significant longevity-extending effects of EGCG on *Caenorhabditis elegans* under stress. *Free Radic Biol Med*. 2009;46(3):414–21.

2272. Niu Y, Na L, Feng R, et al. The phytochemical, EGCG, extends lifespan by reducing liver and kidney function damage and improving age-associated inflammation and oxidative stress in healthy rats. *Aging Cell*. 2013;12(6):1041–9.
2273. Yi M, Wu X, Zhuang W, et al. Tea consumption and health outcomes: umbrella review of meta-analyses of observational studies in humans. *Mol Nutr Food Res*. 2019;63(16):e1900389.
2274. Spiegelhalter D. Using speed of ageing and "microlives" to communicate the effects of lifetime habits and environment. *BMJ*. 2012;345:e8223.
2275. Yi M, Wu X, Zhuang W, et al. Tea consumption and health outcomes: umbrella review of meta-analyses of observational studies in humans. *Mol Nutr Food Res*. 2019;63(16):e1900389.
2276. Jochmann N, Lorenz M, von Krosigk A, et al. The efficacy of black tea in ameliorating endothelial function is equivalent to that of green tea. *Br J Nutr*. 2008;99(4):863–8.
2277. Lorenz M, Jochmann N, von Krosigk A, et al. Addition of milk prevents vascular protective effects of tea. *Eur Heart J*. 2007;28(2):219–23.
2278. Ahmad AF, Rich L, Koch H, et al. Effect of adding milk to black tea on vascular function in healthy men and women: a randomised controlled crossover trial. *Food Funct*. 2018;9(12):6307–14.
2279. Serafini M, Testa MF, Villaño D, et al. Antioxidant activity of blueberry fruit is impaired by association with milk. *Free Radic Biol Med*. 2009;46(6):769–74.
2280. Serafini M, Bugianesi R, Maiani G, Valtuena S, De Santis S, Crozier A. Plasma antioxidants from chocolate. *Nature*. 2003;424(6952):1013.
2281. Duarte GS, Farah A. Effect of simultaneous consumption of milk and coffee on chlorogenic acids' bioavailability in humans. *J Agric Food Chem*. 2011;59(14):7925–31.
2282. Chen W, Sudji IR, Wang E, Joubert E, van Wyk BE, Wink M. Ameliorative effect of aspalathin from rooibos (*Aspalathus linearis*) on acute oxidative stress in *Caenorhabditis elegans*. *Phytomedicine*. 2013;20(3–4):380–6.

2283. Yoo KM, Hwang IK, Moon B. Comparative flavonoids contents of selected herbs and associations of their radical scavenging activity with antiproliferative actions in V79–4 cells. *J Food Sci*. 2009;74(6):C419–25.
2284. Damiani E, Carloni P, Rocchetti G, et al. Impact of cold versus hot brewing on the phenolic profile and antioxidant capacity of rooibos (*Aspalathus linearis*) herbal tea. *Antioxidants (Basel)*. 2019;8(10):499.
2285. Cleverdon R, Elhalaby Y, McAlpine MD, Gittings W, Ward WE. Total polyphenol content and antioxidant capacity of tea bags: comparison of black, green, red rooibos, chamomile and peppermint over different steep times. *Beverages*. 2018;4(1):15.
2286. Peterson J, Dwyer J, Jacques P, Rand W, Prior R, Chui K. Tea variety and brewing techniques influence flavonoid content of black tea. *J Food Compost Anal*. 2004;17(3–4):397–405.
2287. Saklar S, Ertas E, Ozdemir IS, Karadeniz B. Effects of different brewing conditions on catechin content and sensory acceptance in Turkish green tea infusions. *J Food Sci Technol*. 2015;52(10):6639–46.
2288. Pérez-Burillo S, Giménez R, Rufián-Henares JA, Pastoriza S. Effect of brewing time and temperature on antioxidant capacity and phenols of white tea: relationship with sensory properties. *Food Chem*. 2018;248:111–8.
2289. Nikniaz Z, Mahdavi R, Ghaemmaghami SJ, Yagin NL, Nikniaz L. Effect of different brewing times on antioxidant activity and polyphenol content of loosely packed and bagged black teas (*Camellia sinensis* L.). *Avicenna J Phytomed*. 2016;6(3):313–21.
2290. Malik VS, Li Y, Pan A, et al. Long-term consumption of sugar-sweetened and artificially sweetened beverages and risk of mortality in US adults. *Circulation*. 2019;139(18):2113–25.
2291. Zhang YB, Jiang YW, Chen JX, Xia PF, Pan A. Association of consumption of sugar-sweetened beverages or artificially sweetened beverages with mortality: a systematic review and dose-response meta-analysis of prospective cohort studies. *Adv Nutr*. 2021;12(2):374–83.

2292. Huang C, Huang J, Tian Y, Yang X, Gu D. Sugar sweetened beverages consumption and risk of coronary heart disease: a meta-analysis of prospective studies. *Atherosclerosis*. 2014;234(1):11–6.
2293. Imamura F, O'Connor L, Ye Z, et al. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. *BMJ*. 2015;351:h3576.
2294. Zhang YB, Jiang YW, Chen JX, Xia PF, Pan A. Association of consumption of sugar-sweetened beverages or artificially sweetened beverages with mortality: a systematic review and dose-response meta-analysis of prospective cohort studies. *Adv Nutr*. 2021;12(2):374–83.
2295. Gardener H, Elkind MSV. Artificial sweeteners, real risks. *Stroke*. 2019;50(3):549–51.
2296. Huang CW, Wang HD, Bai H, et al. Tequila regulates insulin-like signaling and extends life span in *Drosophila melanogaster*. *J Gerontol A Biol Sci Med Sci*. 2015;70(12):1461–9.
2297. Didelot G, Molinari F, Tchénio P, et al. Tequila, a neurotrypsin ortholog, regulates long-term memory formation in *Drosophila*. *Science*. 2006;313(5788):851–3.
2298. Griswold MG, Fullman N, Hawley C, et al. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2018;392(10152):1015–35.
2299. Degenhardt L, Charlson F, Ferrari A, et al. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Psychiatry*. 2018;5(12):987–1012.
2300. CDC Morbidity and Mortality Weekly Report. Alcohol-attributable deaths and years of potential life lost—United States, 2001. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5337a2.htm. Published September 24, 2004. Accessed October 31. 2021.
2301. Martinez P, Kerr WC, Subbaraman MS, Roberts SCM. New estimates of the mean ethanol content of beer, wine, and spirits sold in the United States show a greater increase in per capita alcohol

consumption than previous estimates. *Alcohol Clin Exp Res*. 2019;43(3):509–21.
2302. Editorial. Alcohol and health: time for an overdue conversation. *Lancet Gastroenterol Hepatol*. 2020;5(3):229.
2303. Seyedsadjadi N, Grant R. The potential benefit of monitoring oxidative stress and inflammation in the prevention of non-communicable diseases (NCDs). *Antioxidants (Basel)*. 2020;10(1):15.
2304. Guest J, Guillemin GJ, Heng B, Grant R. Lycopene pretreatment ameliorates acute ethanol induced NAD^+ depletion in human astroglial cells. Oxid Med Cell Longev. 2015;2015:1–8.
2305. Chen H, Chen T, Giudici P, Chen F. Vinegar functions on health: constituents, sources, and formation mechanisms. *Compr Rev Food Sci Food Saf*. 2016;15(6):1124–38.
2306. Ali Z, Wang Z, Amir RM, et al. Potential uses of vinegar as a medicine and related in vivo mechanisms. *Int J Vitam Nutr Res*. 2018;86(3–4):1–12.
2307. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer*. 2015;112(3):580–93.
2308. Choi YJ, Myung SK, Lee JH. Light alcohol drinking and risk of cancer: a meta-analysis of cohort studies. *Cancer Res Treat*. 2018;50(2):474–87.
2309. Testino G, Leone S, Sumberaz A, Borro P. Alcohol and cancer. *Alcohol Clin Exp Res*. 2015;39(11):2261.
2310. Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. *BMJ*. 2011;342:d636.
2311. Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet*. 2012;380(9841):572–80.
2312. Linsel-Nitschke P, Götz A, Erdmann J, et al. Lifelong reduction of LDL-cholesterol related to a common variant in the LDL-receptor gene decreases the risk of coronary artery disease—a Mendelian randomisation study. *PLoS One*. 2008;3(8):e2986.

2313. Britton AR, Grobbee DE, den Ruijter HM, et al. Alcohol consumption and common carotid intima-media thickness: the USE-IMT Study. *Alcohol Alcohol*. 2017;52(4):483–6.
2314. Pletcher MJ, Varosy P, Kiefe CI, Lewis CE, Sidney S, Hulley SB. Alcohol consumption, binge drinking, and early coronary calcification: findings from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Epidemiol*. 2005;161(5):423–33.
2315. McFadden CB, Brensinger CM, Berlin JA, Townsend RR. Systematic review of the effect of daily alcohol intake on blood pressure. *Am J Hypertens*. 2005;18(2):276–86.
2316. Xi B, Veeranki SP, Zhao M, Ma C, Yan Y, Mi J. Relationship of alcohol consumption to all-cause, cardiovascular, and cancer-related mortality in U.S. adults. *J Am Coll Cardiol*. 2017;70(8):913–22.
2317. Xi B, Veeranki SP, Zhao M, Ma C, Yan Y, Mi J. Relationship of alcohol consumption to all-cause, cardiovascular, and cancer-related mortality in U.S. adults. *J Am Coll Cardiol*. 2017;70(8):913–22.
2318. Stockwell T, Zhao J. Alcohol's contribution to cancer is underestimated for exactly the same reason that its contribution to cardioprotection is overestimated. *Addiction*. 2017;112(2):230–2.
2319. Doll R, Peto R, Boreham J, Sutherland I. Mortality from cancer in relation to smoking: 50 years observations on British doctors. *Br J Cancer*. 2005;92(3):426–9.
2320. Stockwell T, Zhao J, Panwar S, Roemer A, Naimi T, Chikritzhs T. Do "moderate" drinkers have reduced mortality risk? A systematic review and meta-analysis of alcohol consumption and all-cause mortality. *J Stud Alcohol Drugs*. 2016;77(2):185–98.
2321. Sattar N, Preiss D. Reverse causality in cardiovascular epidemiological research: more common than imagined? *Circulation*. 2017;135(24):2369–72.
2322. Costantino G, Montano N, Casazza G. When should we change our clinical practice based on the results of a clinical study? The hierarchy of evidence. *Intern Emerg Med*. 2015;10(6):745–7.
2323. Huynh K. Reducing alcohol intake improves heart health. *Nat Rev Cardiol*. 2014;11(9):495.

2324. Stott DJ. Alcohol and mortality in older people: understanding the J-shaped curve. *Age Ageing*. 2020;49(3):332–3.
2325. Costantino G, Montano N, Casazza G. When should we change our clinical practice based on the results of a clinical study? The hierarchy of evidence. *Intern Emerg Med*. 2015;10(6):745–7.
2326. Mohammadi-Shemirani P, Chong M, Pigeyre M, Morton RW, Gerstein HC, Paré G. Effects of lifelong testosterone exposure on health and disease using Mendelian randomization. *Elife*. 2020;9:e58914.
2327. Zuccolo L, Holmes MV. Commentary: Mendelian randomization-inspired causal inference in the absence of genetic data. *Int J Epidemiol*. 2017;46(3):962–5.
2328. Zuccolo L, Holmes MV. Commentary: Mendelian randomization-inspired causal inference in the absence of genetic data. *Int J Epidemiol*. 2017;46(3):962–5.
2329. Goulden R. Moderate alcohol consumption is not associated with reduced all-cause mortality. *Am J Med*. 2016;129(2):180–6.e4.
2330. Zuccolo L, Holmes MV. Commentary: Mendelian randomization-inspired causal inference in the absence of genetic data. *Int J Epidemiol*. 2017;46(3):962–5.
2331. Holmes MV, Dale CE, Zuccolo L, et al. Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. *BMJ*. 2014;349:g4164.
2332. Xi B, Veeranki SP, Zhao M, Ma C, Yan Y, Mi J. Relationship of alcohol consumption to all-cause, cardiovascular, and cancer-related mortality in U.S. adults. *J Am Coll Cardiol*. 2017;70(8):913–22.
2333. Costanzo S, de Gaetano G, Di Castelnuovo A, Djoussé L, Poli A, van Velden DP. Moderate alcohol consumption and lower total mortality risk: justified doubts or established facts? *Nutr Metab Cardiovasc Dis*. 2019;29(10):1003–8.
2334. Oppenheimer GM, Bayer R. Is moderate drinking protective against heart disease? The science, politics and history of a public health conundrum. *Milbank Q*. 2020;98(1):39–56.
2335. Skovenborg E, Grønbæk M, Ellison RC. Benefits and hazards of alcohol-the J-shaped curve and public health. *DAT*. 2021;21(1):54–69.

2336. Golder S, McCambridge J. Alcohol, cardiovascular disease and industry funding: a co-authorship network analysis of systematic reviews. *Soc Sci Med*. 2021;289:114450.
2337. Costanzo S, de Gaetano G, Di Castelnuovo A, Djoussé L, Poli A, van Velden DP. Moderate alcohol consumption and lower total mortality risk: justified doubts or established facts? *Nutr Metab Cardiovasc Dis*. 2019;29(10):1003–8.
2338. Connor J. Why do alcohol's assumed benefits have any role in policymaking? *J Stud Alcohol Drugs*. 2016;77(2):201–2.
2339. Rabin RC. Federal agency courted alcohol industry to fund study on benefits of moderate drinking. *The New York Times*. https://www.nytimes.com/2018/03/17/health/nih-alcohol-study-liquor-industry.html. Published March 17, 2018. Accessed October 21, 2021.
2340. Rabin RC. Federal agency courted alcohol industry to fund study on benefits of moderate drinking. *The New York Times*. https://www.nytimes.com/2018/03/17/health/nih-alcohol-study-liquor-industry.html. Published March 17, 2018. Accessed October 21, 2021.
2341. Rabin RC. Major study of drinking will be shut down. *The New York Times*. https://www.nytimes.com/2018/06/15/health/alcohol-nih-drinking.html. Published June 15, 2018. Accessed October 21, 2021.
2342. Rabin RC. Federal agency courted alcohol industry to fund study on benefits of moderate drinking. *The New York Times*. https://www.nytimes.com/2018/03/17/health/nih-alcohol-study-liquor-industry.html. Published March 17, 2018. Accessed October 21, 2021.
2343. Braillon A, Wilson M. Does moderate alcohol consumption really have health benefits? *BMJ*. 2018;362:k3888.
2344. Oppenheimer GM, Bayer R. Is moderate drinking protective against heart disease? The science, politics and history of a public health conundrum. *Milbank Q*. 2020;98(1):39–56.
2345. Britton A. Moderate alcohol consumption and total mortality risk: do not advocate drinking for "health benefits." *Nutr Metab Cardiovasc Dis*. 2019;29(10):1009–10.

2346. Burton R, Sheron N. No level of alcohol consumption improves health. *Lancet*. 2018;392(10152):987–8.
2347. Britton A. Moderate alcohol consumption and total mortality risk: do not advocate drinking for “health benefits.” *Nutr Metab Cardiovasc Dis*. 2019;29(10):1009–10.
2348. Manolis TA, Manolis AA, Manolis AS. Cardiovascular effects of alcohol: a double-edged sword / how to remain at the nadir point of the J-curve? *Alcohol*. 2019;76:117–29.
2349. Arora M, ElSayed A, Beger B, et al. The impact of alcohol consumption on cardiovascular health: myths and measures. *Glob Heart*. 2022;17(1):45.
2350. Griswold MG, Fullman N, Hawley C, et al. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2018;392(10152):1015–35.
2351. Holahan CJ, Schutte KK, Brennan PL, et al. Wine consumption and 20-year mortality among late-life moderate drinkers. *J Stud Alcohol Drugs*. 2012;73(1):80–8.
2352. Frankel EN, Kanner J, German JB, Parks E, Kinsella JE. Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. *Lancet*. 1993;341(8843):454–7.
2353. Meagher EA, Barry OP, Burke A, et al. Alcohol-induced generation of lipid peroxidation products in humans. *J Clin Invest*. 1999;104(6):805–13.
2354. Di Renzo L, Carraro A, Valente R, Iacopino L, Colica C, De Lorenzo A. Intake of red wine in different meals modulates oxidized LDL level, oxidative and inflammatory gene expression in healthy people: a randomized crossover trial. *Oxid Med Cell Longev*. 2014;2014:681318.
2355. Caccetta RAA, Burke V, Mori TA, Beilin LJ, Puddey IB, Croft KD. Red wine polyphenols, in the absence of alcohol, reduce lipid peroxidative stress in smoking subjects. *Free Radic Biol Med*. 2001;30(6):636–42.
2356. Schrieks IC, van den Berg R, Sierksma A, Beulens JWJ, Vaes WHJ, Hendriks HFJ. Effect of red wine consumption on biomarkers of oxidative stress. *Alcohol Alcohol*. 2013;48(2):153–9.

2357. Chiva-Blanch G, Urpi-Sarda M, Ros E, et al. Dealcoholized red wine decreases systolic and diastolic blood pressure and increases plasma nitric oxide: short communication. *Circ Res*. 2012;111(8):1065–8.
2358. Naissides M, Mamo JCL, James AP, Pal S. The effect of acute red wine polyphenol consumption on postprandial lipaemia in postmenopausal women. *Atherosclerosis*. 2004;177(2):401–8.
2359. Williams MJA, Sutherland WHF, Whelan AP, McCormick MP, de Jong SA. Acute effect of drinking red and white wines on circulating levels of inflammation-sensitive molecules in men with coronary artery disease. *Metabolism*. 2004;53(3):318–23.
2360. Agewall S, Wright S, Doughty RN, Whalley GA, Duxbury M, Sharpe N. Does a glass of red wine improve endothelial function? *Eur Heart J*. 2000;21(1):74–8.
2361. Hashimoto M, Kim S, Eto M, et al. Effect of acute intake of red wine on flow-mediated vasodilatation of the brachial artery. *Am J Cardiol*. 2001;88(12):1457–60.
2362. Boban M, Modun D, Music I, et al. Red wine induced modulation of vascular function: separating the role of polyphenols, ethanol, and urates. *J Cardiovasc Pharmacol*. 2006;47(5):695–701.
2363. Whelan AP, Sutherland WHF, McCormick MP, Yeoman DJ, de Jong SA, Williams MJA. Effects of white and red wine on endothelial function in subjects with coronary artery disease. *Intern Med J*. 2004;34(5):224–8.
2364. Karatzi K, Papamichael C, Aznaouridis K, et al. Constituents of red wine other than alcohol improve endothelial function in patients with coronary artery disease. *Coron Artery Dis*. 2004;15(8):485–90.
2365. Shukitt-Hale B, Carey A, Simon L, Mark DA, Joseph JA. Effects of Concord grape juice on cognitive and motor deficits in aging. *Nutrition*. 2006;22(3):295–302.
2366. Smith JM, Stouffer EM. Concord grape juice reverses the age-related impairment in latent learning in rats. *Nutr Neurosci*. 2014;17(2):81–7.
2367. Krikorian R, Nash TA, Shidler MD, Shukitt-Hale B, Joseph JA. Concord grape juice supplementation improves memory function in older adults with mild cognitive impairment. *Br J Nutr*. 2010;103(5):730–4.

2368. Wang DD, Li Y, Bhupathiraju SN, et al. Fruit and vegetable intake and mortality: results from 2 prospective cohort studies of US men and women and a meta-analysis of 26 cohort studies. *Circulation*. 2021;143(17):1642–54.
2369. Dai Q, Borenstein AR, Wu Y, Jackson JC, Larson EB. Fruit and vegetable juices and Alzheimer's disease: the *Kame* Project. *Am J Med*. 2006;119(9):751–9.
2370. Dai Q, Borenstein AR, Wu Y, Jackson JC, Larson EB. Fruit and vegetable juices and Alzheimer's disease: the *Kame* Project. *Am J Med*. 2006;119(9):751–9.
2371. Mee KA, Gee DL. Apple fiber and gum arabic lowers total and low-density lipoprotein cholesterol levels in men with mild hypercholesterolemia. *J Am Diet Assoc*. 1997;97(4):422–4.
2372. Buscemi S, Rosafio G, Arcoleo G, et al. Effects of red orange juice intake on endothelial function and inflammatory markers in adult subjects with increased cardiovascular risk. *Am J Clin Nutr*. 2012;95(5):1089–95.
2373. Hägele FA, Büsing F, Nas A, et al. High orange juice consumption with or in-between three meals a day differently affects energy balance in healthy subjects. *Nutr Diabetes*. 2018;8(1):19.
2374. Silaste ML, Alfthan G, Aro A, Kesäniemi YA, Hörkkö S. Tomato juice decreases LDL cholesterol levels and increases LDL resistance to oxidation. *Br J Nutr*. 2007;98(6):1251–8.
2375. Samaras A, Tsarouhas K, Paschalidis E, et al. Effect of a special carbohydrate-protein bar and tomato juice supplementation on oxidative stress markers and vascular endothelial dynamics in ultra-marathon runners. *Food Chem Toxicol*. 2014;69:231–6.
2376. Mazidi M, Katsiki N, George ES, Banach M. Tomato and lycopene consumption is inversely associated with total and cause-specific mortality: a population-based cohort study, on behalf of the International Lipid Expert Panel (ILEP). *Br J Nutr*. 2020;124(12):1303–10.
2377. Pan B, Ge L, Lai H, et al. Association of soft drink and 100% fruit juice consumption with all-cause mortality, cardiovascular diseases mortality, and cancer mortality: a systematic review and dose-

response meta-analysis of prospective cohort studies. *Crit Rev Food Sci Nutr*. 2021;Jun 13:1–12.
2378. Scheffers FR, Boer JMA. Sugar intake and all-cause mortality-differences between sugar-sweetened beverages, artificially sweetened beverages, and pure fruit juices. *BMC Med*. 2020;18(1):112.
2379. Yip CSC, Chan W, Fielding R. The associations of fruit and vegetable intakes with burden of diseases: a systematic review of meta-analyses. *J Acad Nutr Diet*. 2019;119(3):464–81.
2380. Leaf A. Long-lived populations: extreme old age. *J Am Geriatr Soc*. 1982;30(8):485–7.
2381. Zak N. Evidence that Jeanne Calment died in 1934, not 1997. *Rejuvenation Res*. 2019;22(1):3–12.
2382. Leaf A. Long-lived populations: extreme old age. *J Am Geriatr Soc*. 1982;30(8):485–7.
2383. Mazess RB, Forman SH. Longevity and age exaggeration in Vilcabamba, Ecuador. *J Gerontol*. 1979;34(1):94–8.
2384. Poulain M, Herm A, Pes G. The Blue Zones: areas of exceptional longevity around the world. *Vienna Yearb Popul Res*. 2014;11:87–108.
2385. Willcox BJ, Willcox DC, Ferrucci L. Secrets of healthy aging and longevity from exceptional survivors around the globe: lessons from octogenarians to supercentenarians. *J Gerontol A Biol Sci Med Sci*. 2008;63(11):1181–5.
2386. Willcox DC, Willcox BJ, Poon LW. Centenarian studies: important contributors to our understanding of the aging process and longevity. *Curr Gerontol Geriatr Res*. 2010;2010:484529.
2387. Poulain M, Herm A, Pes G. The Blue Zones: areas of exceptional longevity around the world. *Vienna Yearb Popul Res*. 2014;11:87–108.
2388. Carter ED. Making the Blue Zones: neoliberalism and nudges in public health promotion. *Soc Sci Med*. 2015;133:374–82.
2389. Madrigal-Leer F, Martìnez-Montandòn A, Solìs-Umaña M, et al. Clinical, functional, mental and social profile of the Nicoya Peninsula centenarians, Costa Rica, 2017. *Aging Clin Exp Res*. 2020;32(2):313–21.

2390. Vatner SF, Zhang J, Oydanich M, Berkman T, Naftalovich R, Vatner DE. Healthful aging mediated by inhibition of oxidative stress. *Ageing Res Rev*. 2020;64:101194.
2391. Marston HR, Niles-Yokum K, Silva PA. A commentary on Blue Zones®: a critical review of age-friendly environments in the 21st century and beyond. *Int J Environ Res Public Health*. 2021;18(2):837.
2392. Panagiotakos DB, Chrysohoou C, Siasos G, et al. Sociodemographic and lifestyle statistics of oldest old people (>80 years) living in Ikaria Island: the Ikaria Study. *Cardiol Res Pract*. 2011;2011:679187.
2393. Food guidelines. BlueZones.com. https://www.bluezones.com/recipes/food-guidelines/. Accessed December 28, 2022.
2394. Meccariello R, D'Angelo S. Impact of polyphenolic-food on longevity: an elixir of life. An overview. *Antioxidants (Basel)*. 2021;10(4):507.
2395. Fraser GE, Shavlik DJ. Ten years of life: is it a matter of choice? *Arch Intern Med*. 2001;161(13):1645–52.
2396. Food guidelines. BlueZones.com. https://www.bluezones.com/recipes/food-guidelines/. Accessed December 28, 2022.
2397. Weber H. A lecture on means for the prolongation of life: delivered before the Royal College of Physicians of London. *BMJ*. 1903;2(2240):1445–51.
2398. Stathakos D, Pratsinis H, Zachos I, et al. Greek centenarians: assessment of functional health status and life-style characteristics. *Exp Gerontol*. 2005;40(6):512–8.
2399. Chen C. A survey of the dietary nutritional composition of centenarians. *Chin Med J (Engl)*. 2001;114(10):1095–7.
2400. Li Y, Bai Y, Tao QL, et al. Lifestyle of Chinese centenarians and their key beneficial factors in Chongqing, China. *Asia Pac J Clin Nutr*. 2014;23(2):309–14.
2401. Ye JJ, Li JC, Peng L, et al. Nonagenarians and centenarians in a rural Han Chinese population: lifestyle and epidemics: letters to the editor. *J Am Geriatr Soc*. 2009;57(9):1723–4.

2402. Vatner SF, Zhang J, Oydanich M, Berkman T, Naftalovich R, Vatner DE. Healthful aging mediated by inhibition of oxidative stress. *Ageing Res Rev*. 2020;64:101194.
2403. Buettner D. The Blue Zones: 9 Lessons for Living Longer from the People Who've Lived the Longest. National Geographic; 2012.
2404. Darmadi-Blackberry I, Wahlqvist ML, Kouris-Blazos A, et al. Legumes: the most important dietary predictor of survival in older people of different ethnicities. *Asia Pac J Clin Nutr.* 2004;13(2):217–20.
2405. Agricultural Research Service, United States Department of Agriculture. Beans, NFS. FoodDataCentral. https://fdc.nal.usda.gov/fdc-app.html#/food-details/1100362/portions. Published October 30, 2020. Accessed February 16, 2022.
2406. Fadnes LT, Økland JM, Haaland ØA, Johansson KA. Estimating impact of food choices on life expectancy: a modeling study. *PLoS Med*. 2022;19(2):e1003889.
2407. U.S. Department of Agriculture. Beans, peas, and lentils. MyPlate.gov. https://www.myplate.gov/eat-healthy/protein-foods/beans-and-peas. Accessed February 16, 2022.
2408. Drewnowski A, Rehm CD. Vegetable cost metrics show that potatoes and beans provide most nutrients per penny. *PLoS One*. 2013;8(5):e63277.
2409. Kabagambe EK, Baylin A, Ruiz-Narvarez E, Siles X, Campos H. Decreased consumption of dried mature beans is positively associated with urbanization and nonfatal acute myocardial infarction. *J Nutr*. 2005;135(7):1770–5.
2410. Luyken R, Pikaar NA, Polman H, Schippers FA. The influence of legumes on the serum cholesterol level. *Voeding*. 1962;23:447–53.
2411. Ferreira H, Vasconcelos M, Gil AM, Pinto E. Benefits of pulse consumption on metabolism and health: a systematic review of randomized controlled trials. *Crit Rev Food Sci Nutr*. 2021;61(1):85–96.
2412. Abeysekara S, Chilibeck PD, Vatanparast H, Zello GA. A pulse-based diet is effective for reducing total and LDL-cholesterol in older adults. *Br J Nutr*. 2012;108 Suppl 1:S103–10.

2413. Tokede OA, Onabanjo TA, Yansane A, Gaziano JM, Djoussé L. Soya products and serum lipids: a meta-analysis of randomised controlled trials. *Br J Nutr*. 2015;114(6):831–43.
2414. Kou T, Wang Q, Cai J, et al. Effect of soybean protein on blood pressure in postmenopausal women: a meta-analysis of randomized controlled trials. *Food Funct*. 2017;8(8):2663–71.
2415. Bazzano LA, Thompson AM, Tees MT, Nguyen CH, Winham DM. Non-soy legume consumption lowers cholesterol levels: a meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis*. 2011;21(2):94–103.
2416. Sievenpiper JL, Kendall CW, Esfahani A, et al. Effect of non-oil-seed pulses on glycaemic control: a systematic review and meta-analysis of randomised controlled experimental trials in people with and without diabetes. *Diabetologia*. 2009;52(8):1479–95.
2417. Palmer SM, Winham DM, Hradek C. Knowledge gaps of the health benefits of beans among low-income women. *Am J Health Behav*. 2018;42(1):27–38.
2418. Hosseinpour-Niazi S, Mirmiran P, Fallah-Ghohroudi A, Azizi F. Non-soya legume-based therapeutic lifestyle change diet reduces inflammatory status in diabetic patients: a randomised cross-over clinical trial. *Br J Nutr*. 2015;114(2):213–9.
2419. Mirmiran P, Hosseinpour-Niazi S, Azizi F. Therapeutic lifestyle change diet enriched in legumes reduces oxidative stress in overweight type 2 diabetic patients: a crossover randomised clinical trial. *Eur J Clin Nutr*. 2018;72(1):174–6.
2420. Mullins AP, Arjmandi BH. Health benefits of plant-based nutrition: focus on beans in cardiometabolic diseases. *Nutrients*. 2021;13(2):519.
2421. Mathur KS, Khan MA, Sharma RD. Hypocholesterolaemic effect of Bengal gram: a long-term study in man. *Br Med J.* 1968;1(5583):30–1.
2422. Esselstyn CB. In cholesterol lowering, moderation kills. *Cleve Clin J Med*. 2000;67(8):560–4.
2423. Tor-Roca A, Garcia-Aloy M, Mattivi F, Llorach R, Andres-Lacueva C, Urpi-Sarda M. Phytochemicals in legumes: a qualitative reviewed analysis. *J Agric Food Chem*. 2020;68(47):13486–96.

2424. Bruno JA, Feldman CH, Konas DW, Kerrihard AL, Matthews EL. Incorporating sprouted chickpea flour in pasta increases brachial artery flow-mediated dilation. *Physiol Int*. 2019;106(3):207–12.
2425. Zahradka P, Wright B, Weighell W, et al. Daily non-soy legume consumption reverses vascular impairment due to peripheral artery disease. *Atherosclerosis*. 2013;230(2):310–4.
2426. West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. *Science*. 1997;276(5309):122–6.
2427. Levine HJ. Rest heart rate and life expectancy. *J Am Coll Cardiol*. 1997;30(4):1104–6.
2428. Cook S, Hess OM. Resting heart rate and cardiovascular events: time for a new crusade? *Eur Heart J*. 2010;31(5):517–9.
2429. Woodward M, Webster R, Murakami Y, et al. The association between resting heart rate, cardiovascular disease and mortality: evidence from 112,680 men and women in 12 cohorts. *Eur J Prev Cardiol*. 2014;21(6):719–26.
2430. Woodward M, Webster R, Murakami Y, et al. The association between resting heart rate, cardiovascular disease and mortality: evidence from 112,680 men and women in 12 cohorts. *Eur J Prev Cardiol*. 2014;21(6):719–26.
2431. Teodorescu C, Reinier K, Uy-Evanado A, Gunson K, Jui J, Chugh SS. Resting heart rate and risk of sudden cardiac death in the general population: influence of left ventricular systolic dysfunction and heart rate-modulating drugs. *Heart Rhythm*. 2013;10(8):1153–8.
2432. Cooney MT, Vartiainen E, Laatikainen T, Juolevi A, Dudina A, Graham IM. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. *Am Heart J*. 2010;159(4):612–9.e3.
2433. Jenkins DJA, Kendall CWC, Augustin LSA, et al. Effect of legumes as part of a low glycemic index diet on glycemic control and cardiovascular risk factors in type 2 diabetes mellitus: a randomized controlled trial. *Arch Intern Med*. 2012;172(21):1653–60.
2434. Sloan RP, Shapiro PA, DeMeersman RE, et al. The effect of aerobic training and cardiac autonomic regulation in young adults. *Am J Public Health*. 2009;99(5):921–8.

2435. Viguiliouk E, Glenn AJ, Nishi SK, et al. Associations between dietary pulses alone or with other legumes and cardiometabolic disease outcomes: an umbrella review and updated systematic review and meta-analysis of prospective cohort studies. *Adv Nutr*. 2019;10(Suppl_4):S308–19.
2436. Fadnes LT, Økland JM, Haaland ØA, Johansson KA. Estimating impact of food choices on life expectancy: a modeling study. *PLoS Med*. 2022;19(2):e1003889.
2437. Schwingshackl L, Schwedhelm C, Hoffmann G, et al. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr*. 2017;105(6):1462–73.
2438. Liu W, Hu B, Dehghan M, et al. Fruit, vegetable, and legume intake and the risk of all-cause, cardiovascular, and cancer mortality: a prospective study. *Clin Nutr*. 2021;40(6):4316–23.
2439. Krebs-Smith SM, Guenther PM, Subar AF, Kirkpatrick SI, Dodd KW. Americans do not meet federal dietary recommendations. *J Nutr.* 2010;140(10):1832–8.
2440. Desrochers N, Brauer PM. Legume promotion in counselling: an e-mail survey of dietitians. *Can J Diet Pract Res.* 2001;62(4):193–8.
2441. Winham DM, Hutchins AM. Perceptions of flatulence from bean consumption among adults in 3 feeding studies. *Nutr J*. 2011;10(1):128.
2442. Winham DM, Hutchins AM. Perceptions of flatulence from bean consumption among adults in 3 feeding studies. *Nutr J*. 2011;10(1):128.
2443. Steggerda FR, Dimmick JF. Effects of bean diets on concentration of carbon dioxide in flatus. *Am J Clin Nutr*. 1966;19(2):120–4.
2444. McEligot AJ, Gilpin EA, Rock CL, et al. High dietary fiber consumption is not associated with gastrointestinal discomfort in a diet intervention trial. *J Am Diet Assoc*. 2002;102(4):549–51.
2445. How you can limit your gas production. 12 tips for dealing with flatulence. *Harv Health Lett*. 2007;32(12):3.
2446. Zartl B, Silberbauer K, Loeppert R, Viernstein H, Praznik W, Mueller M. Fermentation of non-digestible raffinose family oligosaccharides and galactomannans by probiotics. *Food Funct*. 2018;9(3):1638–46.

2447. Winham DM, Hutchins AM. Perceptions of flatulence from bean consumption among adults in 3 feeding studies. *Nutr J.* 2011;10:128.
2448. Spiro HM. Fat, foreboding, and flatulence. *Ann Intern Med.* 1999;130(4 Pt 1):320–2.
2449. Schneiderman N, Chirinos DA, Avilés-Santa ML, Heiss G. Challenges in preventing heart disease in hispanics: early lessons learned from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Prog Cardiovasc Dis*. 2014;57(3):253–61.
2450. Kochanek KD, Murphy SL, Xu J, Arias E. Mortality in the United States, 2013. Centers for Disease Control and Prevention. NCHS Data Brief. No. 178. Published December 2014. Accessed December 26, 2021.
2451. The Hispanic paradox. *Lancet*. 2015;385(9981):1918.
2452. Colón-Ramos U, Thompson FE, Yaroch AL, et al. Differences in fruit and vegetable intake among Hispanic subgroups in California: results from the 2005 California Health Interview Survey. *J Am Diet Assoc*. 2009;109(11):1878–85.
2453. Reyes-Ortiz CA, Ju H, Eschbach K, Kuo YF, Goodwin JS. Neighbourhood ethnic composition and diet among Mexican-Americans. *Public Health Nutr*. 2009;12(12):2293–301.
2454. Nieddu A, Vindas L, Errigo A, Vindas J, Pes GM, Dore MP. Dietary habits, anthropometric features and daily performance in two independent long-lived populations from *Nicoya peninsula* (Costa Rica) and *Ogliastra* (Sardinia). *Nutrients*. 2020;12(6):E1621.
2455. Reyes-Ortiz CA, Ju H, Eschbach K, Kuo YF, Goodwin JS. Neighbourhood ethnic composition and diet among Mexican-Americans. *Public Health Nutr*. 2009;12(12):2293–301.
2456. Shen J, Shan J, Zhu X, et al. Sex specific effects of capsaicin on longevity regulation. *Exp Gerontol*. 2020;130:110788.
2457. Bonaccio M, Di Castelnuovo A, Costanzo S, et al. Chili pepper consumption and mortality in Italian adults. *J Am Coll Cardiol*. 2019;74(25):3139–49.
2458. Chopan M, Littenberg B. The association of hot red chili pepper consumption and mortality: a large population-based cohort study. *PLoS One*. 2017;12(1):e0169876.

2459. Lv J, Qi L, Yu C, et al. Consumption of spicy foods and total and cause specific mortality: population based cohort study. *BMJ.* 2015;351:h3942.
2460. Hashemian M, Poustchi H, Murphy G, et al. Turmeric, pepper, cinnamon, and saffron consumption and mortality. *J Am Heart Assoc.* 2019;8(18):e012240.
2461. Janssens PLHR, Hursel R, Martens EAP, Westerterp-Plantenga MS. Acute effects of capsaicin on energy expenditure and fat oxidation in negative energy balance. *PLoS One*. 2013;8(7):e67786.
2462. Bonaccio M, Di Castelnuovo A, Costanzo S, et al. Chili pepper consumption and mortality in Italian adults. *J Am Coll Cardiol*. 2019;74(25):3139–49.
2463. American Heart Association News. Retired? Hardly—at 99, this pioneering heart doctor is still leading the way. American Heart Association. https://www.heart.org/en/news/2019/10/18/retired-hardly-at-99-this-pioneering-heart-doctor-is-still-leading-the-way. Published October 18, 2019. Accessed December 27, 2021.
2464. Stamler J. Toward a modern Mediterranean diet for the 21st century. *Nutr Metab Cardiovasc Dis*. 2013;23(12):1159–62.
2465. Nestle M. Mediterranean diets: historical and research overview. *Am J Clin Nutr*. 1995;61(6 Suppl):1313S-20S.
2466. Keys A, Menotti A, Karvonen MJ, et al. The diet and 15-year death rate in the Seven Countries Study. *Am J Epidemiol*. 1986;124(6):903–15.
2467. Davinelli S, Trichopoulou A, Corbi G, De Vivo I, Scapagnini G. The potential nutrigeroprotective role of Mediterranean diet and its functional components on telomere length dynamics. *Ageing Res Rev*. 2019;49:1–10.
2468. Keys A. Mediterranean diet and public health: personal reflections. *Am J Clin Nutr*. 1995;61(6 Suppl):1321S-3S.
2469. Russo GL, Siani A, Fogliano V, et al. The Mediterranean diet from past to future: key concepts from the second "Ancel Keys" International Seminar. *Nutr Metab Cardiovasc Dis*. 2021;31(3):717–32.
2470. Voukiklaris GE, Kafatos A, Dontas AS. Changing prevalence of coronary heart disease risk factors and cardiovascular diseases in men

of a rural area of Crete from 1960 to 1991. *Angiology*. 1996;47(1):43–9.
2471. Altomare R, Cacciabaudo F, Damiano G, et al. The Mediterranean diet: a history of health. *Iran J Public Health*. 2013;42(5):449–57.
2472. Keys A. Mediterranean diet and public health: personal reflections. *Am J Clin Nutr*. 1995;61(6 Suppl):1321S-3S.
2473. Sofi F, Macchi C, Abbate R, Gensini GF, Casini A. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. *Public Health Nutr*. 2014;17(12):2769–82.
2474. Kastorini CM, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *J Am Coll Cardio*l. 2011;57(11):1299–313.
2475. Soltani S, Jayedi A, Shab-Bidar S, Becerra-Tomás N, Salas-Salvadó J. Adherence to the Mediterranean diet in relation to all-cause mortality: a systematic review and dose-response meta-analysis of prospective cohort studies. *Adv Nutr*. 2019;10(6):1029–39.
2476. Bellavia A, Tektonidis TG, Orsini N, Wolk A, Larsson SC. Quantifying the benefits of Mediterranean diet in terms of survival. *Eur J Epidemiol*. 2016;31(5):527–30.
2477. Critselis E, Panagiotakos D. Adherence to the Mediterranean diet and healthy ageing: current evidence, biological pathways, and future directions. *Crit Rev Food Sci Nutr*. 2020;60(13):2148–57.
2478. Wang Y, Hao Q, Su L, Liu Y, Liu S, Dong B. Adherence to the Mediterranean diet and the risk of frailty in old people: a systematic review and meta-analysis. *J Nutr Health Aging*. 2018;22(5):613–8.
2479. Eleftheriou D, Benetou V, Trichopoulou A, La Vecchia C, Bamia C. Mediterranean diet and its components in relation to all-cause mortality: meta-analysis. *Br J Nutr*. 2018;120(10):1081–97.
2480. Pett KD, Willett WC, Vartiainen E, Katz DL. The Seven Countries Study. *Eur Heart J*. 2017;38(42):3119–21.
2481. Montani JP. Ancel Keys: the legacy of a giant in physiology, nutrition, and public health. *Obes Rev*. 2021;22 Suppl 2:e13196.
2482. Sparling PB. Legacy of nutritionist Ancel Keys. *Mayo Clin Proc*. 2020;95(3):615–7.

2483. American Heart Association News. Retired? Hardly—at 99, this pioneering heart doctor is still leading the way. American Heart Association. https://www.heart.org/en/news/2019/10/18/retired-hardly-at-99-this-pioneering-heart-doctor-is-still-leading-the-way. Published October 18, 2019. Accessed December 27, 2021.
2484. Paul M. As Jeremiah Stamler turns 100, 'he continues to do brilliant science'. Northwestern Now. https://news.northwestern.edu/stories/2019/10/jeremiah-stamler/. Published October 29, 2019. Accessed December 27, 2021.
2485. Winter L. "Father of Preventive Cardiology" Jeremiah Stamler dies at 102. *The Scientist*. https://www.the-scientist.com/news-opinion/father-of-preventive-cardiology-jeremiah-stamler-dies-at-102–69718. Published February 18, 2022. Accessed April 4, 2022.
2486. Bes-Rastrollo M, Sánchez-Villegas A, de la Fuente C, de Irala J, Martínez JA, Martínez-González MA. Olive oil consumption and weight change: the SUN prospective cohort study. *Lipids*. 2006;41(3):249–56.
2487. Guasch-Ferré M, Liu G, Li Y, et al. Olive oil consumption and cardiovascular risk in U.S. adults. *J Am Coll Cardiol*. 2020;75(15):1729–39.
2488. Blankenhorn DH, Johnson RL, Mack WJ, El Zein HA, Vailas LI. The influence of diet on the appearance of new lesions in human coronary arteries. *JAMA*. 1990;263(12):1646–52.
2489. Schwingshackl L, Bogensberger B, Benčič A, Knüppel S, Boeing H, Hoffmann G. Effects of oils and solid fats on blood lipids: a systematic review and network meta-analysis. *J Lipid Res*. 2018;59(9):1771–82.
2490. Tentolouris N, Arapostathi C, Perrea D, Kyriaki D, Revenas C, Katsilambros N. Differential effects of two isoenergetic meals rich in saturated or monounsaturated fat on endothelial function in subjects with type 2 diabetes. *Diabetes Care*. 2008;31(12):2276–8.
2491. Cortés B, Núñez I, Cofán M, et al. Acute effects of high-fat meals enriched with walnuts or olive oil on postprandial endothelial function. *J Am Coll Cardiol*. 2006;48(8):1666–71.
2492. Vogel RA, Corretti MC, Plotnick GD. The postprandial effect of components of the Mediterranean diet on endothelial function. *J Am*

Coll Cardiol. 2000;36(5):1455–60.
2493. Vogel RA. Brachial artery ultrasound: a noninvasive tool in the assessment of triglyceride-rich lipoproteins. *Clin Cardiol*. 1999;22(Suppl II):II-34–9.
2494. Rueda-Clausen CF, Silva FA, Lindarte MA, et al. Olive, soybean and palm oils intake have a similar acute detrimental effect over the endothelial function in healthy young subjects. *Nutr Metab Cardiovasc Dis*. 2007;17(1):50–7.
2495. Ong PJ, Dean TS, Hayward CS, Della Monica PL, Sanders TAB, Collins P. Effect of fat and carbohydrate consumption on endothelial function. *Lancet*. 1999;354(9196):2134.
2496. Casas-Agustench P, López-Uriarte P, Ros E, Bulló M, Salas-Salvadó J. Nuts, hypertension and endothelial function. *Nutr Metab Cardiovasc Dis.* 2011;21 Suppl 1:S21–33.
2497. Park E, Edirisinghe I, Burton-Freeman B. Avocado fruit on postprandial markers of cardio-metabolic risk: a randomized controlled dose response trial in overweight and obese men and women. *Nutrients*. 2018;10(9):E1287.
2498. Agricultural Research Service, United States Department of Agriculture. Olives, ripe, canned (jumbo-super colossal). FoodData Central. https://fdc.nal.usda.gov/fdc-app.html#/food-details/169095/nutrients. Published April 1, 2019. Accessed December 28, 2022.
2499. Martínez-González MÁ, Corella D, Salas-Salvadó J, et al. Cohort profile: design and methods of the PREDIMED study. *Int J Epidemiol.* 2012;41(2):377–85.
2500. Martínez-González MÁ, Corella D, Salas-Salvadó J, et al. Cohort profile: design and methods of the PREDIMED study. *Int J Epidemiol*. 2012;41(2):377–85.
2501. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med*. 2013;368(14):1279–90.
2502. Agarwal A, Ioannidis JPA. PREDIMED trial of Mediterranean diet: retracted, republished, still trusted? *BMJ*. 2019;364:l341.
2503. Rees K, Takeda A, Martin N, et al. Mediterranean-style diet for the primary and secondary prevention of cardiovascular disease.

Cochrane Database Syst Rev. 2019;3:CD009825.
2504. Martínez-González MA, Gea A, Ruiz-Canela M. The Mediterranean diet and cardiovascular health. *Circ Res*. 2019;124(5):779–98.
2505. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. 2018;378(25):e34.
2506. Sala-Vila A, Romero-Mamani ES, Gilabert R, et al. Changes in ultrasound-assessed carotid intima-media thickness and plaque with a Mediterranean diet: a substudy of the PREDIMED trial. *Arterioscler Thromb Vasc Biol*. 2014;34(2):439–45.
2507. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. 2018;378(25):e34.
2508. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. *Circulation*. 2022;145(8):e153–639.
2509. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. 2018;378(25):e34.
2510. Guasch-Ferré M, Bulló M, Martínez-González MÁ, et al. Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial. *BMC Med.* 2013;11:164.
2511. Guasch-Ferré M, Hu FB, Martínez-González MA, et al. Olive oil intake and risk of cardiovascular disease and mortality in the PREDIMED Study. *BMC Med.* 2014;12:78.
2512. Keys A. Olive oil and coronary heart disease. *Lancet.* 1987;1(8539):983–4.
2513. Valls-Pedret C, Sala-Vila A, Serra-Mir M, et al. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. *JAMA Intern Med*. 2015;175(7):1094–103.
2514. Martínez-González MÁ, Toledo E, Arós F, et al. Extra-virgin olive oil consumption reduces risk of atrial fibrillation: the PREDIMED trial. *Circulation*. 2014;130(1):18–26.
2515. Ruiz-Canela M, Estruch R, Corella D, Salas-Salvadó J, Martínez-González MA. Association of Mediterranean diet with peripheral

artery disease: the PREDIMED randomized trial. *JAMA*. 2014;311(4):415–7.

2516. Salas-Salvadó J, Bulló M, Estruch R, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. *Ann Intern Med*. 2014;160(1):1–10.

2517. Díaz-López A, Babio N, Martínez-González MA, et al. Erratum. Mediterranean diet, retinopathy, nephropathy, and microvascular diabetes complications: a post hoc analysis of a randomized trial. *Diabetes Care* 2015;38:2134–2141. *Diabetes Care*. 2018;41(10):2260–1.

2518. Martínez-Lapiscina EH, Clavero P, Toledo E, et al. Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized, trial. *J Nutr Health Aging*. 2013;17(6):544–52.

2519. Toledo E, Salas-Salvadó J, Donat-Vargas C, et al. Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial: a randomized clinical trial. *JAMA Intern Med*. 2015;175(11):1752–60.

2520. Bogani P, Galli C, Villa M, Visioli F. Postprandial anti-inflammatory and antioxidant effects of extra virgin olive oil. *Atherosclerosis*. 2007;190(1):181–6.

2521. Visioli F, Caruso D, Galli C, Viappiani S, Galli G, Sala A. Olive oils rich in natural catecholic phenols decrease isoprostane excretion in humans. *Biochem Biophys Res Commun*. 2000;278(3):797–9.

2522. Bucciantini M, Leri M, Nardiello P, Casamenti F, Stefani M. Olive polyphenols: antioxidant and anti-inflammatory properties. *Antioxidants (Basel)*. 2021;10(7):1044.

2523. Tiong SH, Saparin N, Teh HF, et al. Natural organochlorines as precursors of 3-monochloropropanediol esters in vegetable oils. *J Agric Food Chem*. 2018;66(4):999–1007.

2524. Gao B, Li Y, Huang G, Yu L. Fatty acid esters of 3-monochloropropanediol: a review. *Annu Rev Food Sci Technol*. 2019;10:259–84.

2525. Yan J, Oey SB, van Leeuwen SPJ, van Ruth SM. Discrimination of processing grades of olive oil and other vegetable oils by

monochloropropanediol esters and glycidyl esters. *Food Chem*. 2018;248:93–100.

2526. Mossoba MM, Azizian H, Fardin-Kia AR, Karunathilaka SR, Kramer JKG. First application of newly developed FT-NIR spectroscopic methodology to predict authenticity of extra virgin olive oil retail products in the USA. *Lipids*. 2017;52(5):443–55.

2527. Frankel EN, Mailed RJ, Wang SC, et al. Evaluation of extra-virgin olive oil sold in California. UC Davis Olive Center. https://olivecenter.ucdavis.edu/media/files/report2011three.pdf. Published April 2011. Accessed December 28, 2021.

2528. Martínez-González MA, Gea A, Ruiz-Canela M. The Mediterranean diet and cardiovascular health. *Circ Res*. 2019;124(5):779–98.

2529. Huedo-Medina TB, Garcia M, Bihuniak JD, Kenny A, Kerstetter J. Methodologic quality of meta-analyses and systematic reviews on the Mediterranean diet and cardiovascular disease outcomes: a review. *Am J Clin Nutr*. 2016;103(3):841–50.

2530. Galbete C, Schwingshackl L, Schwedhelm C, Boeing H, Schulze MB. Evaluating Mediterranean diet and risk of chronic disease in cohort studies: an umbrella review of meta-analyses. *Eur J Epidemiol*. 2018;33(10):909–31.

2531. Martínez-González MA, Gea A, Ruiz-Canela M. The Mediterranean diet and cardiovascular health. *Circ Res*. 2019;124(5):779–98.

2532. Galbete C, Schwingshackl L, Schwedhelm C, Boeing H, Schulze MB. Evaluating Mediterranean diet and risk of chronic disease in cohort studies: an umbrella review of meta-analyses. *Eur J Epidemiol*. 2018;33(10):909–31.

2533. Martínez-González MA, Gea A, Ruiz-Canela M. The Mediterranean diet and cardiovascular health. *Circ Res*. 2019;124(5):779–98.

2534. White C. Suspected research fraud: difficulties of getting at the truth. *BMJ*. 2005;331(7511):281–8.

2535. Horton R. Expression of concern: Indo-Mediterranean diet heart study. *Lancet.* 2005;366(9483):354–6.

2536. de Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet*. 1994;343(8911):1454–9.

2537. Simopoulos AP. Omega-3 fatty acids and antioxidants in edible wild plants. *Biol Res*. 2004;37(2):263–77.
2538. Pourrajab B, Sharifi-Zahabi E, Soltani S, Shahinfar H, Shidfar F. Comparison of canola oil and olive oil consumption on the serum lipid profile in adults: a systematic review and meta-analysis of randomized controlled trials. *Crit Rev Food Sci Nutr*. Published online July 22, 2022:1–15.
2539. Vogel RA, Corretti MC, Plotnick GD. The postprandial effect of components of the Mediterranean diet on endothelial function. *J Am Coll Cardiol*. 2000;36(5):1455–60.
2540. de Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet*. 1994;343(8911):1454–9.
2541. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99(6):779–85.
2542. Esselstyn CB, Gendy G, Doyle J, Golubic M, Roizen MF. A way to reverse CAD? *J Fam Pract*. 2014;63(7):356–64b.
2543. Rimm EB, Stampfer MJ. Diet, lifestyle, and longevity—the next steps? *JAMA*. 2004;292(12):1490–2.
2544. Drewnowski A, Hill JO, Wansink B, Murray R, Diekman C. Achieve better health with nutrient-rich foods. *Nutr Today*. 2012;47(1):23–9.
2545. Willcox DC, Willcox BJ, Todoriki H, Suzuki M. The Okinawan diet: health implications of a low-calorie, nutrient-dense, antioxidant-rich dietary pattern low in glycemic load. *J Am Coll Nutr*. 2009;28 Suppl:500S-16S.
2546. Willcox DC, Willcox BJ, He Q, Wang NC, Suzuki M. They really are that old: a validation study of centenarian prevalence in Okinawa. *J Gerontol A Biol Sci Med Sci*. 2008;63(4):338–49.
2547. Shao A, Drewnowski A, Willcox DC, et al. Optimal nutrition and the ever-changing dietary landscape: a conference report. *Eur J Nutr*. 2017;56(Suppl 1):1–21.
2548. Willcox DC, Scapagnini G, Willcox BJ. Healthy aging diets other than the Mediterranean: a focus on the Okinawan diet. *Mech Ageing Dev*. 2014;136–137:148–62.

2549. Willcox BJ, Willcox DC, Todoriki H, et al. Caloric restriction, the traditional Okinawan diet, and healthy aging: the diet of the world's longest-lived people and its potential impact on morbidity and life span. *Ann N Y Acad Sci*. 2007;1114:434–55.
2550. Willcox BJ, Willcox DC, Todoriki H, et al. Caloric restriction, the traditional Okinawan diet, and healthy aging: the diet of the world's longest-lived people and its potential impact on morbidity and life span. *Ann N Y Acad Sci*. 2007;1114:434–55.
2551. Willcox DC, Willcox BJ, Todoriki H, Suzuki M. The Okinawan diet: health implications of a low-calorie, nutrient-dense, antioxidant-rich dietary pattern low in glycemic load. *J Am Coll Nutr*. 2009;28 Suppl:500S-16S.
2552. Suzuki M, Willcox DC, Rosenbaum MW, Willcox BJ. Oxidative stress and longevity in Okinawa: an investigation of blood lipid peroxidation and tocopherol in Okinawan centenarians. *Curr Gerontol Geriatr Res*. 2010;2010:380460.
2553. Suzuki M, Wilcox BJ, Wilcox CD. Implications from and for food cultures for cardiovascular disease: longevity. *Asia Pac J Clin Nutr*. 2001;10(2):165–71.
2554. Willcox DC, Willcox BJ, Todoriki H, Suzuki M. The Okinawan diet: health implications of a low-calorie, nutrient-dense, antioxidant-rich dietary pattern low in glycemic load. *J Am Coll Nutr*. 2009;28 Suppl:500S-16S.
2555. Willcox DC, Scapagnini G, Willcox BJ. Healthy aging diets other than the Mediterranean: a focus on the Okinawan diet. *Mech Ageing Dev*. 2014;136–7:148–62.
2556. Willcox BJ, Willcox DC. Caloric restriction, caloric restriction mimetics, and healthy aging in Okinawa: controversies and clinical implications. *Curr Opin Clin Nutr Metab Care.* 2014;17(1):51–8.
2557. Chen X, Jiao J, Zhuang P, et al. Current intake levels of potatoes and all-cause mortality in China: a population-based nationwide study. *Nutrition*. 2021;81:110902.
2558. Center for Science in the Public Interest. 10 Best Foods. https://cspinet.org/eating-healthy/what-eat/10-best-foods. Accessed January 5, 2022.

2559. Wilson CD, Pace RD, Bromfield E, Jones G, Lu JY. Consumer acceptance of vegetarian sweet potato products intended for space missions. *Life Support Biosph Sci*. 1998;5(3):339–46.
2560. Drewnowski A. New metrics of affordable nutrition: which vegetables provide most nutrients for least cost? *J Acad Nutr Diet*. 2013;113(9):1182–7.
2561. Sunthonkun P, Palajai R, Somboon P, Suan CL, Ungsurangsri M, Soontorngun N. Life-span extension by pigmented rice bran in the model yeast *Saccharomyces cerevisiae*. *Sci Rep*. 2019;9(1):18061.
2562. Chen W, Müller D, Richling E, Wink M. Anthocyanin-rich purple wheat prolongs the life span of *Caenorhabditis elegans* probably by activating the DAF-16/FOXO transcription factor. *J Agric Food Chem*. 2013;61(12):3047–53.
2563. Zuo Y, Peng C, Liang Y, et al. Black rice extract extends the lifespan of fruit flies. *Food Funct*. 2012;3(12):1271–9.
2564. Lu X, Zhou Y, Wu T, Hao L. Ameliorative effect of black rice anthocyanin on senescent mice induced by D-galactose. *Food Funct*. 2014;5(11):2892–7.
2565. Kano M, Takayanagi T, Harada K, Makino K, Ishikawa F. Antioxidative activity of anthocyanins from purple sweet potato, *Ipomoera batatas* cultivar Ayamurasaki. *Biosci Biotechnol Biochem*. 2005;69(5):979–88.
2566. Majid M, Nasir B, Zahra SS, Khan MR, Mirza B, Haq I. *Ipomoea batatas* L. Lam. ameliorates acute and chronic inflammations by suppressing inflammatory mediators, a comprehensive exploration using in vitro and in vivo models. *BMC Complement Altern Med*. 2018;18(1):216.
2567. Wang YJ, Zheng YL, Lu J, et al. Purple sweet potato color suppresses lipopolysaccharide-induced acute inflammatory response in mouse brain. *Neurochem Int*. 2010;56(3):424–30.
2568. Wu DM, Lu J, Zheng YL, Zhou Z, Shan Q, Ma DF. Purple sweet potato color repairs D-galactose-induced spatial learning and memory impairment by regulating the expression of synaptic proteins. *Neurobiol Learn Mem*. 2008;90(1):19–27.
2569. Sun C, Diao Q, Lu J, et al. Purple sweet potato color attenuated NLRP3 inflammasome by inducing autophagy to delay endothelial

senescence. *J Cell Physiol.* 2019;234(5):5926–39.
2570. Su W, Zhang C, Chen F, et al. Purple sweet potato color protects against hepatocyte apoptosis through Sirt1 activation in high-fat-diet-treated mice. *Food Nutr Res*. 2020;64:10.29219/fnr.v64.1509.
2571. Han Y, Guo Y, Cui SW, Li H, Shan Y, Wang H. Purple Sweet Potato Extract extends lifespan by activating autophagy pathway in male *Drosophila melanogaster*. *Exp Gerontol*. 2021;144:111190.
2572. Zhang X, Yang Y, Wu Z, Weng P. The modulatory effect of anthocyanins from purple sweet potato on human intestinal microbiota in vitro. *J Agric Food Chem*. 2016;64(12):2582–90.
2573. Suda I, Ishikawa F, Hatakeyama M, et al. Intake of purple sweet potato beverage affects on serum hepatic biomarker levels of healthy adult men with borderline hepatitis. *Eur J Clin Nutr*. 2008;62(1):60–7.
2574. Willcox DC, Willcox BJ, Todoriki H, Suzuki M. The Okinawan diet: health implications of a low-calorie, nutrient-dense, antioxidant-rich dietary pattern low in glycemic load. *J Am Coll Nutr*. 2009;28(sup4):500S-16S.
2575. Shi Z, Zhang T, Byles J, Martin S, Avery JC, Taylor AW. Food habits, lifestyle factors and mortality among oldest old Chinese: the Chinese Longitudinal Healthy Longevity Survey (CLHLS). *Nutrients*. 2015;7(9):7562–79.
2576. Mejia SB, Messina M, Li SS, et al. A meta-analysis of 46 studies identified by the FDA demonstrates that soy protein decreases circulating LDL and total cholesterol concentrations in adults. *J Nutr*. 2019;149(6):968–81.
2577. Mosallanezhad Z, Mahmoodi M, Ranjbar S, et al. Soy intake is associated with lowering blood pressure in adults: a systematic review and meta-analysis of randomized double-blind placebo-controlled trials. *Complement Ther Med*. 2021;59:102692.
2578. Bazzano LA, Thompson AM, Tees MT, Nguyen CH, Winham DM. Non-soy legume consumption lowers cholesterol levels: a meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis.* 2011;21(2):94–103.
2579. Mejia SB, Messina M, Li SS, et al. A meta-analysis of 46 studies identified by the FDA demonstrates that soy protein decreases

circulating LDL and total cholesterol concentrations in adults. *J Nutr*. 2019;149(6):968–81.

2580. Tokede OA, Onabanjo TA, Yansane A, Gaziano JM, Djoussé L. Soya products and serum lipids: a meta-analysis of randomised controlled trials. *Br J Nutr*. 2015;114(6):831–43.

2581. Yan Z, Zhang X, Li C, Jiao S, Dong W. Association between consumption of soy and risk of cardiovascular disease: a meta-analysis of observational studies. *Eur J Prev Cardiol*. 2017;24(7):735–47.

2582. Nachvak SM, Moradi S, Anjom-Shoae J, et al. Soy, soy isoflavones, and protein intake in relation to mortality from all causes, cancers, and cardiovascular diseases: a systematic review and dose-response meta-analysis of prospective cohort studies. *J Acad Nutr Diet*. 2019;119(9):1483–1500.e17.

2583. D'elia L, Rossi G, Ippolito R, Cappuccio FP, Strazzullo P. Habitual salt intake and risk of gastric cancer: a meta-analysis of prospective studies. *Clin Nutr.* 2012;31(4):489–98.

2584. Kanda A, Hoshiyama Y, Kawaguchi T. Association of lifestyle parameters with the prevention of hypertension in elderly Japanese men and women: a four-year follow-up of normotensive subjects. *Asia Pac J Public Health.* 1999;11(2):77–81.

2585. Ito K. Review of the health benefits of habitual consumption of miso soup: focus on the effects on sympathetic nerve activity, blood pressure, and heart rate. *Environ Health Prev Med*. 2020;25(1):45.

2586. Kondo H, Tomari HS, Yamakawa S, et al. Long-term intake of miso soup decreases nighttime blood pressure in subjects with high-normal blood pressure or stage I hypertension. *Hypertens Res*. 2019;42(11):1757–67.

2587. Du DD, Yoshinaga M, Sonoda M, Kawakubo K, Uehara Y. Blood pressure reduction by Japanese traditional Miso is associated with increased diuresis and natriuresis through dopamine system in Dahl salt-sensitive rats. *Clin Exp Hypertens*. 2014;36(5):359–66.

2588. Willcox BJ, Willcox DC. Caloric restriction, caloric restriction mimetics, and healthy aging in Okinawa: controversies and clinical implications. *Curr Opin Clin Nutr Metab Care.* 2014;17(1):51–8.

2589. Iso H, Kubota Y. Nutrition and disease in the Japan Collaborative Cohort Study for evaluation of cancer (JACC). *Asian Pac J Cancer Prev*. 2007;8 Suppl:35–80.
2590. Lashmanova E, Proshkina E, Zhikrivetskaya S, et al. Fucoxanthin increases lifespan of *Drosophila melanogaster* and *Caenorhabditis elegans*. *Pharmacol Res*. 2015;100:228–41.
2591. Zhao T, Zhang Q, Qi H, Liu X, Li Z. Extension of life span and improvement of vitality of *Drosophila melanogaster* by long-term supplementation with different molecular weight polysaccharides from *Porphyra haitanensis*. *Pharmacol Res*. 2008;57(1):67–72.
2592. Wada K, Nakamura K, Tamai Y, et al. Seaweed intake and blood pressure levels in healthy pre-school Japanese children. *Nutr J*. 2011;10:83.
2593. Ono A, Shibaoka M, Yano J, Asai Y, Fujita T. Eating habits and intensity of medication in elderly hypertensive outpatients. *Hypertens Res*. 2000;23(3):195–200.
2594. Teas J, Baldeón ME, Chiriboga DE, Davis JR, Sarriés AJ, Braverman LE. Could dietary seaweed reverse the metabolic syndrome? *Asia Pac J Clin Nutr*. 2009;18(2):145–54.
2595. Ma W, He X, Braverman L. Iodine content in milk alternatives. *Thyroid*. 2016;26(9):1308–10.
2596. Flachowsky G, Franke K, Meyer U, Leiterer M, Schöne F. Influencing factors on iodine content of cow milk. *Eur J Nutr*. 2014;53(2):351–65.
2597. Teas J, Pino S, Critchley A, Braverman LE. Variability of iodine content in common commercially available edible seaweeds. *Thyroid*. 2004;14(10):836–41.
2598. Combet E. Iodine status, thyroid function, and vegetarianism. In: *Vegetarian and Plant-Based Diets in Health and Disease Prevention*. Elsevier; 2017:769–90.
2599. Willcox DC, Willcox BJ, Todoriki H, Suzuki M. The Okinawan diet: health implications of a low-calorie, nutrient-dense, antioxidant-rich dietary pattern low in glycemic load. *J Am Coll Nutr*. 2009;28 Suppl:500S-16S.
2600. Sánchez JE, Jiménez-Pérez G, Liedo P. Can consumption of antioxidant rich mushrooms extend longevity?: antioxidant activity of

Pleurotus spp. and its effects on Mexican fruit flies' (*Anastrepha ludens*) longevity. *Age (Dordr)*. 2015;37(6):107.
2601. Beelman RB, Kalaras MD, Phillips AT, Richie JP. Is ergothioneine a 'longevity vitamin' limited in the American diet? *J Nutr Sci*. 2020;9:e52.
2602. Beelman RB, Kalaras MD, Phillips AT, Richie JP. Is ergothioneine a 'longevity vitamin' limited in the American diet? *J Nutr Sci*. 2020;9:e52.
2603. Ames BN. Prolonging healthy aging: longevity vitamins and proteins. *Proc Natl Acad Sci U S A*. 2018;115(43):10836–44.
2604. Smith E, Ottosson F, Hellstrand S, et al. Ergothioneine is associated with reduced mortality and decreased risk of cardiovascular disease. *Heart*. 2020;106(9):691–7.
2605. Paul BD, Snyder SH. The unusual amino acid L-ergothioneine is a physiologic cytoprotectant. *Cell Death Differ.* 2010;17(7):1134–40.
2606. Beelman RB, Kalaras MD, Phillips AT, Richie JP. Is ergothioneine a 'longevity vitamin' limited in the American diet? *J Nutr Sci*. 2020;9:e52.
2607. Beelman RB, Kalaras MD, Richie JP. Micronutrients and bioactive compounds in mushrooms: a recipe for healthy aging? *Nutr Today*. 2019;54(1):16–22.
2608. Ba DM, Gao X, Al-Shaar L, et al. Prospective study of dietary mushroom intake and risk of mortality: results from continuous National Health and Nutrition Examination Survey (NHANES) 2003–2014 and a meta-analysis. *Nutr J*. 2021;20(1):80.
2609. Cheah IK, Feng L, Tang RMY, Lim KHC, Halliwell B. Ergothioneine levels in an elderly population decrease with age and incidence of cognitive decline; a risk factor for neurodegeneration? *Biochem Biophys Res Commun*. 2016;478(1):162–7.
2610. Kameda M, Teruya T, Yanagida M, Kondoh H. Frailty markers comprise blood metabolites involved in antioxidation, cognition, and mobility. *Proc Natl Acad Sci U S A*. 2020;117(17):9483–9.
2611. Cheah IK, Feng L, Tang RMY, Lim KHC, Halliwell B. Ergothioneine levels in an elderly population decrease with age and incidence of cognitive decline; a risk factor for neurodegeneration? *Biochem Biophys Res Commun*. 2016;478(1):162–7.

2612. Lagrange E, Vernoux JP. Warning on false or true morels and button mushrooms with potential toxicity linked to hydrazinic toxins: an update. *Toxins (Basel)*. 2020;12(8):482.
2613. Heer RS, Patel NB, Mandal AKJ, Lewis F, Missouris CG. Not a fungi to be with: shiitake mushroom flagellate dermatitis. *Am J Emerg Med*. 2020;38(2):412.e1–2.
2614. Stijve T, Pittet A. Absence of agaritine in *Pleurotus* species and in other cultivated and wild-growing mushrooms not belonging to the genus *Agaricus*. *Dtsch Lebensm-Rundsch*. 2000;96(7):251–4.
2615. Money NP. Are mushrooms medicinal? *Fungal Biol*. 2016;120(4):449–53.
2616. Money NP. Are mushrooms medicinal? *Fungal Biol*. 2016;120(4):449–53.
2617. Litten W. The most poisonous mushrooms. *Sci Am*. 1975;232(3):90–101.
2618. Lim CS, Chhabra N, Leikin S, Fischbein C, Mueller GM, Nelson ME. Atlas of select poisonous plants and mushrooms. *Dis Mon*. 2016;62(3):41–66.
2619. Culliton BJ. The destroying angel: a story of a search for an antidote. *Science*. 1974;185(4151):600–1.
2620. Loyd AL, Richter BS, Jusino MA, et al. Identifying the "mushroom of immortality": assessing the *Ganoderma* species composition in commercial reishi products. *Front Microbiol*. 2018;9:1557.
2621. Wang J, Cao B, Zhao H, Feng J. Emerging roles of *Ganoderma lucidum* in anti-aging. *Aging Dis*. 2017;8(6):691–707.
2622. Pan Y, Lin Z. Anti-aging effect of *Ganoderma* (Lingzhi) with health and fitness. *Adv Exp Med Bio*. 2019;1182:299–309.
2623. Cuong VT, Chen W, Shi J, et al. The anti-oxidation and anti-aging effects of *Ganoderma lucidum* in *Caenorhabditis elegans*. *Exp Gerontol*. 2019;117:99–105.
2624. Wang J, Cao B, Zhao H, Feng J. Emerging roles of *Ganoderma lucidum* in anti-aging. *Aging Dis*. 2017;8(6):691–707.
2625. Hsu KD, Cheng KC. From nutraceutical to clinical trial: frontiers in *Ganoderma* development. *App Microbiol Biotechnol*. 2018;102(21).
2626. Loyd AL, Richter BS, Jusino MA, et al. Identifying the "mushroom of immortality": assessing the *Ganoderma* species composition in

commercial reishi products. *Front Microbiol*. 2018;9:1557.
2627. Loyd AL, Richter BS, Jusino MA, et al. Identifying the "mushroom of immortality": assessing the *Ganoderma* species composition in commercial reishi products. *Front Microbiol*. 2018;9:1557.
2628. Totelin L. When foods become remedies in ancient Greece: The curious case of garlic and other substances. *J Ethnopharmacol*. 2015;167:30–7.
2629. Shi X, Lv Y, Mao C, et al. Garlic consumption and all-cause mortality among Chinese oldest-old individuals: a population-based cohort study. *Nutrients*. 2019;11(7):E1504.
2630. Lau KK, Chan YH, Wong YK, et al. Garlic intake is an independent predictor of endothelial function in patients with ischemic stroke. *J Nutr Health Aging*. 2013;17(7):600–4.
2631. Mahdavi-Roshan M, Mirmiran P, Arjmand M, Nasrollahzadeh J. Effects of garlic on brachial endothelial function and capacity of plasma to mediate cholesterol efflux in patients with coronary artery disease. *Anatol J Cardiol*. 2017;18(2):116–21.
2632. Mahdavi-Roshan M, Zahedmehr A, Mohammad-Zadeh A, et al. Effect of garlic powder tablet on carotid intima-media thickness in patients with coronary artery disease: a preliminary randomized controlled trial. *Nutr Health*. 2013;22(2):143–55.
2633. Shabani E, Sayemiri K, Mohammadpour M. The effect of garlic on lipid profile and glucose parameters in diabetic patients: a systematic review and meta-analysis. *Prim Care Diabetes*. 2019;13(1):28–42.
2634. Xiong XJ, Wang PQ, Li SJ, Li XK, Zhang YQ, Wang J. Garlic for hypertension: a systematic review and meta-analysis of randomized controlled trials. *Phytomedicine*. 2015;22(3):352–61.
2635. Atkin M, Laight D, Cummings MH. The effects of garlic extract upon endothelial function, vascular inflammation, oxidative stress and insulin resistance in adults with type 2 diabetes at high cardiovascular risk. A pilot double blind randomized placebo controlled trial. *J Diabetes Complications*. 2016;30(4):723–7.
2636. Soleimani D, Paknahad Z, Askari G, Iraj B, Feizi A. Effect of garlic powder consumption on body composition in patients with nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled trial. *Adv Biomed Res*. 2016;5:2.

2637. Shabani E, Sayemiri K, Mohammadpour M. The effect of garlic on lipid profile and glucose parameters in diabetic patients: a systematic review and meta-analysis. *Prim Care Diabetes*. 2019;13(1):28–42.
2638. Rajan TV, Hein M, Porte P, Wikel S. A double-blinded, placebo-controlled trial of garlic as a mosquito repellant: a preliminary study. *Med Vet Entomol*. 2005;19(1):84–9.
2639. Stjernberg L, Berglund J. Garlic as an insect repellent. *JAMA*. 2000;284(7):831.
2640. Tunón H. Garlic as a tick repellent. *JAMA*. 2001;285(1):41–2.
2641. Yusof YAM. Gingerol and its role in chronic diseases. *Adv Exp Med Biol*. 2016;929:177–207.
2642. Liu J, Shi JZ, Yu LM, Goyer RA, Waalkes MP. Mercury in traditional medicines: is cinnabar toxicologically similar to common mercurials? *Exp Biol Med (Maywood)*. 2008;233(7):810–7.
2643. Anh NH, Kim SJ, Long NP, et al. Ginger on human health: a comprehensive systematic review of 109 randomized controlled trials. *Nutrients*. 2020;12(1):E157.
2644. Bodagh MN, Maleki I, Hekmatdoost A. Ginger in gastrointestinal disorders: a systematic review of clinical trials. *Food Sci Nutr*. 2018;7(1):96–108.
2645. Mowrey DB, Clayson DE. Motion sickness, ginger, and psychophysics. *Lancet.* 1982;1(8273):655–7.
2646. Palatty PL, Haniadka R, Valder B, Arora R, Baliga MS. Ginger in the prevention of nausea and vomiting: a review. *Crit Rev Food Sci Nutr.* 2013;53(7):659–69.
2647. Adib-Hajbaghery M, Hosseini FS. Investigating the effects of inhaling ginger essence on post-nephrectomy nausea and vomiting. *Complement Ther Med*. 2015;23(6):827–31.
2648. Bartels EM, Folmer VN, Bliddal H, et al. Efficacy and safety of ginger in osteoarthritis patients: a meta-analysis of randomized placebo-controlled trials. *Osteoarthritis Cartilage*. 2015;23(1):13–21.
2649. Khayat S, Kheirkhah M, Behboodi Moghadam Z, Fanaei H, Kasaeian A, Javadimehr M. Effect of treatment with ginger on the severity of premenstrual syndrome symptoms. *ISRN Obstet Gynecol*. 2014;2014:792708.

2650. Ozgoli G, Goli M, Moattar F. Comparison of effects of ginger, mefenamic acid, and ibuprofen on pain in women with primary dysmenorrhea. *J Altern Complement Med*. 2009;15(2):129–32.
2651. Martins LB, Rodrigues AMdS, Monteze NM, et al. Double-blind placebo-controlled randomized clinical trial of ginger (*Zingiber officinale* Rosc.) in the prophylactic treatment of migraine. *Cephalalgia*. 2020;40(1):88–95.
2652. Chen L, Cai Z. The efficacy of ginger for the treatment of migraine: a meta-analysis of randomized controlled studies. *Am J Emerg Med*. 2021;46:567–71.
2653. Pourmasoumi M, Hadi A, Rafie N, Najafgholizadeh A, Mohammadi H, Rouhani MH. The effect of ginger supplementation on lipid profile: a systematic review and meta-analysis of clinical trials. *Phytomedicine*. 2018;43:28–36.
2654. Makhdoomi Arzati M, Mohammadzadeh Honarvar N, Saedisomeolia A, et al. The effects of ginger on fasting blood sugar, hemoglobin A1c, and lipid profiles in patients with type 2 diabetes. *Int J Endocrinol Metab*. 2017;15(4):e57927.
2655. Hasani H, Arab A, Hadi A, Pourmasoumi M, Ghavami A, Miraghajani M. Does ginger supplementation lower blood pressure? A systematic review and meta-analysis of clinical trials. *Phytother Res*. 2019;33(6):1639–47.
2656. Maharlouei N, Tabrizi R, Lankarani KB, et al. The effects of ginger intake on weight loss and metabolic profiles among overweight and obese subjects: a systematic review and meta-analysis of randomized controlled trials. *Crit Rev Food Sci Nutr*. 2018:1–14.
2657. Morvaridzadeh M, Sadeghi E, Agah S, et al. Effect of ginger (*Zingiber officinale*) supplementation on oxidative stress parameters: a systematic review and meta-analysis. *J Food Biochem*. 2021;45(2):e13612.
2658. Mazidi M, Gao HK, Rezaie P, Ferns GA. The effect of ginger supplementation on serum C-reactive protein, lipid profile and glycaemia: a systematic review and meta-analysis. *Food Nutr Res*. 2016;60:32613.
2659. Choi JG, Kim SY, Jeong M, Oh MS. Pharmacotherapeutic potential of ginger and its compounds in age-related neurological disorders.

Pharmacol Ther. 2018;182:56–69.
2660. Bischoff-Kont I, Fürst R. Benefits of ginger and its constituent 6-shogaol in inhibiting inflammatory processes. *Pharmaceuticals (Basel)*. 2021;14(6):571.
2661. Teschke R, Xuan TD. Viewpoint: a contributory role of shell ginger (*Alpinia zerumbet*) for human longevity in Okinawa, Japan? *Nutrients*. 2018;10(2):166.
2662. Upadhyay A, Chompoo J, Taira N, Fukuta M, Tawata S. Significant longevity-extending effects of *Alpinia zerumbet* leaf extract on the life span of *Caenorhabditis elegans*. *Biosci Biotechnol Biochem*. 2013;77(2):217–23.
2663. Rasheed N. Ginger and its active constituents as therapeutic agents: recent perspectives with molecular evidences. *Int J Health Sci (Qassim)*. 2020;14(6):1–3.
2664. Lee EB, Kim JH, Kim YJ, et al. Lifespan-extending property of 6-shogaol from *Zingiber officinale* Roscoe in *Caenorhabditis elegans*. *Arch Pharm Res*. 2018;41(7):743–52.
2665. Percival SS, Vanden Heuvel JP, Nieves CJ, Montero C, Migliaccio AJ, Meadors J. Bioavailability of herbs and spices in humans as determined by ex vivo inflammatory suppression and DNA strand breaks. *J Am Coll Nutr*. 2012;31(4):288–94.
2666. Stępień K, Wojdyła D, Nowak K, Mołoń M. Impact of curcumin on replicative and chronological aging in the *Saccharomyces cerevisiae* yeast. *Biogerontology*. 2020;21(1):109–23.
2667. Liao VHC, Yu CW, Chu YJ, Li WH, Hsieh YC, Wang TT. Curcumin-mediated lifespan extension in *Caenorhabditis elegans*. *Mech Ageing Dev*. 2011;132(10):480–7.
2668. Suckow BK, Suckow MA. Lifespan extension by the antioxidant curcumin in *Drosophila melanogaster*. *Int J Biomed Sci*. 2006;2(4):402–5.
2669. Kitani K, Osawa T, Yokozawa T. The effects of tetrahydrocurcumin and green tea polyphenol on the survival of male C57BL/6 mice. *Biogerontology*. 2007;8(5):567–73.
2670. Lao CD, Ruffin MT IV, Normolle D, et al. Dose escalation of a curcuminoid formulation. *BMC Complement Altern Med*. 2006;6:10.

2671. Bala K, Tripathy BC, Sharma D. Neuroprotective and anti-ageing effects of curcumin in aged rat brain regions. *Biogerontology*. 2006;7(2):81–9.
2672. Percival SS, Vanden Heuvel JP, Nieves CJ, Montero C, Migliaccio AJ, Meadors J. Bioavailability of herbs and spices in humans as determined by ex vivo inflammatory suppression and DNA strand breaks. *J Am Coll Nutr*. 2012;31(4):288–94.
2673. Percival SS, Vanden Heuvel JP, Nieves CJ, Montero C, Migliaccio AJ, Meadors J. Bioavailability of herbs and spices in humans as determined by ex vivo inflammatory suppression and DNA strand breaks. *J Am Coll Nutr*. 2012;31(4):288–94.
2674. DiSilvestro RA, Joseph E, Zhao S, Bomser J. Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. *Nutr J*. 2012;11:79.
2675. Rakha A, Rehman K, Babar Imran M, Shahid M, Jahan N. Mitigation of ^{131}-I induced oxidative stress by supplementation of turmeric and green cardamom in thyroid patients. *Int J Radiat Res*. 2022;20(1):29–36.
2676. Thorogood M, Appleby PN, Key TJ, Mann J. Relation between body mass index and mortality in an unusually slim cohort. *J Epidemiol Community Health*. 2003;57(2):130–3.
2677. Aune D, Sen A, Prasad M, et al. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. *BMJ*. 2016;353:i2156.
2678. Willcox DC, Willcox BJ, Todoriki H, Curb JD, Suzuki M. Caloric restriction and human longevity: what can we learn from the Okinawans? *Biogerontology*. 2006;7(3):173–7.
2679. Willcox DC, Scapagnini G, Willcox BJ. Healthy aging diets other than the Mediterranean: a focus on the Okinawan diet. *Mech Ageing Dev*. 2014;136–7:148–62.
2680. Willcox BJ, Willcox DC, Todoriki H, et al. Caloric restriction, the traditional Okinawan diet, and healthy aging: the diet of the world's longest-lived people and its potential impact on morbidity and life span. *Ann N Y Acad Sci*. 2007;1114:434–55.

2681. Fraser GE, Shavlik DJ. Ten years of life: is it a matter of choice? *Arch Intern Med*. 2001;161(13):1645–52.
2682. Willcox BJ, Willcox DC. Caloric restriction, caloric restriction mimetics, and healthy aging in Okinawa: controversies and clinical implications. *Curr Opin Clin Nutr Metab Care*. 2014;17(1):51–8.
2683. Fraser GE, Shavlik DJ. Ten years of life: is it a matter of choice? *Arch Intern Med*. 2001;161(13):1645–52.
2684. Gavrilova NS, Gavrilov LA. Comments on dietary restriction, Okinawa diet and longevity. *Gerontology*. 2012;58(3):221–3.
2685. Willcox DC, Willcox BJ, Todoriki H, Suzuki M. The Okinawan diet: health implications of a low-calorie, nutrient-dense, antioxidant-rich dietary pattern low in glycemic load. *J Am Coll Nutr*. 2009;28 Suppl:500S-16S.
2686. Willcox DC, Scapagnini G, Willcox BJ. Healthy aging diets other than the Mediterranean: a focus on the Okinawan diet. *Mech Ageing Dev*. 2014;136–7:148–62.
2687. Martínez-González MA, Gea A, Ruiz-Canela M. The Mediterranean diet and cardiovascular health. *Circ Res*. 2019;124(5):779–98.
2688. Marston HR, Niles-Yokum K, Silva PA. A commentary on Blue Zones®: a critical review of age-friendly environments in the 21st century and beyond. *Int J Environ Res Public Health*. 2021;18(2):837.
2689. Willcox DC, Scapagnini G, Willcox BJ. Healthy aging diets other than the Mediterranean: a focus on the Okinawan diet. *Mech Ageing Dev*. 2014;136–7:148–62.
2690. Cockerham WC, Yamori Y. Okinawa: an exception to the social gradient of life expectancy in Japan. *Asia Pac J Clin Nutr*. 2001;10(2):154–8.
2691. Willcox DC, Willcox BJ, Todoriki H, Suzuki M. The Okinawan diet: health implications of a low-calorie, nutrient-dense, antioxidant-rich dietary pattern low in glycemic load. *J Am Coll Nutr*. 2009;28(sup4):500S-16S.
2692. Bajpai P. World's 5 richest nations by GDP per capita. Nasdaq. https://www.nasdaq.com/articles/worlds-5-richest-nations-by-gdp-per-capita-2021–05–20. Published May 20, 2021. Accessed January 10, 2022.

2693. Robert L, Fulop T. Longevity and its regulation: centenarians and beyond. *Interdiscip Top Gerontol*. 2014;39:198–211.
2694. Fraser GE, Shavlik DJ. Ten years of life: is it a matter of choice? *Arch Intern Med*. 2001;161(13):1645–52.
2695. Kent LM, Morton DP, Ward EJ, et al. The influence of religious affiliation on participant responsiveness to the Complete Health Improvement Program (CHIP) lifestyle intervention. *J Relig Health*. 2016;55(5):1561–73.
2696. Fraser GE. Diet as primordial prevention in Seventh-Day Adventists. *Prev Med*. 1999;29(6):S18–23.
2697. Orlich MJ, Chiu THT, Dhillon PK, et al. Vegetarian epidemiology: review and discussion of findings from geographically diverse cohorts. *Adv Nutr*. 2019;10(Suppl_4):S284–95.
2698. Sloan RP, Bagiella E, Powell T. Religion, spirituality, and medicine. *Lancet*. 1999;353(9153):664–7.
2699. Chida Y, Steptoe A, Powell LH. Religiosity/spirituality and mortality: a systematic quantitative review. *Psychother Psychosom*. 2009;78(2):81–90.
2700. Sullivan AR. Mortality differentials and religion in the United States: religious affiliation and attendance. *J Sci Study Relig*. 2010;49(4):740–53.
2701. Schnall E, Wassertheil-Smoller S, Swencionis C, et al. The relationship between religion and cardiovascular outcomes and all-cause mortality in the Women's Health Initiative Observational Study. *Psychol Health*. 2010;25(2):249–63.
2702. Hill TD, Ellison CG, Burdette AM, Taylor J, Friedman KL. Dimensions of religious involvement and leukocyte telomere length. *Soc Sci Med*. 2016;163:168–75.
2703. Koenig HG, Nelson B, Shaw SF, Saxena S, Cohen HJ. Religious involvement and telomere length in women family caregivers. *J Nerv Ment Dis*. 2016;204(1):36–42.
2704. Schnall E, Wassertheil-Smoller S, Swencionis C, et al. The relationship between religion and cardiovascular outcomes and all-cause mortality in the Women's Health Initiative Observational Study. *Psychol Health*. 2010;25(2):249–63.

2705. Sloan RP, Bagiella E, Powell T. Religion, spirituality, and medicine. *Lancet*. 1999;353(9153):664–7.
2706. Morton D, Rankin P, Kent L, Dysinger W. The Complete Health Improvement Program (CHIP): history, evaluation, and outcomes. *Am J Lifestyle Med*. 2016;10(1):64–73.
2707. Kent LM, Morton DP, Ward EJ, et al. The influence of religious affiliation on participant responsiveness to the Complete Health Improvement Program (CHIP) lifestyle intervention. *J Relig Health*. 2016;55(5):1561–73.
2708. World Health Organization. WHO Laboratory Manual for the Examination and Processing of Human Semen. 5th ed. WHO Press; 2010.
2709. Orzylowska EM, Jacobson JD, Bareh GM, Ko EY, Corselli JU, Chan PJ. Food intake diet and sperm characteristics in a blue zone: a Loma Linda Study. *Eur J Obstet Gynecol Reprod Biol*. 2016;203:112–5.
2710. Messina M, Watanabe S, Setchell KDR. Report on the 8th international symposium on the role of soy in health promotion and chronic disease prevention and treatment. *J Nutr*. 2009;139(4):796S-802S.
2711. Zhang Y, Hood WR. Current versus future reproduction and longevity: a re-evaluation of predictions and mechanisms. *J Exp Biol*. 2016;219(Pt 20):3177–89.
2712. Mukhopadhyay A, Tissenbaum HA. Reproduction and longevity: secrets revealed by *C. elegans*. *Trends Cell Biol*. 2007;17(2):65–71.
2713. Hsin H, Kenyon C. Signals from the reproductive system regulate the lifespan of *C. elegans*. *Nature*. 1999;399(6734):362–6.
2714. Flatt T, Min KJ, D'Alterio C, et al. *Drosophila* germ-line modulation of insulin signaling and lifespan. *Proc Natl Acad Sci U S A*. 2008;105(17):6368–73.
2715. American Veterinary Medical Association. Banfield: spaying, neutering correlate with longer lives. JAVMA News. https://www.avma.org/javma-news/2013–07–01/banfield-spaying-neutering-correlate-longer-lives. Published June 19, 2013. Accessed January 10, 2022.
2716. Banfield Pet Hospital. State of Pet Health 2013 Report. Banfield.com. https://www.banfield.com/-/media/Project/Banfield/Main/en/general/

SOPH-Infographic/PDFs/Banfield-State-of-Pet-Health-Report_2013.pdf?rev=a8612f3fa39141e3bf2876a5ed6760de&hash=D79B771D2C3539DF737353E65D310504. Accessed February 21, 2022.

2717. Min KJ, Lee CK, Park HN. The lifespan of Korean eunuchs. *Curr Biol*. 2012;22(18):R792–3.

2718. Reilly PR. Involuntary sterilization in the United States: a surgical solution. *Q Rev Biol*. 1987;62(2):153–70.

2719. *Buck v. Bell*, 274 US 200 (1927).

2720. Hamilton JB, Mestler GE. Mortality and survival: comparison of eunuchs with intact men and women in a mentally retarded population. *J Gerontol*. 1969;24(4):395–411.

2721. Hsu CH, Posegga O, Fischbach K, Engelhardt H. Examining the trade-offs between human fertility and longevity over three centuries using crowdsourced genealogy data. *PLoS One*. 2021;16(8):e0255528.

2722. Tabatabaie V, Atzmon G, Rajpathak SN, Freeman R, Barzilai N, Crandall J. Exceptional longevity is associated with decreased reproduction. *Aging (Albany NY)*. 2011;3(12):1202–5.

2723. Zwaan B, Bijlsma R, Hoekstra RF. Direct selection on life span in *Drosophila melanogaster*. *Evolution*. 1995;49(4):649–59.

2724. Mukhopadhyay A, Tissenbaum HA. Reproduction and longevity: secrets revealed by *C. elegans*. *Trends Cell Biol*. 2007;17(2):65–71.

2725. Franklin JC, Scheile BC, Brozek J, Keys A. Observations on human behavior in experimental semi-starvation and rehabilitation. *J Clin Psychol*. 1948;4(1):28–45.

2726. Templeman NM, Murphy CT. Regulation of reproduction and longevity by nutrient-sensing pathways. *J Cell Biol*. 2018;217(1):93–106.

2727. Chen X, Liu Y, Sun X, et al. Age at menarche and risk of all-cause and cardiovascular mortality: a systematic review and dose-response meta-analysis. *Menopause*. 2018;26(6):670–6.

2728. Fuhrman BJ, Moore SC, Byrne C, et al. Association of the age at menarche with site-specific cancer risks in pooled data from nine cohorts. *Cancer Res*. 2021;81(8):2246–55.

2729. Chen X, Liu Y, Sun X, et al. Age at menarche and risk of all-cause and cardiovascular mortality: a systematic review and dose-response meta-analysis. *Menopause*. 2018;26(6):670–6.
2730. Goldberg M, D'Aloisio AA, O'Brien KM, Zhao S, Sandler DP. Pubertal timing and breast cancer risk in the Sister Study cohort. *Breast Cancer Res*. 2020;22(1):112.
2731. Fuhrman BJ, Moore SC, Byrne C, et al. Association of the age at menarche with site-specific cancer risks in pooled data from nine cohorts. *Cancer Res*. 2021;81(8):2246–55.
2732. Lee HS. Why should we be concerned about early menarche? *Clin Exp Pediatr*. 2020;64(1):26–7.
2733. Martinez GM. Trends and patterns in menarche in the United States: 1995 through 2013–2017. *Natl Health Stat Report*. 2020;(146):1–12.
2734. Eckert-Lind C, Busch AS, Petersen JH, et al. Worldwide secular trends in age at pubertal onset assessed by breast development among girls: a systematic review and meta-analysis. *JAMA Pediatr*. 2020;174(4):e195881.
2735. Thankamony A, Ong KK, Ahmed ML, Ness AR, Holly JMP, Dunger DB. Higher levels of IGF-I and adrenal androgens at age 8 years are associated with earlier age at menarche in girls. *J Clin Endocrinol Metab*. 2012;97(5):E786–90.
2736. Günther ALB, Karaolis-Danckert N, Kroke A, Remer T, Buyken AE. Dietary protein intake throughout childhood is associated with the timing of puberty. *J Nutr*. 2010;140(3):565–71.
2737. Nguyen NTK, Fan HY, Tsai MC, et al. Nutrient intake through childhood and early menarche onset in girls: systematic review and meta-analysis. *Nutrients*. 2020;12(9):2544.
2738. Rogers IS, Northstone K, Dunger DB, Cooper AR, Ness AR, Emmett PM. Diet throughout childhood and age at menarche in a contemporary cohort of British girls. *Public Health Nutr*. 2010;13(12):2052–63.
2739. Jansen EC, Marín C, Mora-Plazas M, Villamor E. Higher childhood red meat intake frequency is associated with earlier age at menarche. *J Nutr*. 2015;146(4):792–8.
2740. Schecter A, Cramer P, Boggess K, Stanley J, Olson JR. Levels of dioxins, dibenzofurans, PCB and DDE congeners in pooled food

samples collected in 1995 at supermarkets across the United States. *Chemosphere*. 1997;34(5–7):1437–47.
2741. Ouyang F, Perry MJ, Venners SA, et al. Serum DDT, age at menarche, and abnormal menstrual cycle length. *Occup Environ Med*. 2005;62(12):878–84.
2742. Kahleova H, Levin S, Barnard ND. Plant-based diets for healthy aging. *J Am Coll Nutr*. 2021;40(5):478–9.
2743. Fraser GE, Cosgrove CM, Mashchak AD, Orlich MJ, Altekruse SF. Lower rates of cancer and all-cause mortality in an Adventist cohort compared with a US Census population. *Cancer*. 2020;126(5):1102–11.
2744. Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple health outcomes: a systematic review with meta-analysis of observational studies. *Crit Rev Food Sci Nutr*. 2017;57(17):3640–9.
2745. Singh PN, Arthur KN, Orlich MJ, et al. Global epidemiology of obesity, vegetarian dietary patterns, and noncommunicable disease in Asian Indians. *Am J Clin Nutr*. 2014;100 Suppl 1:359S-64S.
2746. Singh PN, Sabaté J, Fraser GE. Does low meat consumption increase life expectancy in humans? *Am J Clin Nutr*. 2003;78(3 Suppl):526S-32S.
2747. Giem P, Beeson WL, Fraser GE. The incidence of dementia and intake of animal products: preliminary findings from the Adventist Health Study. *Neuroepidemiology*. 1993;12(1):28–36.
2748. Donner Y, Fortney K, Calimport SRG, Pfleger K, Shah M, Betts-LaCroix J. Great desire for extended life and health amongst the American public. *Front Genet*. 2015;6:353.
2749. Fraser GE, Shavlik DJ. Ten years of life: is it a matter of choice? *Arch Intern Med*. 2001;161(13):1645–52.
2750. Lin CL, Wang JH, Chang CC, Chiu THT, Lin MN. Vegetarian diets and medical expenditure in Taiwan—a matched cohort study. *Nutrients*. 2019;11(11):E2688.
2751. Kahleova H, Hrachovinova T, Hill M, et al. Vegetarian diet in type 2 diabetes—improvement in quality of life, mood and eating behaviour. *Diabet Med*. 2013;30(1):127–9.

2752. Trapp C, Barnard N, Katcher H. A plant-based diet for type 2 diabetes. *Diabetes Educ*. 2010;36(1):33–48.
2753. Barnard N, Scialli AR, Bertron P, Hurlick D, Edmondset K. Acceptability of a therapeutic low-fat, vegan diet in premenopausal women. *J Nutr Educ*. 2000;32(6):314–9.
2754. Trapp C, Barnard N, Katcher H. A plant-based diet for type 2 diabetes. *Diabetes Educ*. 2010;36(1):33–48.
2755. Hemler EC, Hu FB. Plant-based diets for cardiovascular disease prevention: all plant foods are not created equal. *Curr Atheroscler Rep*. 2019;21(5):18.
2756. Kim H, Caulfield LE, Garcia-Larsen V, Steffen LM, Coresh J, Rebholz CM. Plant-based diets are associated with a lower risk of incident cardiovascular disease, cardiovascular disease mortality, and all-cause mortality in a general population of middle-aged adults. *J Am Heart Assoc*. 2019;8(16):e012865.
2757. Huang J, Liao LM, Weinstein SJ, Sinha R, Graubard BI, Albanes D. Association between plant and animal protein intake and overall and cause-specific mortality. *JAMA Intern Med*. 2020;180(9):1173–84.
2758. Huang J, Liao LM, Weinstein SJ, Sinha R, Graubard BI, Albanes D. Association between plant and animal protein intake and overall and cause-specific mortality. *JAMA Intern Med*. 2020;180(9):1173–84.
2759. Sinha R, Cross AJ, Graubard BI, Leitzmann MF, Schatzkin A. Meat intake and mortality: a prospective study of over half a million people. *Arch Intern Med*. 2009;169(6):562–71.
2760. Popkin BM. Reducing meat consumption has multiple benefits for the world's health. *Arch Intern Med*. 2009;169(6):543.
2761. Huang J, Liao LM, Weinstein SJ, Sinha R, Graubard BI, Albanes D. Association between plant and animal protein intake and overall and cause-specific mortality. *JAMA Intern Med*. 2020;180(9):1173–84.
2762. Ortolá R, Struijk EA, García-Esquinas E, Rodríguez-Artalejo F, Lopez-Garcia E. Changes in dietary intake of animal and vegetable protein and unhealthy aging. *Am J Med*. 2020;133(2):231–9.
2763. Ortolá R, Struijk EA, García-Esquinas E, Rodríguez-Artalejo F, Lopez-Garcia E. Changes in dietary intake of animal and vegetable protein and unhealthy aging. *Am J Med*. 2020;133(2):231–9.

2764. Norman K, Klaus S. Veganism, aging and longevity: new insight into old concepts. *Curr Opin Clin Nutr Metab Care*. 2020;23(2):145–50.
2765. Eleftheriou D, Benetou V, Trichopoulou A, La Vecchia C, Bamia C. Mediterranean diet and its components in relation to all-cause mortality: meta-analysis. *Br J Nutr*. 2018;120(10):1081–97.
2766. Martínez-González MA, Sánchez-Tainta A, Corella D, et al. A provegetarian food pattern and reduction in total mortality in the Prevención con Dieta Mediterránea (PREDIMED) study. *Am J Clin Nutr*. 2014;100 Suppl 1:320S-8S.
2767. Tuso PJ, Ismail MH, Ha BP, Bartolotto C. Nutritional update for physicians: plant-based diets. *Perm J*. 2013;17(2):61–6.
2768. Tuso PJ, Ismail MH, Ha BP, Bartolotto C. Nutritional update for physicians: plant-based diets. *Perm J*. 2013;17(2):61–6.
2769. Kaiser Permanente. Plant-based eating: using the healthy plate to eat well. Center for Healthy Living. https://thrive.kaiserpermanente.org/care-near-you/southern-california/center-for-healthy-living/wp-content/uploads/sites/30/2020/03/plant_based_diet_e.pdf. Updated 2019. Accessed January 17, 2022.
2770. Martínez-González MÁ, Hershey MS, Zazpe I, Trichopoulou A. Transferability of the Mediterranean diet to non-Mediterranean countries. What is and what is not the Mediterranean diet. *Nutrients*. 2017;9(11):E1226.
2771. Avital K, Buch A, Hollander I, Brickner T, Goldbourt U. Adherence to a Mediterranean diet by vegetarians and vegans as compared to omnivores. *Int J Food Sci Nutr*. 2020;71(3):378–87.
2772. M Nestle. Mediterranean diets: historical and research overview. *Am J Clin Nutr*. 1995;61(6):1313S–20S.
2773. Sofi F, Dinu M, Pagliai G, et al. Low-calorie vegetarian versus Mediterranean diets for reducing body weight and improving cardiovascular risk profile: CARDIVEG study (cardiovascular prevention with vegetarian diet). *Circulation*. 2018;137(11):1103–13.
2774. Barnard ND, Alwarith J, Rembert E, et al. A Mediterranean diet and low-fat vegan diet to improve body weight and cardiometabolic risk factors: a randomized, cross-over trial. *J Am Nutr Assoc*. 2022;41(2):127–39.

2775. Tuso PJ, Ismail MH, Ha BP, Bartolotto C. Nutritional update for physicians: plant-based diets. *Perm J.* 2013;17(2):61–6.
2776. Lane MM, Davis JA, Beattie S, et al. Ultraprocessed food and chronic noncommunicable diseases: a systematic review and meta-analysis of 43 observational studies. *Obes Rev*. 2021;22(3):e13146.
2777. Katz DL. Plant-based diets for reversing disease and saving the planet: past, present, and future. *Adv Nutr*. 2019;10(Suppl_4):S304–7.
2778. Gehring J, Touvier M, Baudry J, et al. Consumption of ultra-processed foods by pesco-vegetarians, vegetarians, and vegans: associations with duration and age at diet initiation. *J Nutr*. 2021;151(1):120–31.
2779. Radnitz C, Ni J, Dennis D, Cerrito B. Health benefits of a vegan diet: current insights. *Nutr Diet Suppl*. 2020;12:57–85.
2780. Neff RA, Edwards D, Palmer A, Ramsing R, Righter A, Wolfson J. Reducing meat consumption in the USA: a nationally representative survey of attitudes and behaviours. *Public Health Nutr*. 2018;21(10):1835–44.
2781. Radnitz C, Ni J, Dennis D, Cerrito B. Health benefits of a vegan diet: current insights. *Nutr Diet Suppl*. 2020;12:57–85.
2782. Almost half of UK vegans made the change in the last year, according to new data. *Vegan Trade Journal*. https://www.vegantradejournal.com/almost-half-of-uk-vegans-made-the-change-in-the-last-year-according-to-new-data/. November 19, 2018. Accessed December 28, 2022.
2783. Radnitz C, Beezhold B, DiMatteo J. Investigation of lifestyle choices of individuals following a vegan diet for health and ethical reasons. *Appetite*. 2015;90:31–6.
2784. Orlich MJ, Chiu THT, Dhillon PK, et al. Vegetarian epidemiology: review and discussion of findings from geographically diverse cohorts. *Adv Nutr*. 2019;10(Suppl_4):S284–95.
2785. Rocha JP, Laster J, Parag B, Shah NU. Multiple health benefits and minimal risks associated with vegetarian diets. *Curr Nutr Rep*. 2019;8(4):374–81.
2786. Singh PN, Arthur KN, Orlich MJ, et al. Global epidemiology of obesity, vegetarian dietary patterns, and noncommunicable disease in

Asian Indians. *Am J Clin Nutr*. 2014;100 Suppl 1:359S-64S.
2787. Campbell EK, Fidahusain M, Campbell TM II. Evaluation of an eight-week whole-food plant-based lifestyle modification program. *Nutrients*. 2019;11(9):E2068.
2788. Willcox DC, Scapagnini G, Willcox BJ. Healthy aging diets other than the Mediterranean: a focus on the Okinawan diet. *Mech Ageing Dev*. 2014;136–7:148–62.
2789. Everitt AV, Hilmer SN, Brand-Miller JC, et al. Dietary approaches that delay age-related diseases. *Clin Interv Aging*. 2006;1(1):11–31.
2790. Jacobs DR Jr, Orlich MJ. Diet pattern and longevity: do simple rules suffice? A commentary. *Am J Clin Nutr*. 2014;100(Suppl 1):313S-9S.
2791. Kim H, Caulfield LE, Rebholz CM. Healthy plant-based diets are associated with lower risk of all-cause mortality in US adults. *J Nutr*. 2018;148(4):624–31.
2792. Orlich MJ, Chiu THT, Dhillon PK, et al. Vegetarian epidemiology: review and discussion of findings from geographically diverse cohorts. *Adv Nutr*. 2019;10(Suppl_4):S284–95.
2793. Hemler EC, Hu FB. Plant-based diets for cardiovascular disease prevention: all plant foods are not created equal. *Curr Atheroscler Rep*. 2019;21(5):18.
2794. Kim H, Caulfield LE, Garcia-Larsen V, Steffen LM, Coresh J, Rebholz CM. Plant-based diets are associated with a lower risk of incident cardiovascular disease, cardiovascular disease mortality, and all-cause mortality in a general population of middle-aged adults. *J Am Heart Assoc*. 2019;8(16):e012865.
2795. Martínez-González MA, Sánchez-Tainta A, Corella D, et al. A provegetarian food pattern and reduction in total mortality in the Prevención con Dieta Mediterránea (PREDIMED) study. *Am J Clin Nutr*. 2014;100 Suppl 1:320S-8S.
2796. Li H, Zeng X, Wang Y, et al. A prospective study of healthful and unhealthful plant-based diet and risk of overall and cause-specific mortality. *Eur J Nutr*. Published online August 11, 2021.
2797. Keaver L, Ruan M, Chen F, et al. Plant- and animal-based diet quality and mortality among US adults: a cohort study. *Br J Nutr*. 2021;125(12):1405–15.

2798. Kim H, Caulfield LE, Garcia-Larsen V, Steffen LM, Coresh J, Rebholz CM. Plant-based diets are associated with a lower risk of incident cardiovascular disease, cardiovascular disease mortality, and all-cause mortality in a general population of middle-aged adults. *J Am Heart Assoc*. 2019;8(16):e012865.
2799. Li H, Zeng X, Wang Y, et al. A prospective study of healthful and unhealthful plant-based diet and risk of overall and cause-specific mortality. *Eur J Nutr*. Published online August 11, 2021.
2800. Baden MY, Liu G, Satija A, et al. Changes in plant-based diet quality and total and cause-specific mortality. *Circulation*. 2019;140(12):979–91.
2801. Keaver L, Ruan M, Chen F, et al. Plant- and animal-based diet quality and mortality among US adults: a cohort study. *Br J Nutr*. 2021;125(12):1405–15.
2802. McCarty MF. Proposal for a dietary "phytochemical index." *Med Hypotheses*. 2004;63(5):813–7.
2803. U.S. Department of Agriculture, Economic Research Service. Loss-adjusted food availability. https://www.ers.usda.gov/webdocs/DataFiles/50472/calories.xls?v=7455.7. Updated August 26, 2019. Accessed January 17, 2022.
2804. U.S. Department of Agriculture, Economic Research Service. Loss-adjusted food availability. https://www.ers.usda.gov/webdocs/DataFiles/50472/calories.xls?v=7455.7. Updated August 26, 2019. Accessed January 17, 2022.
2805. Mirmiran P, Bahadoran Z, Golzarand M, Shiva N, Azizi F. Association between dietary phytochemical index and 3-year changes in weight, waist circumference and body adiposity index in adults: Tehran Lipid and Glucose study. *Nutr Metab (Lond)*. 2012;9(1):108.
2806. Golzarand M, Bahadoran Z, Mirmiran P, Sadeghian-Sharif S, Azizi F. Dietary phytochemical index is inversely associated with the occurrence of hypertension in adults: a 3-year follow-up (the Tehran Lipid and Glucose Study). *Eur J Clin Nutr*. 2015;69(3):392–8.
2807. Abshirini M, Mahaki B, Bagheri F, Siassi F, Koohdani F, Sotoudeh G. Higher intake of phytochemical-rich foods is inversely related to prediabetes: a case-control study. *Int J Prev Med*. 2018;9:64.

2808. Kim M, Park K. Association between phytochemical index and metabolic syndrome. *Nutr Res Pract*. 2020;14(3):252–61.
2809. Golzarand M, Mirmiran P, Bahadoran Z, Alamdari S, Azizi F. Dietary phytochemical index and subsequent changes of lipid profile: a 3-year follow-up in Tehran Lipid and Glucose Study in Iran. *ARYA Atheroscler*. 2014;10(4):203–10.
2810. Darooghegi Mofrad M, Siassi F, Guilani B, Bellissimo N, Azadbakht L. Association of dietary phytochemical index and mental health in women: a cross-sectional study. *Br J Nutr*. 2019;121(9):1049–56.
2811. Aghababayan S, Sheikhi Mobarakeh Z, Qorbani M, et al. Dietary phytochemical index and benign breast diseases: a case-control study. *Nutr Cancer*. 2020;72(6):1067–73.
2812. Bahadoran Z, Karimi Z, Houshiar-Rad A, Mirzayi HR, Rashidkhani B. Dietary phytochemical index and the risk of breast cancer: a case control study in a population of Iranian women. *Asian Pac J Cancer Prev*. 2013;14(5):2747–51.
2813. Bellavia A, Larsson SC, Bottai M, Wolk A, Orsini N. Fruit and vegetable consumption and all-cause mortality: a dose-response analysis. *Am J Clin Nutr*. 2013;98(2):454–9.
2814. Juraske R, Mutel CL, Stoessel F, Hellweg S. Life cycle human toxicity assessment of pesticides: comparing fruit and vegetable diets in Switzerland and the United States. *Chemosphere*. 2009;77(7):939–45.
2815. Bellavia A, Larsson SC, Bottai M, Wolk A, Orsini N. Fruit and vegetable consumption and all-cause mortality: a dose-response analysis. *Am J Clin Nutr*. 2013;98(2):454–9.
2816. Nicklett EJ, Semba RD, Xue QL, et al. Fruit and vegetable intake, physical activity, and mortality in older community-dwelling women. *J Am Geriatr Soc*. 2012;60(5):862–8.
2817. Lo YT, Chang YH, Wahlqvist ML, Huang HB, Lee MS. Spending on vegetable and fruit consumption could reduce all-cause mortality among older adults. *Nutr J.* 2012;11:113.
2818. Dórea JG. Vegetarian diets and exposure to organochlorine pollutants, lead, and mercury. *Am J Clin Nutr*. 2004;80(1):237–8.
2819. Hergenrather J, Hlady G, Wallace B, Savage E. Pollutants in breast milk of vegetarians. *N Engl J Med*. 1981;304(13):792.

2820. Key TJ, Appleby PN, Spencer EA, et al. Cancer incidence in British vegetarians. *Br J Cancer*. 2009;101(1):192–7.
2821. Dearfield KL, Edwards SR, O'Keefe MM, et al. Dietary estimates of dioxins consumed in U.S. Department of Agriculture–regulated meat and poultry products. *J Food Prot*. 2013;76(9):1597–607.
2822. Hernández ÁR, Boada LD, Mendoza Z, et al. Consumption of organic meat does not diminish the carcinogenic potential associated with the intake of persistent organic pollutants (POPs). *Environ Sci Pollut Res Int*. 2017;24(5):4261–73.
2823. U.S. Department of Agriculture, Economic Research Service. Per capita red meat and poultry consumption expected to decrease modestly in 2022. https://www.ers.usda.gov/data-products/chart-gallery/gallery/chart-detail/?chartId=103767. Last updated April 15, 2022. Accessed December 28, 2022.
2824. Hernández ÁR, Boada LD, Mendoza Z, et al. Consumption of organic meat does not diminish the carcinogenic potential associated with the intake of persistent organic pollutants (POPs). *Environ Sci Pollut Res Int*. 2017;24(5):4261–73.
2825. Ta CA, Zee JA, Desrosiers T, et al. Binding capacity of various fibre to pesticide residues under simulated gastrointestinal conditions. *Food Chem Toxicol*. 1999;37(12):1147–51.
2826. Lee YM, Shin JY, Kim SA, Jacobs DR, Lee DH. Can habitual exercise help reduce serum concentrations of lipophilic chemical mixtures? Association between physical activity and persistent organic pollutants. *Diabetes Metab J*. 2020;44(5):764–74.
2827. Genuis SJ, Lane K, Birkholz D. Human elimination of organochlorine pesticides: blood, urine, and sweat study. *Biomed Res Int*. 2016;2016:1624643.
2828. Yiamouyiannis CA, Sanders RA, Watkins JB III, Martin BJ. Chronic physical activity: hepatic hypertrophy and increased total biotransformation enzyme activity. *Biochem Pharmacol*. 1992;44(1):121–7.
2829. Watkins JB, Crawford ST, Sanders RA. Chronic voluntary exercise may alter hepatobiliary clearance of endogenous and exogenous chemicals in rats. *Drug Metab Dispos*. 1994;22(4):537–43.

2830. Lupton SJ, O'Keefe M, Muñiz-Ortiz JG, Clinch N, Basu P. Survey of polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans and non-*ortho*-polychlorinated biphenyls in US meat and poultry, 2012–13: toxic equivalency levels, patterns, temporal trends and implications. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*. 2017;34(11):1970–81.
2831. González N, Marquès M, Nadal M, Domingo JL. Meat consumption: which are the current global risks? A review of recent (2010–2020) evidences. *Food Res Int*. 2020;137:109341.
2832. Melina V, Craig W, Levin S. Position of the Academy of Nutrition and Dietetics: vegetarian diets. *J Acad Nutr Diet*. 2016;116(12):1970–80.
2833. Johnston PK. Recognition: Mervyn G Hardinge. *Am J Clin Nutr*. 1999;70(3):431s-2s.
2834. Ma Y, Pagoto SL, Griffith JA, et al. A dietary quality comparison of popular weight-loss plans. *J Am Diet Assoc*. 2007;107(10):1786–91.
2835. Clarys P, Deliens T, Huybrechts I, et al. Comparison of nutritional quality of the vegan, vegetarian, semi-vegetarian, pesco-vegetarian and omnivorous diet. *Nutrients*. 2014;6(3):1318–32.
2836. Farmer B, Larson BT, Fulgoni VL, Rainville AJ, Liepa GU. A vegetarian dietary pattern as a nutrient-dense approach to weight management: an analysis of the National Health and Nutrition Examination Survey 1999–2004. *J Am Diet Assoc*. 2011;111(6):819–27.
2837. Van Horn L. Achieving nutrient density: a vegetarian approach. *J Am Diet Assoc*. 2011;111(6):799.
2838. Keenan S, Mitts KG, Kurtz CA. Scurvy presenting as a medial head tear of the gastrocnemius. *Orthopedics*. 2002;25(6):689–91.
2839. Mariotti F, ed. Vegetarian and Plant-Based Diets in Health and Disease Prevention. Academic Press; 2017.
2840. Armstrong BK. Absorption of vitamin B_{12} from the human colon. *Am J Clin Nutr*. 1968;21(4):298–9.
2841. Gupta ES, Sheth SP, Ganjiwale JD. Association of vitamin B12 deficiency and use of reverse osmosis processed water for drinking: a

cross-sectional study from Western India. *J Clin Diagn Res*. 2016;10(5):OC37–40.
2842. Pawlak R, Lester SE, Babatunde T. The prevalence of cobalamin deficiency among vegetarians assessed by serum vitamin B12: a review of literature. *Eur J Clin Nutr*. 2014;68(5):541–8.
2843. Herrmann W, Geisel J. Vegetarian lifestyle and monitoring of vitamin B-12 status. *Clin Chim Acta*. 2002;326(1–2):47–59.
2844. Mariotti F, ed. Vegetarian and Plant-Based Diets in Health and Disease Prevention. Academic Press; 2017.
2845. Eitenmiller R, Ye L, Landen WO Jr. Vitamin Analysis for the Health and Food Sciences. 2nd ed. CRC Press; 2007:469.
2846. Del Bo' C, Riso P, Gardana C, Brusamolino A, Battezzati A, Ciappellano S. Effect of two different sublingual dosages of vitamin B_{12} on cobalamin nutritional status in vegans and vegetarians with a marginal deficiency: a randomized controlled trial. *Clin Nutr*. 2019;38(2):575–83.
2847. MacFarlane AJ, Shi Y, Greene-Finestone LS. High-dose compared with low-dose vitamin B-12 supplement use is not associated with higher vitamin B-12 status in children, adolescents, and older adults. *J Nutr*. 2014;144(6):915–20.
2848. Rajan S, Wallace JI, Brodkin KI, Beresford SA, Allen RH, Stabler SP. Response of elevated methylmalonic acid to three dose levels of oral cobalamin in older adults. *J Am Geriatr Soc*. 2002;50(11):1789–95.
2849. Eussen S, de Groot L, Clarke R, et al. Oral cyanocobalamin supplementation in older people with vitamin B_{12} deficiency: a dose-finding trial. *Arch Intern Med*. 2005;165(10):1167–72.
2850. Rizzo G, Laganà AS, Rapisarda AMC, et al. Vitamin B12 among vegetarians: status, assessment and supplementation. *Nutrients*. 2016;8(12):767.
2851. Crane MG, Sample C, Patchett S, Register UD. Vitamin B_{12} studies in total vegetarians (vegans). *J Nutr Med*. 1994;4(4):419–30.
2852. Briani C, Dalla Torre C, Citton V, et al. Cobalamin deficiency: clinical picture and radiological findings. *Nutrients*. 2013;5(11):4521–39.

2853. Crane MG, Sample C, Patchett S, Register UD. Vitamin B_{12} studies in total vegetarians (vegans). *J Nutr Med*. 1994;4(4):419–30.
2854. Mott A, Bradley T, Wright K, et al. Effect of vitamin K on bone mineral density and fractures in adults: an updated systematic review and meta-analysis of randomised controlled trials. *Osteoporos Int*. 2019;30(8):1543–59.
2855. EFSA Panel on Dietetic Products, Nutrition and Allergies, Turck D, Bresson JL, et al. Dietary reference values for vitamin K. *EFSA J*. 2017;15(5):e04780.
2856. Nakagawa K, Hirota Y, Sawada N, et al. Identification of UBIAD1 as a novel human menaquinone-4 biosynthetic enzyme. *Nature*. 2010;468(7320):117–21.
2857. Kwok CS, Gulati M, Michos ED, et al. Dietary components and risk of cardiovascular disease and all-cause mortality: a review of evidence from meta-analyses. *Eur J Prev Cardiol*. 2019;26(13):1415–29.
2858. Shea MK, Barger K, Booth SL, et al. Vitamin K status, cardiovascular disease, and all-cause mortality: a participant-level meta-analysis of 3 US cohorts. *Am J Clin Nutr*. 2020;111(6):1170–7.
2859. Chase P, Mitchell K, Morley JE. In the steps of giants: the early geriatrics texts. *J Am Geriatr Soc*. 2000;48(1):89–94.
2860. Stranges S, Takeda A, Martin N, Rees K. Cochrane corner: does the Mediterranean-style diet help in the prevention of cardiovascular disease? *Heart*. 2019;105(22):1691–4.
2861. Wizard Edison says doctors of future will give no medicine. *The Newark Advocate*. https://archive.org/details/newark-advocate-1903–01–02/mode/1up?view=theater. Published January 2, 1903;46:47:1. Accessed February 21, 2023.
2862. American College of Lifestyle Medicine. About us. http://lifestylemedicine.org/about-us/. Accessed December 28, 2022.
2863. Mokdad AH, Ballestros K, Echko M, et al. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319(14):1444–72.
2864. Vodovotz Y, Barnard N, Hu FB, et al. Prioritized research for the prevention, treatment, and reversal of chronic disease:

recommendations from the Lifestyle Medicine Research Summit. *Front Med (Lausanne)*. 2020;7:585744.

2865. Zhang YB, Pan XF, Chen J, et al. Combined lifestyle factors, all-cause mortality and cardiovascular disease: a systematic review and meta-analysis of prospective cohort studies. *J Epidemiol Community Health*. 2021;75(1):92–9.

2866. Willcox BJ, Willcox DC, Ferrucci L. Secrets of healthy aging and longevity from exceptional survivors around the globe: lessons from octogenarians to supercentenarians. *J Gerontol A Biol Sci Med Sci*. 2008;63(11):1181–5.

2867. Ford ES, Bergmann MM, Kröger J, Schienkiewitz A, Weikert C, Boeing H. Healthy living is the best revenge: findings from the European Prospective Investigation Into Cancer and Nutrition–Potsdam study. *Arch Intern Med*. 2009;169(15):1355–62.

2868. Platz EA, Willett WC, Colditz GA, Rimm EB, Spiegelman D, Giovannucci E. Proportion of colon cancer risk that might be preventable in a cohort of middle-aged US men. *Cancer Causes Control*. 2000;11(7):579–88.

2869. Ford ES, Bergmann MM, Kröger J, Schienkiewitz A, Weikert C, Boeing H. Healthy living is the best revenge: findings from the European Prospective Investigation Into Cancer and Nutrition–Potsdam study. *Arch Intern Med*. 2009;169(15):1355–62.

2870. Wahls TL. The seventy percent solution. *J Gen Intern Med*. 2011;26(10):1215–6.

2871. Khaw KT, Wareham N, Bingham S, Welch A, Luben R, Day N. Combined impact of health behaviours and mortality in men and women: the EPIC-Norfolk prospective population study. *PLoS Med*. 2008;5(1):e12.

2872. Wang K, Li Y, Liu G, et al. Healthy lifestyle for prevention of premature death among users and nonusers of common preventive medications: a prospective study in 2 US cohorts. *JAHA*. 2020;9(13):e016692.

2873. King DE, Mainous AG III, Geesey ME. Turning back the clock: adopting a healthy lifestyle in middle age. *Am J Med*. 2007;120(7):598–603.

2874. Nyberg ST, Singh-Manoux A, Pentti J, et al. Association of healthy lifestyle with years lived without major chronic diseases. *JAMA Intern Med*. 2020;180(5):760–8.
2875. Hall WJ. Centenarians: metaphor becomes reality. *Arch Intern Med*. 2008;168(3):262–3.
2876. Zhang S, Tomata Y, Discacciati A, et al. Combined healthy lifestyle behaviors and disability-free survival: the Ohsaki Cohort 2006 Study. *J Gen Intern Med*. 2019;34(9):1724–9.
2877. Vallance JK, Gardiner PA, Lynch BM, et al. Evaluating the evidence on sitting, smoking, and health: is sitting really the new smoking? *Am J Public Health*. 2018;108(11):1478–82.
2878. Rezende LFM, Sá TH, Mielke GI, Viscondi JYK, Rey-López JP, Garcia LMT. All-cause mortality attributable to sitting time: analysis of 54 countries worldwide. *Am J Prev Med*. 2016;51(2):253–63.
2879. Vallance JK, Gardiner PA, Lynch BM, et al. Evaluating the evidence on sitting, smoking, and health: is sitting really the new smoking? *Am J Public Health*. 2018;108(11):1478–82.
2880. Taylor DH Jr, Hasselblad V, Henley SJ, Thun MJ, Sloan FA. Benefits of smoking cessation for longevity. *Am J Public Health*. 2002;92(6):990–6.
2881. Engelhard CL, Garson A, Dorn S. Reducing obesity: policy strategies from the tobacco wars. *Methodist Debakey Cardiovasc J*. 2009;5(4):46–50.
2882. Cornelius ME, Wang TW, Jamal A, Loretan CG, Neff LJ. Tobacco product use among adults—United States, 2019. *MMWR Morb Mortal Wkly Rep*. 2020;69(46):1736–42.
2883. Mokdad AH, Ballestros K, Echko M, et al. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319(14):1444–72.
2884. Barnard ND. The physician's role in nutrition-related disorders: from bystander to leader. *Virtual Mentor*. 2013;15(4):367–72.
2885. Ding D, Grunseit AC, Chau JY, Vo K, Byles J, Bauman AE. Retirement—a transition to a healthier lifestyle?: evidence from a large Australian study. *Am J Prev Med*. 2016;51(2):170–8.
2886. Rebelo-Marques A, Lages ADS, Andrade R, et al. Aging hallmarks: the benefits of physical exercise. *Front Endocrinol (Lausanne)*.

2018;9:258.
2887. Wolf AM. Rodent diet aids and the fallacy of caloric restriction. *Mech Ageing Dev*. 2021;200:111584.
2888. Seals DR, Justice JN, LaRocca TJ. Physiological geroscience: targeting function to increase healthspan and achieve optimal longevity. *J Physiol*. 2016;594(8):2001–24.
2889. Lin YH, Chen Y-C, Tseng Y-C, Tsai S-T, Tseng Y-H. Physical activity and successful aging among middle-aged and older adults: a systematic review and meta-analysis of cohort studies. *Aging (Albany NY)*. 2020;12(9):7704–16.
2890. Troiano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc*. 2008;40(1):181–8.
2891. Pedersen BK. Which type of exercise keeps you young? *Curr Opin Clin Nutr Metab Care*. 2019;22(2):167–73.
2892. Di Lorito C, Long A, Byrne A, et al. Exercise interventions for older adults: a systematic review of meta-analyses. *J Sport Health Sci*. 2021;10(1):29–47.
2893. Pahor M, Guralnik JM, Ambrosius WT, et al. Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. *JAMA*. 2014;311(23):2387–96.
2894. Sherrington C, Fairhall N, Kwok W, et al. Evidence on physical activity and falls prevention for people aged 65+ years: systematic review to inform the WHO guidelines on physical activity and sedentary behaviour. *Int J Behav Nutr Phys Act*. 2020;17(1):144.
2895. de Souto Barreto P, Rolland Y, Vellas B, Maltais M. Association of long-term exercise training with risk of falls, fractures, hospitalizations, and mortality in older adults: a systematic review and meta-analysis. *JAMA Intern Med*. 2019;179(3):394–405.
2896. Soltani S, Hunter GR, Kazemi A, Shab-Bidar S. The effects of weight loss approaches on bone mineral density in adults: a systematic review and meta-analysis of randomized controlled trials. *Osteoporos Int*. 2016;27(9):2655–71.
2897. García-Hermoso A, Ramirez-Vélez R, Sáez de Asteasu ML, et al. Safety and effectiveness of long-term exercise interventions in older

adults: a systematic review and meta-analysis of randomized controlled trials. *Sports Med*. 2020;50(6):1095–106.
2898. Di Lorito C, Long A, Byrne A, et al. Exercise interventions for older adults: a systematic review of meta-analyses. *J Sport Health Sci*. 2021;10(1):29–47.
2899. Blumenthal JA, Babyak MA, Doraiswamy PM, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom Med*. 2007;69(7):587–96.
2900. Gerbild H, Larsen CM, Graugaard C, Areskoug Josefsson K. Physical activity to improve erectile function: a systematic review of intervention studies. *Sex Med*. 2018;6(2):75–89.
2901. Marquez DX, Aguiñaga S, Vásquez PM, et al. A systematic review of physical activity and quality of life and well-being. *Transl Behav Med*. 2020;10(5):1098–109.
2902. Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. *Curr Opin Cardiol*. 2017;32(5):541–56.
2903. Fock KM, Khoo J. Diet and exercise in management of obesity and overweight. *J Gastroenterol Hepatol*. 2013;28 Suppl 4:59–63.
2904. Archer E, Hand GA, Blair SN. Correction: Validity of U.S. nutritional surveillance: National Health and Nutrition Examination Survey caloric energy intake data, 1971–2010. *PLoS One*. 2013;8(10):10.1371/annotation/c313df3a-52bd-4cbe-af14–6676480d1a43.
2905. Blair SN. Physical inactivity: the biggest public health problem of the 21st century. *Br J Sports Med*. 2009;43(1):1–2.
2906. Mokdad AH, Ballestros K, Echko M, et al. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319(14):1444–72.
2907. Stanaway JD, Afshin A, Gakidou E, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1923–94.

2908. Mokdad AH, Ballestros K, Echko M, et al. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319(14):1444–72.
2909. Campisi J, Kapahi P, Lithgow GJ, Melov S, Newman JC, Verdin E. From discoveries in ageing research to therapeutics for healthy ageing. *Nature*. 2019;571(7764):183–92.
2910. World Health Organization. Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks. World Health Organization; 2009.
2911. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Impact of physical inactivity on the world's major non-communicable diseases. *Lancet*. 2012;380(9838):219–29.
2912. Strain T, Brage S, Sharp SJ, et al. Use of the prevented fraction for the population to determine deaths averted by existing prevalence of physical activity: a descriptive study. *Lancet Glob Health*. 2020;8(7):e920–30.
2913. Wade KH, Richmond RC, Smith GD. Physical activity and longevity: how to move closer to causal inference. *Br J Sports Med*. 2018;52(14):890–1.
2914. Richard A, Martin B, Wanner M, Eichholzer M, Rohrmann S. Effects of leisure-time and occupational physical activity on total mortality risk in NHANES III according to sex, ethnicity, central obesity, and age. *J Phys Act Health*. 2015;12(2):184–92.
2915. Kujala UM. Is physical activity a cause of longevity? It is not as straightforward as some would believe. A critical analysis. *Br J Sports Med*. 2018;52(14):914–8.
2916. Karvinen S, Waller K, Silvennoinen M, et al. Physical activity in adulthood: genes and mortality. *Sci Rep*. 2015;5:18259.
2917. O'Keefe JH, Franklin B, Lavie CJ. Exercising for health and longevity vs peak performance: different regimens for different goals. *Mayo Clin Proc*. 2014;89(9):1171–5.
2918. O'Keefe JH, Franklin B, Lavie CJ. Exercising for health and longevity vs peak performance: different regimens for different goals. *Mayo Clin Proc*. 2014;89(9):1171–5.
2919. O'Keefe JH, Franklin B, Lavie CJ. Exercising for health and longevity vs peak performance: different regimens for different goals.

Mayo Clin Proc. 2014;89(9):1171–5.
2920. Lee D, Brellenthin AG, Thompson PD, Sui X, Lee IM, Lavie CJ. Running as a key lifestyle medicine for longevity. *Prog Cardiovasc Dis*. 2017;60(1):45–55.
2921. Montgomery MJ, Kandi D. QuickStats: percentage of adults who met federal guidelines for aerobic physical activity through leisure-time activity, by race/ethnicity—National Health Interview Survey, 2008–2017. *MMWR Morb Mortal Wkly Rep*. 2019;68:292.
2922. Lee D, Lavie CJ, Sui X, Blair SN. Running and mortality: is more actually worse? *Mayo Clin Proc*. 2016;91(4):534–6.
2923. Schnohr P, Marott JL, O'Keefe JH. Reply: exercise and mortality reduction: recurring reverse J- or U-curves. *J Am Coll Cardiol*. 2015;65(24):2674–6.
2924. Barnard ND, Goldman DM, Loomis JF, et al. Plant-based diets for cardiovascular safety and performance in endurance sports. *Nutrients*. 2019;11(1):130.
2925. Barnard ND, Goldman DM, Loomis JF, et al. Plant-based diets for cardiovascular safety and performance in endurance sports. *Nutrients*. 2019;11(1):130.
2926. Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. *Circulation*. 2017;136(3):e1–23.
2927. Smith MM, Trexler ET, Sommer AJ, et al. Unrestricted paleolithic diet is associated with unfavorable changes to blood lipids in healthy subjects. *Int J Exerc Sci*. 2014;7(2):128–39. Note this study has been retracted, but evidently for a technicality not data integrity reasons. Han A. Researcher who tangled with CrossFit loses two more papers. Retraction Watch. https://retractionwatch.com/2017/06/30/researcher-tangled-crossfit-loses-two-papers. Published June 30, 2017. Accessed January 31, 2022.
2928. Barnard RJ, Ugianskis EJ, Martin DA, Inkeles SB. Role of diet and exercise in the management of hyperinsulinemia and associated atherosclerotic risk factors. *Am J Cardiol*. 1992;69(5):440–4.
2929. Smith MM, Trexler ET, Sommer AJ, et al. Unrestricted paleolithic diet is associated with unfavorable changes to blood lipids in healthy subjects. *Int J Exerc Sci*. 2014;7(2):128–39. Note this study has been

retracted, but evidently for a technicality not data integrity reasons. Han A. Researcher who tangled with CrossFit loses two more papers. Retraction Watch. https://retractionwatch.com/2017/06/30/researcher-tangled-crossfit-loses-two-papers. Published June 30, 2017. Accessed January 31, 2022.

2930. Craddock JC, Neale EP, Peoples GE, Probst YC. Plant-based eating patterns and endurance performance: a focus on inflammation, oxidative stress and immune responses. *Nutr Bull*. 2020;45(2):123–32.

2931. Barnard ND, Goldman DM, Loomis JF, et al. Plant-based diets for cardiovascular safety and performance in endurance sports. *Nutrients*. 2019;11(1):130.

2932. Lynch HM, Wharton CM, Johnston CS. Cardiorespiratory fitness and peak torque differences between vegetarian and omnivore endurance athletes: a cross-sectional study. *Nutrients*. 2016;8(11):E726.

2933. Boutros GH, Landry-Duval MA, Garzon M, Karelis AD. Is a vegan diet detrimental to endurance and muscle strength? *Eur J Clin Nutr*. 2020;74(11):1550–5.

2934. Król W, Price S, Śliż D, et al. A vegan athlete's heart—is it different? Morphology and function in echocardiography. *Diagnostics (Basel)*. 2020;10(7):E477.

2935. Veleba J, Matoulek M, Hill M, Pelikanova T, Kahleova H. "A vegetarian vs. conventional hypocaloric diet: the effect on physical fitness in response to aerobic exercise in patients with type 2 diabetes." A parallel randomized study. *Nutrients*. 2016;8(11):671.

2936. Veleba J, Matoulek M, Hill M, Pelikanova T, Kahleova H. "A vegetarian vs. conventional hypocaloric diet: the effect on physical fitness in response to aerobic exercise in patients with type 2 diabetes." A parallel randomized study. *Nutrients*. 2016;8(11):671.

2937. Kahleova H, Hrachovinova T, Hill M, Pelikanova T. Vegetarian diet in type 2 diabetes—improvement in quality of life, mood and eating behaviour. *Diabet Med*. 2013;30(1):127–9.

2938. Kien CL, Bunn JY, Tompkins CL, et al. Substituting dietary monounsaturated fat for saturated fat is associated with increased daily physical activity and resting energy expenditure and with changes in mood. *Am J Clin Nutr*. 2013;97(4):689–97.

2939. Dumas JA, Bunn JY, Nickerson J, et al. Dietary saturated fat and monounsaturated fat have reversible effects on brain function and the secretion of pro-inflammatory cytokines in young women. *Metab Clin Exp*. 2016;65(10):1582–8.
2940. Kien CL, Bunn JY, Tompkins CL, et al. Substituting dietary monounsaturated fat for saturated fat is associated with increased daily physical activity and resting energy expenditure and with changes in mood. *Am J Clin Nutr*. 2013;97(4):689–97.
2941. Kahleova H, Matoulek M, Malinska H, et al. Vegetarian diet improves insulin resistance and oxidative stress markers more than conventional diet in subjects with Type 2 diabetes. *Diabet Med*. 2011;28(5):549–59.
2942. Roderka MN, Puri S, Batsis JA. Addressing obesity to promote healthy aging. *Clin Geriatr Med*. 2020;36(4):631–43.
2943. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. *NCHS Data Brief*. 2020;(360):1–8.
2944. Pontzer H, Yamada Y, Sagayama H, et al. Daily energy expenditure through the human life course. *Science*. 2021;373(6556):808–12.
2945. Tam BT, Morais JA, Santosa S. Obesity and ageing: two sides of the same coin. *Obes Rev*. 2020;21(4):e12991.
2946. Himbert C, Thompson H, Ulrich CM. Effects of intentional weight loss on markers of oxidative stress, DNA repair and telomere length —a systematic review. *Obes Facts*. 2017;10(6):648–65.
2947. Bianchi VE. Weight loss is a critical factor to reduce inflammation. *Clin Nutr ESPEN*. 2018;28:21–35.
2948. Tam BT, Morais JA, Santosa S. Obesity and ageing: two sides of the same coin. *Obes Rev*. 2020;21(4):e12991.
2949. Ronan L, Alexander-Bloch AF, Wagstyl K, et al. Obesity associated with increased brain age from midlife. *Neurobiol Aging*. 2016;47:63–70.
2950. Albanese E, Launer LJ, Egger M, et al. Body mass index in midlife and dementia: systematic review and meta-regression analysis of 589,649 men and women followed in longitudinal studies. *Alzheimers Dement (Amst)*. 2017;8:165–78.

2951. Chuang YF, An Y, Bilgel M, et al. Midlife adiposity predicts earlier onset of Alzheimer's dementia, neuropathology and presymptomatic cerebral amyloid accumulation. *Mol Psychiatry*. 2016;21(7):910–5.
2952. Olshansky SJ, Passaro DJ, Hershow RC, et al. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med*. 2005;352(11):1138–45.
2953. Ludwig DS. Lifespan weighed down by diet. *JAMA*. 2016;315(21):2269–70.
2954. Mann CC. Provocative study says obesity may reduce U.S. life expectancy. *Science*. 2005;307(5716):1716–7.
2955. Sun Q, Townsend MK, Okereke OI, Franco OH, Hu FB, Grodstein F. Adiposity and weight change in mid-life in relation to healthy survival after age 70 in women: prospective cohort study. *BMJ*. 2009;339:b3796.
2956. Santos-Lozano A, Pareja-Galeano H, Fuku N, et al. Implications of obesity in exceptional longevity. *Ann Transl Med*. 2016;4(20):416.
2957. Tam BT, Morais JA, Santosa S. Obesity and ageing: two sides of the same coin. *Obes Rev*. 2020;21(4):e12991.
2958. Pararasa C, Bailey CJ, Griffiths HR. Ageing, adipose tissue, fatty acids and inflammation. *Biogerontology*. 2015;16(2):235–48.
2959. Rubin R. Postmenopausal women with a "normal" BMI might be overweight or even obese. *JAMA*. 2018;319(12):1185–7.
2960. Jayedi A, Soltani S, Zargar MS, Khan TA, Shab-Bidar S. Central fatness and risk of all cause mortality: systematic review and dose-response meta-analysis of 72 prospective cohort studies. *BMJ*. 2020;370:m3324.
2961. Klein S, Fontana L, Young VL, et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med*. 2004;350(25):2549–57.
2962. Blackburn G. Effect of degree of weight loss on health benefits. *Obes Res*. 1995;3 Suppl 2:211s-6s.
2963. Klein S, Fontana L, Young VL, et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med*. 2004;350(25):2549–57.
2964. Chaston TB, Dixon JB. Factors associated with percent change in visceral versus subcutaneous abdominal fat during weight loss:

findings from a systematic review. *Int J Obes (Lond).* 2008;32(4):619–28.
2965. Haywood C, Sumithran P. Treatment of obesity in older persons—a systematic review. *Obes Rev*. 2019;20(4):588–98.
2966. Muzumdar R, Allison DB, Huffman DM, et al. Visceral adipose tissue modulates mammalian longevity. *Aging Cell*. 2008;7(3):438–40.
2967. Wiggins T, Guidozzi N, Welbourn R, Ahmed AR, Markar SR. Association of bariatric surgery with all-cause mortality and incidence of obesity-related disease at a population level: a systematic review and meta-analysis. *PLoS Med*. 2020;17(7):e1003206.
2968. Kritchevsky SB, Beavers KM, Miller ME, et al. Intentional weight loss and all-cause mortality: a meta-analysis of randomized clinical trials. *PLoS One*. 2015;10(3):e0121993.
2969. Wright N, Wilson L, Smith M, Duncan B, McHugh P. The BROAD study: a randomised controlled trial using a whole food plant-based diet in the community for obesity, ischaemic heart disease or diabetes. *Nutr Diabetes.* 2017;7(3):e256.
2970. Hall KD, Guo J, Courville AB, et al. Effect of a plant-based, low-fat diet versus an animal-based, ketogenic diet on ad libitum energy intake. *Nat Med*. 2021;27(2):344–53.
2971. Piers LS, Walker KZ, Stoney RM, Soares MJ, O'Dea K. Substitution of saturated with monounsaturated fat in a 4-week diet affects body weight and composition of overweight and obese men. *Br J Nutr*. 2003;90(3):717–27.
2972. Rosqvist F, Iggman D, Kullberg J, et al. Overfeeding polyunsaturated and saturated fat causes distinct effects on liver and visceral fat accumulation in humans. *Diabetes*. 2014;63(7):2356–68.
2973. Krishnan S, Cooper JA. Effect of dietary fatty acid composition on substrate utilization and body weight maintenance in humans. *Eur J Nutr*. 2014;53(3):691–710.
2974. Jonnalagadda SS, Egan SK, Heimbach JT, et al. Fatty acid consumption pattern of Americans: 1987–1988 USDA Nationwide Food Consumption Survey. *Nutr Res*. 1995;15(12):1767–81.

2975. Pimenta AS, Gaidhu MP, Habib S, et al. Prolonged exposure to palmitate impairs fatty acid oxidation despite activation of AMP-activated protein kinase in skeletal muscle cells. *J Cell Physiol*. 2008;217(2):478–85.
2976. Chen YC, Cypess AM, Chen YC, et al. Measurement of human brown adipose tissue volume and activity using anatomic MR imaging and functional MR imaging. *J Nucl Med*. 2013;54(9):1584–7.
2977. Darcy J, Tseng YH. ComBATing aging—does increased brown adipose tissue activity confer longevity? *GeroScience*. 2019;41(3):285–96.
2978. Darcy J, Tseng YH. ComBATing aging—does increased brown adipose tissue activity confer longevity? *GeroScience*. 2019;41(3):285–96.
2979. Ortega-Molina A, Efeyan A, Lopez-Guadamillas E, et al. Pten positively regulates brown adipose function, energy expenditure, and longevity. *Cell Metab*. 2012;15(3):382–94.
2980. Vatner DE, Zhang J, Oydanich M, et al. Enhanced longevity and metabolism by brown adipose tissue with disruption of the regulator of G protein signaling 14. *Aging Cell*. 2018;17(4):e12751.
2981. Hoffman JM, Valencak TG. Sex differences and aging: is there a role of brown adipose tissue? *Mol Cell Endocrinol*. 2021;531:111310.
2982. Dong M, Lin J, Lim W, Jin W, Lee HJ. Role of brown adipose tissue in metabolic syndrome, aging, and cancer cachexia. *Front Med*. 2018;12(2):130–8.
2983. Rogers NH. Brown adipose tissue during puberty and with aging. *Ann Med*. 2015;47(2):142–9.
2984. Fuse S, Endo T, Tanaka R, et al. Effects of capsinoid intake on brown adipose tissue vascular density and resting energy expenditure in healthy, middle-aged adults: a randomized, double-blind, placebo-controlled study. *Nutrients*. 2020;12(9):E2676.
2985. Smeets AJ, Janssens PL, Westerterp-Plantenga MS. Addition of capsaicin and exchange of carbohydrate with protein counteract energy intake restriction effects on fullness and energy expenditure. *J Nutr.* 2013;143(4):442–7.

2986. Sugita J, Yoneshiro T, Hatano T, et al. Grains of paradise (*Aframomum melegueta*) extract activates brown adipose tissue and increases whole-body energy expenditure in men. *Br J Nutr.* 2013;110(4):733–8.
2987. Maharlouei N, Tabrizi R, Lankarani KB, et al. The effects of ginger intake on weight loss and metabolic profiles among overweight and obese subjects: a systematic review and meta-analysis of randomized controlled trials. *Crit Rev Food Sci Nutr.* 2018:1–14.
2988. Pellagra: secondary to antiobesity diet. *Postgrad Med*. 1955;17(3):37.
2989. Afshin A, Forouzanfar MH, Reitsma BS, et al. Correspondence: health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377(1):13–27.
2990. Berrigan D, Troiano RP, Graubard BI. BMI and mortality: the limits of epidemiological evidence. *Lancet*. 2016;388(10046):734–6.
2991. Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med*. 2010;363(23):2211–9.
2992. Afshin A, Forouzanfar MH, Reitsma BS, et al. Correspondence: health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377(1):13–27.
2993. Aune D, Sen A, Prasad M, et al. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. *BMJ*. 2016;353:i2156.
2994. Greger M, Stone G. *How Not to Die*. Flatiron Books; 2015.
2995. Rae DE, Ebrahim I, Roden LC. Sleep: a serious contender for the prevention of obesity and non-communicable diseases. *JEMDSA*. 2016;21(1):1–2.
2996. Liu H, Chen A. Roles of sleep deprivation in cardiovascular dysfunctions. *Life Sci*. 2019;219:231–7.
2997. Möller-Levet CS, Archer SN, Bucca G, et al. Effects of insufficient sleep on circadian rhythmicity and expression amplitude of the human blood transcriptome. *Proc Natl Acad Sci U S A*. 2013;110(12):E1132–41.
2998. Calvin AD, Covassin N, Kremers WK, et al. Experimental sleep restriction causes endothelial dysfunction in healthy humans. *J Am*

Heart Assoc. 2014;3(6):e001143.
2999. Kohansieh M, Makaryus AN. Sleep deficiency and deprivation leading to cardiovascular disease. *Int J Hypertens*. 2015;2015:615681.
3000. Calvin AD, Covassin N, Kremers WK, et al. Experimental sleep restriction causes endothelial dysfunction in healthy humans. *J Am Heart Assoc*. 2014;3(6):e001143.
3001. Krueger PM, Friedman EM. Sleep duration in the United States: a cross-sectional population-based study. *Am J Epidemiol*. 2009;169(9):1052–63.
3002. Golem DL, Martin-Biggers JT, Koenings MM, Davis KF, Byrd-Bredbenner C. An integrative review of sleep for nutrition professionals. *Adv Nutr*. 2014;5(6):742–59.
3003. Shen J, Yang P, Luo X, et al. Green light extends *Drosophila* longevity. *Exp Gerontol*. 2021;147:111268.
3004. Shen J, Yang P, Luo X, et al. Green light extends *Drosophila* longevity. *Exp Gerontol*. 2021;147:111268.
3005. Bosman ES, Albert AY, Lui H, Dutz JP, Vallance BA. Skin exposure to narrow band ultraviolet (UVB) light modulates the human intestinal microbiome. *Front Microbiol*. 2019;10:2410.
3006. Shen J, Yang P, Luo X, et al. Green light extends *Drosophila* longevity. *Exp Gerontol*. 2021;147:111268.
3007. Li Q, Kobayashi M, Wakayama Y, et al. Effect of phytoncide from trees on human natural killer cell function. *Int J Immunopathol Pharmacol*. 2009;22(4):951–9.
3008. Opperhuizen AL, Stenvers DJ, Jansen RD, Foppen E, Fliers E, Kalsbeek A. Light at night acutely impairs glucose tolerance in a time-, intensity- and wavelength-dependent manner in rats. *Diabetologia*. 2017;60(7):1333–43.
3009. Kurina LM, McClintock MK, Chen JH, Waite LJ, Thisted RA, Lauderdale DS. Sleep duration and all-cause mortality: a critical review of measurement and associations. *Ann Epidemiol*. 2013;23(6):361–70.
3010. He M, Deng X, Zhu Y, Huan L, Niu W. The relationship between sleep duration and all-cause mortality in the older people: an updated

and dose-response meta-analysis. *BMC Public Health*. 2020;20(1):1179.
3011. Yetish G, Kaplan H, Gurven M, et al. Natural sleep and its seasonal variations in three pre-industrial societies. *Curr Biol*. 2015;25(21):2862–8.
3012. Shen X, Wu Y, Zhang D. Nighttime sleep duration, 24-hour sleep duration and risk of all-cause mortality among adults: a meta-analysis of prospective cohort studies. *Sci Rep*. 2016;6:21480.
3013. García-Perdomo HA, Zapata-Copete J, Rojas-Cerón CA. Sleep duration and risk of all-cause mortality: a systematic review and meta-analysis. *Epidemiol Psychiatr Sci*. 2018;Jul 30:1–11.
3014. Knutson KL, Turek FW. The U-shaped association between sleep and health: the 2 peaks do not mean the same thing. *Sleep*. 2006;29(7):878–9.
3015. Grandner MA, Drummond SPA. Who are the long sleepers? Towards an understanding of the mortality relationship. *Sleep Med Rev*. 2007;11(5):341–60.
3016. Kurina LM, McClintock MK, Chen JH, Waite LJ, Thisted RA, Lauderdale DS. Sleep duration and all-cause mortality: a critical review of measurement and associations. *Ann Epidemiol*. 2013;23(6):361–70.
3017. Hirshkowitz M, Whiton K, Albert SM, et al. National Sleep Foundation's sleep time duration recommendations: methodology and results summary. *Sleep Health*. 2015;1(1):40–3.
3018. Pourmotabbed A, Boozari B, Babaei A, et al. Sleep and frailty risk: a systematic review and meta-analysis. *Sleep Breath*. 2020;24(3):1187–97.
3019. Pourmotabbed A, Ghaedi E, Babaei A, et al. Sleep duration and sarcopenia risk: a systematic review and dose-response meta-analysis. *Sleep Breath*. 2020;24(4):1267–78.
3020. Schwarz EI, Puhan MA, Schlatzer C, Stradling JR, Kohler M. Effect of CPAP therapy on endothelial function in obstructive sleep apnoea: a systematic review and meta-analysis. *Respirology*. 2015;20(6):889–95.
3021. Bjorvatn B, Fiske E, Pallesen S. A self-help book is better than sleep hygiene advice for insomnia: a randomized controlled comparative

study. *Scand J Psychol*. 2011;52(6):580–5.
3022. Ancoli-Israel S. Sleep problems in older adults: putting myths to bed. *Geriatrics*. 1997;52(1):20–30.
3023. Miner B, Kryger MH. Sleep in the aging population. *Sleep Med Clin*. 2017;12(1):31–8.
3024. Lovato N, Lack L. Insomnia and mortality: a meta-analysis. *Sleep Med Rev*. 2019;43:71–83.
3025. Barclay NL, Kocevska D, Bramer WM, Van Someren EJW, Gehrman P. The heritability of insomnia: a meta-analysis of twin studies. *Genes Brain Behav*. 2021;20(4):e12717.
3026. Machado FV, Louzada LL, Cross NE, Camargos EF, Dang-Vu TT, Nóbrega OT. More than a quarter century of the most prescribed sleeping pill: systematic review of zolpidem use by older adults. *Exp Gerontol*. 2020;136:110962.
3027. Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open*. 2012;2(1):1–10.
3028. Baber R. Climacteric commentaries. Better sleep but higher mortality risk. *Climacteric*. 2012;15(4):401.
3029. Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open*. 2012;2(1):1–10.
3030. Rabin RC. New worries about sleeping pills. *The New York Times: Well*. https://well.blogs.nytimes.com/2012/03/12/new-worries-about-sleeping-pills. Published March 12, 2012. Accessed April 17, 2019.
3031. Kripke DF. Mortality risk of hypnotics: strengths and limits of evidence. *Drug Saf*. 2016;39(2):93–107.
3032. Bianchi MT, Thomas RJ, Ellenbogen JM. Hypnotics and mortality risk. *J Clin Sleep Med*. 2012;8(4):351–2.
3033. Kripke DF, Langer RD, Kline LE. Do no harm: not even to some degree. *J Clin Sleep Med*. 2012;8(4):353–4.
3034. Huedo-Medina TB, Kirsch I, Middlemass J, Klonizakis M, Siriwardena AN. Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. *BMJ*. 2012;345.

3035. Buscemi N, Vandermeer B, Friesen C, et al. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. *J Gen Intern Med*. 2007;22(9):1335–50.
3036. Kripke DF, Langer RD, Kline LE. Do no harm: not even to some degree. *J Clin Sleep Med*. 2012;08(04):353–4.
3037. Matheson E, Hainer BL. Insomnia: pharmacologic therapy. *Am Fam Physician*. 2017;96(1):29–35.
3038. Brown RF, Thorsteinsson EB, Smithson M, Birmingham CL, Aljarallah H, Nolan C. Can body temperature dysregulation explain the co-occurrence between overweight/obesity, sleep impairment, late-night eating, and a sedentary lifestyle? *Eat Weight Disord*. 2017;22(4):599–608.
3039. Brown RF, Thorsteinsson EB, Smithson M, Birmingham CL, Aljarallah H, Nolan C. Can body temperature dysregulation explain the co-occurrence between overweight/obesity, sleep impairment, late-night eating, and a sedentary lifestyle? *Eat Weight Disord*. 2017;22(4):599–608.
3040. Sung EJ, Tochihara Y. Effects of bathing and hot footbath on sleep in winter. *J Physiol Anthropol Appl Human Sci*. 2000;19(1):21–7.
3041. Aghamohammadi V, Salmani R, Ivanbagha R, Effati-Daryani F, Nasiri K. Footbath as a safe, simple, and non-pharmacological method to improve sleep quality of menopausal women. *Res Nurs Health*. 2020;43(6):621–8.
3042. Haghayegh S, Khoshnevis S, Smolensky MH, Diller KR, Castriotta RJ. Before-bedtime passive body heating by warm shower or bath to improve sleep: a systematic review and meta-analysis. *Sleep Med Rev*. 2019;46:124–35.
3043. Haghayegh S, Khoshnevis S, Smolensky MH, Diller KR, Castriotta RJ. Before-bedtime passive body heating by warm shower or bath to improve sleep: a systematic review and meta-analysis. *Sleep Med Rev*. 2019;46:124–35.
3044. Liao WC, Wang L, Kuo CP, Lo C, Chiu MJ, Ting H. Effect of a warm footbath before bedtime on body temperature and sleep in older adults with good and poor sleep: an experimental crossover trial. *Int J Nurs Stud*. 2013;50(12):1607–16.

3045. Kräuchi K, Cajochen C, Werth E, Wirz-Justice A. Warm feet promote the rapid onset of sleep. *Nature*. 1999;401(6748):36–7.
3046. Ko Y, Lee JY. Effects of feet warming using bed socks on sleep quality and thermoregulatory responses in a cool environment. *J Physiol Anthropol*. 2018;37(1):13.
3047. Matheson E, Hainer BL. Insomnia: pharmacologic therapy. *Am Fam Physician*. 2017;96(1):29–35.
3048. Morin CM, Inoue Y, Kushida C, et al. Endorsement of European guideline for the diagnosis and treatment of insomnia by the World Sleep Society. *Sleep Med*. 2021;81:124–6.
3049. Fatemeh G, Sajjad M, Niloufar R, Neda S, Leila S, Khadijeh M. Effect of melatonin supplementation on sleep quality: a systematic review and meta-analysis of randomized controlled trials. *J Neurol*. 2022;269(1):205–16.
3050. Brzezinski A, Vangel MG, Wurtman RJ, et al. Effects of exogenous melatonin on sleep: a meta-analysis. *Sleep Med Rev*. 2005;9(1):41–50.
3051. Williamson B, Tomlinson A, Naylor S, Gleich G. Contaminants in commercial preparations of melatonin. *Mayo Clin Proc*. 1997;72(11):1094–5.
3052. Poeggeler B. Melatonin, aging, and age-related diseases: perspectives for prevention, intervention, and therapy. *Endocrine*. 2005;27(2):201–12.
3053. Oaknin-Bendahan S, Anis Y, Nir I, Zisapel N. Effects of long-term administration of melatonin and a putative antagonist on the ageing rat. *Neuroreport*. 1995;6(5):785–8.
3054. Kim J, Lee SL, Kang I, et al. Natural products from single plants as sleep aids: a systematic review. *J Med Food*. 2018;21(5):433–44.
3055. Taibi DM, Landis CA, Petry H, Vitiello MV. A systematic review of valerian as a sleep aid: safe but not effective. *Sleep Med Rev*. 2007;11(3):209–30.
3056. Afrasiabian F, Ardakani MM, Rahmani K, et al. *Aloysia citriodora* Palau (lemon verbena) for insomnia patients: a randomized, double-blind, placebo-controlled clinical trial of efficacy and safety. *Phytother Res*. 2019;33(2):350–9.

3057. Zick SM, Wright BD, Sen A, Arnedt JT. Preliminary examination of the efficacy and safety of a standardized chamomile extract for chronic primary insomnia: a randomized placebo-controlled pilot study. *BMC Complement Altern Med*. 2011;11:78.
3058. Hieu TH, Dibas M, Dila KAS, et al. Therapeutic efficacy and safety of chamomile for state anxiety, generalized anxiety disorder, insomnia, and sleep quality: a systematic review and meta-analysis of randomized trials and quasi-randomized trials. *Phytother Res*. 2019;33(6):1604–15.
3059. St-Onge MP, Roberts A, Shechter A, Choudhury AR. Fiber and saturated fat are associated with sleep arousals and slow wave sleep. *J Clin Sleep Med*. 2016;12(1):19–24.
3060. Grandner MA, Kripke DF, Naidoo N, Langer RD. Relationships among dietary nutrients and subjective sleep, objective sleep, and napping in women. *Sleep Med*. 2010;11(2):180.
3061. McClernon FJ, Yancy WS, Eberstein JA, Atkins RC, Westman EC. The effects of a low-carbohydrate ketogenic diet and a low-fat diet on mood, hunger, and other self-reported symptoms. *Obesity (Silver Spring)*. 2007;15(1):182–7.
3062. Lana A, Struijk EA, Arias-Fernandez L, et al. Habitual meat consumption and changes in sleep duration and quality in older adults. *Aging Dis*. 2019;10(2):267–77.
3063. Hansen AL, Dahl L, Olson G, et al. Fish consumption, sleep, daily functioning, and heart rate variability. *J Clin Sleep Med*. 2014;10(5):567–75.
3064. Lana A, Struijk EA, Arias-Fernandez L, et al. Habitual meat consumption and changes in sleep duration and quality in older adults. *Aging Dis*. 2019;10(2):267–77.
3065. Wurtman RJ, Wurtman JJ, Regan MM, McDermott JM, Tsay RH, Breu JJ. Effects of normal meals rich in carbohydrates or proteins on plasma tryptophan and tyrosine ratios. *Am J Clin Nutr*. 2003;77(1):128–32.
3066. Beezhold BL, Johnston CS. Restriction of meat, fish, and poultry in omnivores improves mood: a pilot randomized controlled trial. *Nutr J*. 2012;11:9.

3067. Merrill RM, Aldana SG, Greenlaw RL, Diehl HA, Salberg A. The effects of an intensive lifestyle modification program on sleep and stress disorders. *J Nutr Health Aging*. 2007;11(3):242–8.
3068. St-Onge MP, Crawford A, Aggarwal B. Plant-based diets: reducing cardiovascular risk by improving sleep quality? *Curr Sleep Med Rep*. 2018;4(1):74–8.
3069. Harsha SN, Anilakumar KR. Anxiolytic property of *Lactuca sativa*, effect on anxiety behaviour induced by novel food and height. *Asian Pac J Trop Med*. 2013;6(7):532–6.
3070. Gonzálex-lima F, Valedón A, Stiehil WL. Depressant pharmacological effects of a component isolated from lettuce, *Lactuca sativa*. *Int J Crude Drug Res*. 1986;24(3):154–66.
3071. Kim H-W, Suh HJ, Choi H-S, Hong K-B, Jo K. Effectiveness of the sleep enhancement by green romaine lettuce (*Lactuca sativa*) in a rodent model. *Biol Pharm Bull*. 2019;42(10):1726–32.
3072. Kim HD, Hong K-B, Noh DO, Suh HJ. Sleep-inducing effect of lettuce (*Lactuca sativa*) varieties on pentobarbital-induced sleep. *Food Sci Biotechnol*. 2017;26(3):807–14.
3073. Pour ZS, Hosseinkhani A, Asadi N, et al. Double-blind randomized placebo-controlled trial on efficacy and safety of *Lactuca sativa* L. seeds on pregnancy-related insomnia. *J Ethnopharmacol*. 2018;227:176–80.
3074. Thomas T. Perls, MD, MPH, FACP. Boston University School of Medicine website. https://www.bumc.bu.edu/busm/profile/thomas-perls/. Accessesd April 3, 2022.
3075. Sebastiani P, Perls TT. The genetics of extreme longevity: lessons from the New England Centenarian Study. *Front Gene*. 2012;3:277.
3076. Tomiyama AJ. Stress and obesity. *Annu Rev Psychol*. 2019;70:703–18.
3077. Baxter AJ, Scott KM, Ferrari AJ, Norman RE, Vos T, Whiteford HA. Challenging the myth of an “epidemic” of common mental disorders: trends in the global prevalence of anxiety and depression between 1990 and 2010. *Depress Anxiety*. 2014;31(6):506–16.
3078. Adam TC, Epel ES. Stress, eating and the reward system. *Physiol Behav*. 2007;91(4):449–58.
3079. Tomiyama A. Stress and obesity. *Annu Rev Psychol*. 2019;70:703–18.

3080. Zellner DA, Loaiza S, Gonzalez Z, et al. Food selection changes under stress. *Physiol Behav*. 2006;87(4):789–93.
3081. Buchmann AF, Laucht M, Schmid B, Wiedemann K, Mann K, Zimmermann US. Cigarette craving increases after a psychosocial stress test and is related to cortisol stress response but not to dependence scores in daily smokers. *J Psychopharmacol*. 2010;24(2):247–55.
3082. Magrys SA, Olmstead MC. Acute stress increases voluntary consumption of alcohol in undergraduates. *Alcohol Alcohol*. 2015;50(2):213–8.
3083. Sinha R, Garcia M, Paliwal P, Kreek MJ, Rounsaville BJ. Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. *Arch Gen Psychiatry*. 2006;63(3):324–31.
3084. Rutters F, Pilz S, Koopman AD, et al. The association between psychosocial stress and mortality is mediated by lifestyle and chronic diseases: the Hoorn Study. *Soc Sci Med*. 2014;118:166–72.
3085. Rodgers J, Cuevas AG, Williams DR, Kawachi I, Subramanian SV. The relative contributions of behavioral, biological, and psychological risk factors in the association between psychosocial stress and all-cause mortality among middle- and older-aged adults in the USA. *Geroscience*. 2021;43(2):655–72.
3086. Strøm A, Jensen RA. Mortality from circulatory diseases in Norway 1940–1945. *Lancet*. 1951;1(6647):126–9.
3087. Keys A. Coronary heart disease—the global picture. *Atherosclerosis*. 1975;22(2):149–92.
3088. Malmros H. The relation of nutrition to health; a statistical study of the effect of the war-time on arteriosclerosis, cardiosclerosis, tuberculosis and diabetes. *Acta Med Scand Suppl*. 1950;246:137–53.
3089. Cronkite W. Poverty and want rip Netherlands; troops say Dutch suffered hunger, cold and lack of clothes under Germans. *The New York Times*. https://www.nytimes.com/1944/09/29/archives/poverty-and-want-rip-netherlands-troops-say-dutch-suffered-hunger.html. Published September 29, 1944. Accessed February 28, 2022.
3090. Diet and stress in vascular disease. *JAMA*. 1961;176(9):806–7.

3091. Hitchcott PK, Fastame MC, Penna MP. More to Blue Zones than long life: positive psychological characteristics. *Health Risk Soc*. 2018;20(3–4):163–81.
3092. Manzoli L, Villari P, M Pirone G, Boccia A. Marital status and mortality in the elderly: a systematic review and meta-analysis. *Soc Sci Med*. 2007;64(1):77–94.
3093. Ennis J, Majid U. "Death from a broken heart": a systematic review of the relationship between spousal bereavement and physical and physiological health outcomes. *Death Stud*. 2021;45(7):538–51.
3094. Friedmann E, Katcher AH, Lynch JJ, Thomas SA. Animal companions and one-year survival of patients after discharge from a coronary care unit. *Public Health Rep*. 1980;95(4):307–12.
3095. Manzoli L, Villari P, M Pirone G, Boccia A. Marital status and mortality in the elderly: a systematic review and meta-analysis. *Soc Sci Med*. 2007;64(1):77–94.
3096. Manzoli L, Villari P, M Pirone G, Boccia A. Marital status and mortality in the elderly: a systematic review and meta-analysis. *Soc Sci Med*. 2007;64(1):77–94.
3097. Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. *Perspect Psychol Sci*. 2015;10(2):227–37.
3098. Rico-Uribe LA, Caballero FF, Martín-María N, Cabello M, Ayuso-Mateos JL, Miret M. Association of loneliness with all-cause mortality: a meta-analysis. *PLoS One*. 2018;13(1):e0190033.
3099. Shor E, Roelfs DJ. Social contact frequency and all-cause mortality: a meta-analysis and meta-regression. *Soc Sci Med*. 2015;128:76–86.
3100. Stickley A, Koyanagi A, Roberts B, et al. Loneliness: its correlates and association with health behaviours and outcomes in nine countries of the former Soviet Union. *PLoS One*. 2013;8(7):e67978.
3101. Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. *Perspect Psychol Sci*. 2015;10(2):227–37.
3102. Kramer CK, Mehmood S, Suen RS. Dog ownership and survival: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2019;12(10):e005554.

3103. Nagasawa M, Mitsui S, En S, et al. Oxytocin-gaze positive loop and the coevolution of human-dog bonds. *Science*. 2015;348(6232):333–6.
3104. Friedmann E, Katcher AH, Lynch JJ, Thomas SA. Animal companions and one-year survival of patients after discharge from a coronary care unit. *Public Health Rep*. 1980;95(4):307–12.
3105. Herzog H. The impact of pets on human health and psychological well-being: fact, fiction, or hypothesis? *Curr Dir Psychol Sci*. 2011;20(4):236–9.
3106. Kazi DS. Who is rescuing whom? Dog ownership and cardiovascular health. *Circ Cardiovasc Qual Outcomes*. 2019;12(10):e005887.
3107. Kazi DS. Who is rescuing whom? Dog ownership and cardiovascular health. *Circ Cardiovasc Qual Outcomes*. 2019;12(10):e005887.
3108. Ko HJ, Youn CH, Kim SH, Kim SY. Effect of pet insects on the psychological health of community-dwelling elderly people: a single-blinded, randomized, controlled trial. *Gerontology*. 2016;62(2):200–9.
3109. Puterbaugh JS. The emperor's tailors: the failure of the medical weight loss paradigm and its causal role in the obesity of America. *Diabetes Obes Metab*. 2009;11(6):557–70.

III. Preserving Function

3110. Berg J, Seyedsadjadi N, Grant R. Increased consumption of plant foods is associated with increased bone mineral density. *J Nutr Health Aging*. 2020;24(4):388–97.

3111. Gupta T, Das N, Imran S. The prevention and therapy of osteoporosis: a review on emerging trends from hormonal therapy to synthetic drugs to plant-based bioactives. *J Diet Suppl*. 2019;16(6):699–713.

3112. Berg J, Seyedsadjadi N, Grant R. Increased consumption of plant foods is associated with increased bone mineral density. *J Nutr Health Aging*. 2020;24(4):388–97.

3113. Berg J, Seyedsadjadi N, Grant R. Increased consumption of plant foods is associated with increased bone mineral density. *J Nutr Health Aging*. 2020;24(4):388–97.

3114. Lorentzon M, Cummings SR. Osteoporosis: the evolution of a diagnosis. *J Intern Med*. 2015;277(6):650–61.

3115. Gupta T, Das N, Imran S. The prevention and therapy of osteoporosis: a review on emerging trends from hormonal therapy to synthetic drugs to plant-based bioactives. *J Diet Suppl*. 2019;16(6):699–713.

3116. Sahota O, Masud T. Osteoporosis: fact, fiction, fallacy and the future. *Age Ageing*. 1999;28(5):425–8.

3117. Michaëlsson K, Melhus H, Ferm H, Ahlbom A, Pedersen NL. Genetic liability to fractures in the elderly. *Arch Intern Med*. 2005;165(16):1825–30.

3118. Kanis JA, Odén A, McCloskey EV, et al. A systematic review of hip fracture incidence and probability of fracture worldwide. *Osteoporos Int*. 2012;23(9):2239–56.

3119. Final recommendation statement: osteoporosis to prevent fractures: screening. U.S. Preventative Services Task Force website. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/osteoporosis-screening. Published June 26, 2018. Accessed March 6, 2022.

3120. Luo H, Fan Q, Xiao S, Chen K. Changes in proton pump inhibitor prescribing trend over the past decade and pharmacists' effect on prescribing practice at a tertiary hospital. *BMC Health Serv Res*. 2018;18(1):537.
3121. Poly TN, Islam MM, Yang HC, Wu CC, Li YCJ. Proton pump inhibitors and risk of hip fracture: a meta-analysis of observational studies. *Osteoporos Int*. 2019;30(1):103–14.
3122. Xun X, Yin Q, Fu Y, He X, Dong Z. Proton pump inhibitors and the risk of community-acquired pneumonia: an updated meta-analysis. *Ann Pharmacother*. 2022;56(5):524–32.
3123. Moayyedi P, Lewis MA. Proton pump inhibitors and dementia: deciphering the data. *Am J Gastroenterol*. 2017;112(12):1809–11.
3124. Vengrus CS, Delfino VD, Bignardi PR. Proton pump inhibitors use and risk of chronic kidney disease and end-stage renal disease. *Minerva Urol Nephrol*. 2021;73(4):462–70.
3125. D'Silva KM, Mehta R, Mitchell M, et al. Proton pump inhibitor use and risk for recurrent *Clostridioides difficile* infection: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2021;27(5):697–703.
3126. Salvo EM, Ferko NC, Cash SB, Gonzalez A, Kahrilas PJ. Umbrella review of 42 systematic reviews with meta-analyses: the safety of proton pump inhibitors. *Aliment Pharmacol Ther*. 2021;54(2):129–43.
3127. Sun S, Cui Z, Zhou M, et al. Proton pump inhibitor monotherapy and the risk of cardiovascular events in patients with gastro-esophageal reflux disease: a meta-analysis. *Neurogastroenterol Motil*. 2017;29(2):e12926.
3128. Ben-Eltriki M, Green CJ, Maclure M, Musini V, Bassett KL, Wright JM. Do proton pump inhibitors increase mortality? A systematic review and in-depth analysis of the evidence. *Pharmacol Res Perspect*. 2020;8(5):e00651.
3129. Safer DJ. Overprescribed medications for US adults: four major examples. *J Clin Med Res*. 2019;11(9):617–22.
3130. Safer DJ. Overprescribed medications for US adults: four major examples. *J Clin Med Res*. 2019;11(9):617–22.

3131. Ness-Jensen E, Hveem K, El-Serag H, Lagergren J. Lifestyle intervention in gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2016;14(2):175–82.e1–3.
3132. Andrici J, Cox MR, Eslick GD. Cigarette smoking and the risk of Barrett's esophagus: a systematic review and meta-analysis. *J Gastroenterol Hepatol*. 2013;28(8):1258–73.
3133. Fan WJ, Hou YT, Sun XH, et al. Effect of high-fat, standard, and functional food meals on esophageal and gastric pH in patients with gastroesophageal reflux disease and healthy subjects. *J Dig Dis*. 2018;19(11):664–73.
3134. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol*. 2013;108(3):308–28.
3135. Newberry C, Lynch K. The role of diet in the development and management of gastroesophageal reflux disease: why we feel the burn. *J Thorac Dis*. 2019;11(Suppl 12):S1594–601.
3136. Jung JG, Kang HW. Vegetarianism and the risk of gastroesophageal reflux disease. In: *Vegetarian and Plant-Based Diets in Health and Disease Prevention*. Elsevier; 2017:463–72.
3137. Law MR, Hackshaw AK. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. *BMJ*. 1997;315(7112):841–6.
3138. Patel RA, Wilson RF, Patel PA, Palmer RM. The effect of smoking on bone healing. *Bone Joint Res*. 2013;2(6):102–11.
3139. Kim JH, Patel S. Is it worth discriminating against patients who smoke? A systematic literature review on the effects of tobacco use in foot and ankle surgery. *J Foot Ankle Surg*. 2017;56(3):594–9.
3140. Bourne D, Plinke W, Hooker ER, Nielson CM. Cannabis use and bone mineral density: NHANES 2007–2010. *Arch Osteoporos*. 2017;12(1):29.
3141. Sophocleous A, Robertson R, Ferreira NB, McKenzie J, Fraser WD, Ralston SH. Heavy cannabis use is associated with low bone mineral density and an increased risk of fractures. *Am J Med*. 2017;130(2):214–21.
3142. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*.

2014;25(10):2359–81.
3143. Wright J. Marketing disease: is osteoporosis an example of “disease mongering”? *Br J Nurs*. 2009;18(17):1064–7.
3144. Hudson B, Zarifeh A, Young L, Wells JE. Patients’ expectations of screening and preventive treatments. *Ann Fam Med*. 2012;10(6):495–502.
3145. Black DM, Rosen CJ. Postmenopausal osteoporosis. N Engl J Med. 2016;374(21):2096–7.
3146. Lems WF, Raterman HG. Critical issues and current challenges in osteoporosis and fracture prevention. An overview of unmet needs. *Ther Adv Musculoskelet Dis*. 2017;9(12):299–316.
3147. Kolata G. Fearing drugs’ rare side effects, millions take their chances with osteoporosis. *The New York Times*. https://www.nytimes.com/2016/06/02/health/osteoporosis-drugs-bones.html. Published June 1, 2016. Accessed March 6, 2022.
3148. Sales LP, Pinto AJ, Rodrigues SF, et al. Creatine supplementation (3 g/d) and bone health in older women: a 2-year, randomized, placebo-controlled trial. *J Gerontol A Biol Sci Med Sci*. 2020;75(5):931–8.
3149. Candow DG, Forbes SC, Kirk B, Duque G. Current evidence and possible future applications of creatine supplementation for older adults. *Nutrients*. 2021;13(3):745.
3150. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA*. 2001;285(6):785–95.
3151. Nestle M, Nesheim MC. To supplement or not to supplement: the U.S. Preventive Services Task Force recommendations on calcium and vitamin D. *Ann Intern Med*. 2013;158(9):701–2.
3152. Grossman DC, Curry SJ, Owens DK, et al. Vitamin D, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;319(15):1592–9.
3153. Bolland MJ, Grey A, Reid IR. Calcium supplements and cardiovascular risk: 5 years on. *Ther Adv Drug Saf*. 2013;4(5):199–210.
3154. Reid IR, Bristow SM, Bolland MJ. Calcium supplements: benefits and risks. *J Intern Med*. 2015;278(4):354–68.

3155. Reid IR, Bolland MJ. Risk factors: calcium supplements and cardiovascular risk. *Nat Rev Cardiol*. 2012;9(9):497–8.
3156. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. *Am J Clin Nutr*. 2007;86(6):1780–90.
3157. Bolland MJ, Grey A, Reid IR. Calcium supplements and cardiovascular risk: 5 years on. *Ther Adv Drug Saf*. 2013;4(5):199–210.
3158. Willett WC, Ludwig DS. Milk and health. *N Engl J Med*. 2020;382(7):644–54.
3159. Dawson-Hughes B, Jacques P, Shipp C. Dietary calcium intake and bone loss from the spine in healthy postmenopausal women. *Am J Clin Nutr*. 1987;46(4):685–7.
3160. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA*. 2010;303(18):1815–22.
3161. Ginde AA, Blatchford P, Breese K, et al. High-dose monthly vitamin D for prevention of acute respiratory infection in older long-term care residents: a randomized clinical trial. *J Am Geriatr Soc*. 2017;65(3):496–503.
3162. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. *JAMA Intern Med*. 2016;176(2):175–83.
3163. Smith LM, Gallagher JC, Suiter C. Medium doses of vitamin D decrease falls and higher doses of daily vitamin D3 increase falls: a randomized clinical trial. *J Steroid Biochem Mol Biol*. 2017;173:317–22.
3164. Burt LA, Billington EO, Rose MS, Raymond DA, Hanley DA, Boyd SK. Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: a randomized clinical trial. *JAMA*. 2019;322(8):736–45.
3165. Burt LA, Billington EO, Rose MS, Kremer R, Hanley DA, Boyd SK. Adverse effects of high-dose vitamin D supplementation on

volumetric bone density are greater in females than males. *J Bone Miner Res*. 2020;35(12):2404–14.
3166. Iuliano S, Hill TR. Dairy foods and bone health throughout the lifespan: a critical appraisal of the evidence. *Br J Nutr*. 2019;121(7):763–72.
3167. Byberg L, Warensjö-Lemming E. Milk consumption for the prevention of fragility fractures. *Nutrients*. 2020;12(9):E2720.
3168. Willett WC, Ludwig DS. Milk and health. *N Engl J Med*. 2020;382(7):644–54.
3169. Phillip A. Study: milk may not be very good for bones or the body. *The Washington Post*. https://www.washingtonpost.com/news/to-your-health/wp/2014/10/31/study-milk-may-not-be-very-good-for-bones-or-the-body/. Published October 31, 2014. Accessed March 23, 2022.
3170. Michaëlsson K, Wolk A, Langenskiöld S, et al. Milk intake and risk of mortality and fractures in women and men: cohort studies. *BMJ*. 2014;349:g6015.
3171. Cui X, Wang L, Zuo P, et al. D-galactose-caused life shortening in *Drosophila melanogaster* and *Musca domestica* is associated with oxidative stress. *Biogerontology*. 2004;5(5):317–25.
3172. Cui X, Zuo P, Zhang Q, et al. Chronic systemic D-galactose exposure induces memory loss, neurodegeneration, and oxidative damage in mice: protective effects of R-alpha-lipoic acid. *J Neurosci Res*. 2006;84(3):647–54.
3173. Simoons FJ. A geographic approach to senile cataracts: possible links with milk consumption, lactase activity, and galactose metabolism. *Dig Dis Sci*. 1982;27(3):257–64.
3174. Sella R, Afshari NA. Nutritional effect on age-related cataract formation and progression. *Curr Opin Ophthalmol*. 2019;30(1):63–9.
3175. Ding M, Li J, Qi L, et al. Associations of dairy intake with risk of mortality in women and men: three prospective cohort studies. *BMJ*. 2019;367:l6204.
3176. Grey A, Bolland M. Web of industry, advocacy, and academia in the management of osteoporosis. *BMJ*. 2015;351:h3170.
3177. Byberg L, Warensjö-Lemming E. Milk consumption for the prevention of fragility fractures. *Nutrients*. 2020;12(9):E2720.

3178. Willett WC, Ludwig DS. Milk and health. *N Engl J Med*. 2020;382(7):644–54.
3179. Dai Z, Kroeger CM, Lawrence M, Scrinis G, Bero L. Comparison of methodological quality between the 2007 and 2019 Canadian dietary guidelines. *Public Health Nutr*. 2020;23(16):2879–85.
3180. Ausman LM, Oliver LM, Goldin BR, Woods MN, Gorbach SL, Dwyer JT. Estimated net acid excretion inversely correlates with urine pH in vegans, lacto-ovo vegetarians, and omnivores. *J Ren Nutr*. 2008;18(5):456–65.
3181. Kerstetter JE, O'Brien KO, Caseria DM, Wall DE, Insogna KL. The impact of dietary protein on calcium absorption and kinetic measures of bone turnover in women. *J Clin Endocrinol Metab*. 2005;90(1):26–31.
3182. Dawson-Hughes B, Harris SS, Ceglia L. Alkaline diets favor lean tissue mass in older adults. *Am J Clin Nutr*. 2008;87(3):662–5.
3183. Groesbeck DK, Bluml RM, Kossoff EH. Long-term use of the ketogenic diet in the treatment of epilepsy. *Dev Med Child Neurol*. 2006;48(12):978–81.
3184. Heikura IA, Burke LM, Hawley JA, et al. A short-term ketogenic diet impairs markers of bone health in response to exercise. *Front Endocrinol (Lausanne)*. 2020;10:880.
3185. Simm PJ, Bicknell-Royle J, Lawrie J, et al. The effect of the ketogenic diet on the developing skeleton. *Epilepsy Res*. 2017;136:62–6.
3186. Bergqvist AG, Schall JI, Stallings VA, Zemel BS. Progressive bone mineral content loss in children with intractable epilepsy treated with the ketogenic diet. *Am J Clin Nutr*. 2008;88(6):1678–84.
3187. Yancy WS, Olsen MK, Dudley T, Westman EC. Acid-base analysis of individuals following two weight loss diets. *Eur J Clin Nutr*. 2007;61(12):1416–22.
3188. Gunaratnam K, Vidal C, Gimble JM, Duque G. Mechanisms of palmitate-induced lipotoxicity in human osteoblasts. *Endocrinology*. 2014;155(1):108–16.
3189. Mozaffari H, Djafarian K, Mofrad MD, Shab-Bidar S. Dietary fat, saturated fatty acid, and monounsaturated fatty acid intakes and risk

of bone fracture: a systematic review and meta-analysis of observational studies. *Osteoporos Int*. 2018;29(9):1949–61.

3190. Frassetto L, Sebastian A. Age and systemic acid-base equilibrium: analysis of published data. *J Gerontol A Biol Sci Med Sci*. 1996;51(1):B91–9.

3191. Frassetto L, Banerjee T, Powe N, Sebastian A. Acid balance, dietary acid load, and bone effects—a controversial subject. *Nutrients*. 2018;10(4):517.

3192. Cao JJ, Whigham LD, Jahns L. Depletion and repletion of fruit and vegetable intake alters serum bone turnover markers: a 28-week single-arm experimental feeding intervention. *Br J Nutr*. 2018;120(5):500–7.

3193. Hayhoe RPG, Abdelhamid A, Luben RN, Khaw KT, Welch AA. Dietary acid-base load and its association with risk of osteoporotic fractures and low estimated skeletal muscle mass. *Eur J Clin Nutr*. 2020;74(Suppl 1):33–42.

3194. Macdonald R, Black A, Sandison R, Aucott L, et al. Two year double blind randomized controlled trial in postmenopausal women shows no gain in BMD with potassium citrate treatment. Paper presented at: 28th Annual Meeting of the American Society of Bone and Mineral Research; September 15–19, 2006; Philadelphia, PA.

3195. Dawson-Hughes B. Acid-base balance of the diet-implications for bone and muscle. *Eur J Clin Nutr*. 2020;74(Suppl 1):7–13.

3196. Jehle S, Hulter HN, Krapf R. Effect of potassium citrate on bone density, microarchitecture, and fracture risk in healthy older adults without osteoporosis: a randomized controlled trial. *J Clin Endocrinol Metab*. 2013;98(1):207–17.

3197. Fang Y, Zhu J, Fan J, et al. Dietary Inflammatory Index in relation to bone mineral density, osteoporosis risk and fracture risk: a systematic review and meta-analysis. *Osteoporos Int*. 2021;32(4):633–43.

3198. Mun H, Liu B, Pham THA, Wu Q. C-reactive protein and fracture risk: an updated systematic review and meta-analysis of cohort studies through the use of both frequentist and Bayesian approaches. *Osteoporos Int*. 2021;32(3):425–35.

3199. Zhao F, Guo L, Wang X, Zhang Y. Correlation of oxidative stress-related biomarkers with postmenopausal osteoporosis: a systematic

review and meta-analysis. *Arch Osteoporos*. 2021;16(1):4.
3200. Brondani JE, Comim FV, Flores LM, Martini LA, Premaor MO. Fruit and vegetable intake and bones: a systematic review and meta-analysis. *PLoS One*. 2019;14(5):e0217223.
3201. Zeng LF, Luo MH, Liang GH, et al. Can dietary intake of vitamin C–oriented foods reduce the risk of osteoporosis, fracture, and BMD loss? Systematic review with meta-analyses of recent studies. *Front Endocrinol (Lausanne)*. 2019;10:844.
3202. Sun Y, Liu C, Bo Y, et al. Dietary vitamin C intake and the risk of hip fracture: a dose-response meta-analysis. *Osteoporos Int*. 2018;29(1):79–87.
3203. Mühlbauer RC, Lozano A, Reinli A, Wetli H. Various selected vegetables, fruits, mushrooms and red wine residue inhibit bone resorption in rats. *J Nutr*. 2003;133(11):3592–7.
3204. Hooshmand S, Kern M, Metti D, et al. The effect of two doses of dried plum on bone density and bone biomarkers in osteopenic postmenopausal women: a randomized, controlled trial. *Osteoporos Int*. 2016;27(7):2271–9.
3205. Law YY, Chiu HF, Lee HH, Shen YC, Venkatakrishnan K, Wang CK. Consumption of onion juice modulates oxidative stress and attenuates the risk of bone disorders in middle-aged and post-menopausal healthy subjects. *Food Funct*. 2016;7(2):902–12.
3206. Mackinnon ES, Rao AV, Josse RG, Rao LG. Supplementation with the antioxidant lycopene significantly decreases oxidative stress parameters and the bone resorption marker N-telopeptide of type I collagen in postmenopausal women. *Osteoporos Int*. 2011;22(4):1091–101.
3207. Russo C, Ferro Y, Maurotti S, et al. Lycopene and bone: an in vitro investigation and a pilot prospective clinical study. *J Transl Med*. 2020;18(1):43.
3208. Gunn CA, Weber JL, McGill AT, Kruger MC. Increased intake of selected vegetables, herbs and fruit may reduce bone turnover in post-menopausal women. *Nutrients*. 2015;7(4):2499–517.
3209. Cheraghi Z, Doosti-Irani A, Almasi-Hashiani A, et al. The effect of alcohol on osteoporosis: a systematic review and meta-analysis. *Drug Alcohol Depend*. 2019;197:197–202.

3210. Godos J, Giampieri F, Chisari E, et al. Alcohol consumption, bone mineral density, and risk of osteoporotic fractures: a dose-response meta-analysis. *Int J Environ Res Public Health*. 2022;19(3):1515.
3211. Lems WF, Raterman HG. Critical issues and current challenges in osteoporosis and fracture prevention. An overview of unmet needs. *Ther Adv Musculoskelet Dis*. 2017;9(12):299–316.
3212. Ahn H, Park YK. Sugar-sweetened beverage consumption and bone health: a systematic review and meta-analysis. *Nutr J*. 2021;20(1):41.
3213. Fatahi S, Namazi N, Larijani B, Azadbakht L. The association of dietary and urinary sodium with bone mineral density and risk of osteoporosis: a systematic review and meta-analysis. *J Am Coll Nutr*. 2018;37(6):522–32.
3214. Mortensen SJ, Beeram I, Florance J, et al. Modifiable lifestyle factors associated with fragility hip fracture: a systematic review and meta-analysis. *J Bone Miner Metab*. 2021;39(5):893–902.
3215. Shen CL, Chyu MC, Yeh JK, et al. Effect of green tea and Tai Chi on bone health in postmenopausal osteopenic women: a 6-month randomized placebo-controlled trial. *Osteoporos Int*. 2012;23(5):1541–52.
3216. Shen CL, Wang P, Guerrieri J, Yeh JK, Wang JS. Protective effect of green tea polyphenols on bone loss in middle-aged female rats. *Osteoporos Int*. 2008;19(7):979–90.
3217. Dostal AM, Arikawa A, Espejo L, Kurzer MS. Long-term supplementation of green tea extract does not modify adiposity or bone mineral density in a randomized trial of overweight and obese postmenopausal women. *J Nutr*. 2016;146(2):256–64.
3218. Platt ID, Josse AR, Kendall CWC, Jenkins DJA, El-Sohemy A. Postprandial effects of almond consumption on human osteoclast precursors—an ex vivo study. *Metabolism*. 2011;60(7):923–9.
3219. Fugh-Berman A, Pearson C. The overselling of hormone replacement therapy. *Pharmacotherapy*. 2002;22(9):1205–8.
3220. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321–33.

3221. Oseni T, Patel R, Pyle J, Jordan VC. Selective estrogen receptor modulators and phytoestrogens. *Planta Med*. 2008;74(13):1656–65.
3222. McCarty MF. Isoflavones made simple—genistein's agonist activity for the beta-type estrogen receptor mediates their health benefits. *Med Hypotheses*. 2006;66(6):1093–114.
3223. Chi F, Wu R, Zeng YC, Xing R, Liu Y, Xu ZG. Post-diagnosis soy food intake and breast cancer survival: a meta-analysis of cohort studies. *Asian Pac J Cancer Prev*. 2013;14(4):2407–12.
3224. Sansai K, Na Takuathung M, Khatsri R, Teekachunhatean S, Hanprasertpong N, Koonrungsesomboon N. Effects of isoflavone interventions on bone mineral density in postmenopausal women: a systematic review and meta-analysis of randomized controlled trials. *Osteoporos Int*. 2020;31(10):1853–64.
3225. Morabito N, Crisafulli A, Vergara C, et al. Effects of genistein and hormone-replacement therapy on bone loss in early postmenopausal women: a randomized double-blind placebo-controlled study. *J Bone Miner Res*. 2002;17(10):1904–12.
3226. Lydeking-Olsen E, Beck-Jensen JE, Setchell KDR, Holm-Jensen T. Soymilk or progesterone for prevention of bone loss: a 2 year randomized, placebo-controlled trial. *Eur J Nutr*. 2004;43(4):246–57.
3227. Koch L. Nutrition: High isoflavone intake delays puberty onset and may reduce breast cancer risk in girls. *Nat Rev Endocrinol*. 2010;6(11):595.
3228. Jacobsen BK, Knutsen SF, Fraser GE. Does high soy milk intake reduce prostate cancer incidence? The Adventist Health Study (United States). *Cancer Causes Control*. 1998;9(6):553–7.
3229. Fujisawa T, Ohashi Y, Shin R, Narai-Kanayama A, Nakagaki T. The effect of soymilk intake on the fecal microbiota, particularly *Bifidobacterium* species, and intestinal environment of healthy adults: a pilot study. *Biosci Microbiota Food Health*. 2017;36(1):33–7.
3230. Eslami O, Shidfar F, Maleki Z, et al. Effect of soy milk on metabolic status of patients with nonalcoholic fatty liver disease: a randomized clinical trial. *J Am Coll Nutr*. 2019;38(1):51–8.
3231. Mitchell JH, Collins AR. Effects of a soy milk supplement on plasma cholesterol levels and oxidative DNA damage in men—a pilot study. *Eur J Nutr*. 1999;38(3):143–8.

3232. Maleki Z, Jazayeri S, Eslami O, et al. Effect of soy milk consumption on glycemic status, blood pressure, fibrinogen and malondialdehyde in patients with non-alcoholic fatty liver disease: a randomized controlled trial. *Complement Ther Med*. 2019;44:44–50.
3233. Liao YH, Chen CN, Hu CY, Tsai SC, Kuo YC. Soymilk ingestion immediately after therapeutic exercise enhances rehabilitation outcomes in chronic stroke patients: a randomized controlled trial. *NeuroRehabilitation*. 2019;44(2):217–29.
3234. Rivas M, Garay RP, Escanero JF, Cia P, Cia P, Alda JO. Soy milk lowers blood pressure in men and women with mild to moderate essential hypertension. *J Nutr*. 2002;132(7):1900–2.
3235. Onuegbu AJ, Olisekodiaka JM, Onibon MO, Adesiyan AA, Igbeneghu CA. Consumption of soymilk lowers atherogenic lipid fraction in healthy individuals. *J Med Food*. 2011;14(3):257–60.
3236. Vanga SK, Raghavan V. How well do plant based alternatives fare nutritionally compared to cow's milk? *J Food Sci Technol*. 2018;55(1):10–20.
3237. Shi Y, Zhan Y, Chen Y, Jiang Y. Effects of dairy products on bone mineral density in healthy postmenopausal women: a systematic review and meta-analysis of randomized controlled trials. *Arch Osteoporos*. 2020;15(1):48.
3238. Byberg L, Warensjö-Lemming E. Milk consumption for the prevention of fragility fractures. *Nutrients*. 2020;12(9):E2720.
3239. Akhavan Zanjani M, Rahmani S, Mehranfar S, et al. Soy foods and the risk of fracture: a systematic review of prospective cohort studies. *Complement Med Res*. 2022;29(2):172–81.
3240. Zhang X, Shu XO, Li H, et al. Prospective cohort study of soy food consumption and risk of bone fracture among postmenopausal women. *Arch Intern Med*. 2005;165(16):1890–5.
3241. Chen Z, Zheng W, Custer LJ, et al. Usual dietary consumption of soy foods and its correlation with the excretion rate of isoflavonoids in overnight urine samples among Chinese women in Shanghai. *Nutr Cancer*. 1999;33(1):82–7.
3242. Prabhakaran MP. Isoflavone levels and the effect of processing on the content of isoflavones during the preparation of soymilk and tofu.

Thesis submitted for the degree of doctor of philosophy to the National University of Singapore. 2005.
3243. Petroski W, Minich DM. Is there such a thing as “anti-nutrients”? A narrative review of perceived problematic plant compounds. *Nutrients*. 2020;12(10):2929.
3244. Berg J, Seyedsadjadi N, Grant R. Increased consumption of plant foods is associated with increased bone mineral density. *J Nutr Health Aging*. 2020;24(4):388–97.
3245. Melaku YA, Gill TK, Appleton SL, Taylor AW, Adams R, Shi Z. Prospective associations of dietary and nutrient patterns with fracture risk: a 20-year follow-up study. *Nutrients*. 2017;9(11):1198.
3246. Iguacel I, Miguel-Berges ML, Gómez-Bruton A, Moreno LA, Julián C. Veganism, vegetarianism, bone mineral density, and fracture risk: a systematic review and meta-analysis. *Nutr Rev*. 2019;77(1):1–18.
3247. Karavasiloglou N, Selinger E, Gojda J, Rohrmann S, Kühn T. Differences in bone mineral density between adult vegetarians and nonvegetarians become marginal when accounting for differences in anthropometric factors. *J Nutr*. 2020;150(5):1266–71.
3248. Iwaniec UT, Turner RT. Influence of body weight on bone mass, architecture and turnover. *J Endocrinol*. 2016;230(3):R115–30.
3249. Tong TYN, Appleby PN, Armstrong MEG, et al. Vegetarian and vegan diets and risks of total and site-specific fractures: results from the prospective EPIC-Oxford study. *BMC Med*. 2020;18(1):353.
3250. Tong TYN, Appleby PN, Armstrong MEG, et al. Vegetarian and vegan diets and risks of total and site-specific fractures: results from the prospective EPIC-Oxford study. Table S6. Risks of hip fractures by age, sex, menopausal status, physical activity and BMI. *BMC Med*. 2020;18(1):353.
3251. Yao P, Bennett D, Mafham M, et al. Vitamin D and calcium for the prevention of fracture: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2(12):e1917789.
3252. Heaney RP. The vitamin D requirement in health and disease. *J Steroid Biochem Mol Biol*. 2005;97(1–2):13–9.
3253. Appleby P, Roddam A, Allen N, Key T. Comparative fracture risk in vegetarians and nonvegetarians in EPIC-Oxford. *Eur J Clin Nutr*. 2007;61(12):1400–6.

3254. Lang T, LeBlanc A, Evans H, Lu Y, Genant H, Yu A. Cortical and trabecular bone mineral loss from the spine and hip in long-duration spaceflight. *J Bone Miner Res*. 2004;19(6):1006–12.
3255. Troy KL, Mancuso ME, Butler TA, Johnson JE. Exercise early and often: effects of physical activity and exercise on women's bone health. *Int J Environ Res Public Health*. 2018;15(5):E878.
3256. Troy KL, Mancuso ME, Butler TA, Johnson JE. Exercise early and often: effects of physical activity and exercise on women's bone health. *Int J Environ Res Public Health*. 2018;15(5):E878.
3257. Lu YH, Rosner B, Chang G, Fishman LM. Twelve-minute daily yoga regimen reverses osteoporotic bone loss. *Top Geriatr Rehabil*. 2016;32(2):81–7.
3258. Sfeir JG, Drake MT, Sonawane VJ, Sinaki M. Vertebral compression fractures associated with yoga: a case series. *Eur J Phys Rehabil Med*. 2018;54(6):947–51.
3259. Cramer H, Ostermann T, Dobos G. Injuries and other adverse events associated with yoga practice: a systematic review of epidemiological studies. *J Sci Med Sport*. 2018;21(2):147–54.
3260. Cramer H, Quinker D, Schumann D, Wardle J, Dobos G, Lauche R. Adverse effects of yoga: a national cross-sectional survey. *BMC Complement Altern Med*. 2019;19(1):190.
3261. Zhu JK, Wu LD, Zheng RZ, Lan SH. Yoga is found hazardous to the meniscus for Chinese women. *Chin J Traumatol*. 2012;15(3):148–51.
3262. Boddu P, Patel S, Shahrrava A. Sudden cardiac arrest from heat stroke: hidden dangers of hot yoga. *Am J Med*. 2016;129(8):e129–30.
3263. insightSlice. Bone densitometer market global sales are expected to grow steadily to reach US$1.75 billion by 2031. Globe Newswire. https://www.globenewswire.com/news-release/2021/07/12/2261344/0/en/Bone-Densitometer-Market-Global-Sales-are-Expected-to-Grow-Steadily-to-Reach-US-1–75-billion-by-2031.html. Published July 12, 2021. Accessed March 18, 2022.
3264. Stone KL, Seeley DG, Lui LY, et al. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. *J Bone Miner Res*. 2003;18(11):1947–54.

3265. De Laet CEDH, van Hout BA, Burger H, Hofman A, Pols HAP. Bone density and risk of hip fracture in men and women: cross sectional analysis. *BMJ*. 1997;315(7102):221–5.
3266. Järvinen TLN, Sievänen H, Khan KM, Heinonen A, Kannus P. Shifting the focus in fracture prevention from osteoporosis to falls. *BMJ*. 2008;336(7636):124–6.
3267. Nordström P, Eklund F, Björnstig U, et al. Do both areal BMD and injurious falls explain the higher incidence of fractures in women than in men? *Calcif Tissue Int*. 2011;89(3):203–10.
3268. Wagner H, Melhus H, Gedeborg R, Pedersen NL, Michaëlsson K. Simply ask them about their balance—future fracture risk in a nationwide cohort study of twins. *Am J Epidemiol*. 2009;169(2):143–9.
3269. Stone KL, Seeley DG, Lui LY, et al. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. *J Bone Miner Res*. 2003;18(11):1947–54.
3270. Järvinen TLN, Michaëlsson K, Aspenberg P, Sievänen H. Osteoporosis: the emperor has no clothes. *J Intern Med*. 2015;277(6):662–73.
3271. Dequeker J, Nijs J, Verstraeten A, Geusens P, Gevers G. Genetic determinants of bone mineral content at the spine and radius: a twin study. *Bone*. 1987;8(4):207–9.
3272. Michaëlsson K, Melhus H, Ferm H, Ahlbom A, Pedersen NL. Genetic liability to fractures in the elderly. *Arch Intern Med*. 2005;165(16):1825–30.
3273. Wagner H, Melhus H, Pedersen NL, Michaëlsson K. Heritability of impaired balance: a nationwide cohort study in twins. *Osteoporos Int*. 2009;20(4):577–83.
3274. Burger H, de Laet CEDH, Weel AEAM, Hofman A, Pols HAP. Added value of bone mineral density in hip fracture risk scores. *Bone*. 1999;25(3):369–74.
3275. Järvinen TLN, Michaëlsson K, Aspenberg P, Sievänen H. Osteoporosis: the emperor has no clothes. *J Intern Med*. 2015;277(6):662–73.
3276. Kannus P, Sievänen H, Palvanen M, Järvinen T, Parkkari J. Prevention of falls and consequent injuries in elderly people. *Lancet*.

2005;366(9500):1885–93.
3277. Järvinen TLN, Michaëlsson K, Aspenberg P, Sievänen H. Osteoporosis: the emperor has no clothes. *J Intern Med*. 2015;277(6):662–73.
3278. Tinetti ME. Preventing falls in elderly persons. *N Engl J Med*. 2003;348(1):42–9.
3279. Sernbo I, Johnell O. Consequences of a hip fracture: a prospective study over 1 year. *Osteoporos Int*. 1993;3(3):148–53.
3280. Tricco AC, Thomas SM, Veroniki AA, et al. Comparisons of interventions for preventing falls in older adults: a systematic review and meta-analysis. *JAMA*. 2017;318(17):1687–99.
3281. Dautzenberg L, Beglinger S, Tsokani S, et al. Interventions for preventing falls and fall-related fractures in community-dwelling older adults: a systematic review and network meta-analysis. *J Am Geriatr Soc*. 2021;69(10):2973–84.
3282. Sherrington C, Fairhall NJ, Wallbank GK, et al. Exercise for preventing falls in older people living in the community. *Cochrane Database Syst Rev*. 2019;1:CD012424.
3283. Wong RMY, Chong KC, Law SW, et al. The effectiveness of exercises on fall and fracture prevention amongst community elderlies: a systematic review and meta-analysis. *J Orthop Translat*. 2020;24:58–65.
3284. Karinkanta S, Heinonen A, Sievänen H, et al. A multi-component exercise regimen to prevent functional decline and bone fragility in home-dwelling elderly women: randomized, controlled trial. *Osteoporos Int*. 2007;18(4):453–62.
3285. Karinkanta S, Kannus P, Uusi-Rasi K, Heinonen A, Sievänen H. Combined resistance and balance-jumping exercise reduces older women's injurious falls and fractures: 5-year follow-up study. *Age Ageing*. 2015;44(5):784–9.
3286. Korall AMB, Feldman F, Scott VJ, et al. Facilitators of and barriers to hip protector acceptance and adherence in long-term care facilities: a systematic review. *J Am Med Dir Assoc*. 2015;16(3):185–93.
3287. Santesso N, Carrasco-Labra A, Brignardello-Petersen R. Hip protectors for preventing hip fractures in older people. *Cochrane Database Syst Rev*. 2014;(3):CD001255.

3288. Dautzenberg L, Beglinger S, Tsokani S, et al. Interventions for preventing falls and fall-related fractures in community-dwelling older adults: a systematic review and network meta-analysis. *J Am Geriatr Soc*. 2021;69(10):2973–84.
3289. STEADI. What you can do to prevent falls. Centers for Disease Control and Prevention. https://www.cdc.gov/steadi/pdf/STEADI-Brochure-WhatYouCanDo-508.pdf. Published 2017. Accessed March 11, 2022.
3290. STEADI. Family caregivers: protect your loved ones from falling. Centers for Disease Control and Prevention. https://www.cdc.gov/steadi/pdf/patient/customizable/Caregiver-Brochure-Final-Customizable-508.pdf. Published 2018. Accessed March 11, 2022.
3291. Pirruccio K, Ahn J. Fractures while walking leashed dogs—reply. *JAMA Surg*. 2019;154(11):1078.
3292. Law MR, Wald NJ, Meade TW. Strategies for prevention of osteoporosis and hip fracture. *BMJ*. 1991;303(6800):453–9.
3293. Järvinen TLN, Michaëlsson K, Aspenberg P, Sievänen H. Osteoporosis: the emperor has no clothes. *J Intern Med*. 2015;277(6):662–73.
3294. Sullivan R. A brief journey into medical care and disease in ancient Egypt. *J R Soc Med*. 1995;88(3):141–5.
3295. Chen TS, Chen PS. Gastroenterology in ancient Egypt. *J Clin Gastroenterol*. 1991;13(2):182–7.
3296. Holl RM. Bowel movement: the sixth vital sign. *Holist Nurs Pract*. 2014;28(3):195–7.
3297. Staller K, Cash BD. Myths and misconceptions about constipation: a new view for the 2020s. *Am J Gastroenterol*. 2020;115(11):1741–5.
3298. Johanson JF, Kralstein J. Chronic constipation: a survey of the patient perspective. *Aliment Pharmacol Ther*. 2007;25(5):599–608.
3299. Gokce AH, Gokce FS. Effects of bilateral transcutaneous tibial nerve stimulation on constipation severity in geriatric patients: a prospective clinical study. *Geriatr Gerontol Int*. 2020;20(2):101–5.
3300. Sonnenberg A, Koch TR. Physician visits in the United States for constipation: 1958 to 1986. *Dig Dis Sci*. 1989;34(4):606–11.

3301. Luthra P, Camilleri M, Burr NE, Quigley EMM, Black CJ, Ford AC. Efficacy of drugs in chronic idiopathic constipation: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol*. 2019;4(11):831–44.
3302. Chen J, Liu X, Bai T, Hou X. Impact of clinical outcome measures on placebo response rates in clinical trials for chronic constipation: a systematic review and meta-analysis. *Clin Transl Gastroenterol*. 2020;11(11):e00255.
3303. Pont LG, Fisher M, Williams K. Appropriate use of laxatives in the older person. *Drugs Aging*. 2019;36(11):999–1005.
3304. Lämås K, Karlsson S, Nolén A, Lövheim H, Sandman PO. Prevalence of constipation among persons living in institutional geriatric-care settings—a cross-sectional study. *Scand J Caring Sci*. 2017;31(1):157–63.
3305. Tvistholm N, Munch L, Danielsen AK. Constipation is casting a shadow over everyday life—a systematic review on older people's experience of living with constipation. *J Clin Nurs*. 2017;26(7–8):902–14.
3306. Belsey J, Greenfield S, Candy D, Geraint M. Systematic review: impact of constipation on quality of life in adults and children. *Aliment Pharmacol Ther*. 2010;31(9):938–49.
3307. Tvistholm N, Munch L, Danielsen AK. Constipation is casting a shadow over everyday life—a systematic review on older people's experience of living with constipation. *J Clin Nurs*. 2017;26(7–8):902–14.
3308. Emmanuel A, Mattace-Raso F, Neri MC, Petersen KU, Rey E, Rogers J. Constipation in older people: a consensus statement. *Int J Clin Pract*. 2017;71(1):e12920.
3309. Pekmezaris R, Aversa L, Wolf-Klein G, Cedarbaum J, Reid-Durant M. The cost of chronic constipation. *J Am Med Dir Assoc*. 2002;3(4):224–8.
3310. Modi RM, Hinton A, Pinkhas D, et al. Implementation of a defecation posture modification device. *J Clin Gastroenterol*. 2019;53(3):216–9.
3311. Burkitt DP. A deficiency of dietary fiber may be one cause of certain colonic and venous disorders. *Am J Dig Dis*. 1976;21(2):104–8.

3312. Burkitt DP. Hiatus hernia: is it preventable? *Am J Clin Nutr*. 1981;34(3):428–31.
3313. Burkitt DP, James PA. Low-residue diets and hiatus hernia. *Lancet*. 1973;2(7821):128–30.
3314. Burkitt DP. A deficiency of dietary fiber may be one cause of certain colonic and venous disorders. *Am J Dig Dis*. 1976;21(2):104–8.
3315. Fox A, Tietze PH, Ramakrishnan K. Anorectal conditions: anal fissure and anorectal fistula. *FP Essent*. 2014;419:20–7.
3316. Burkitt DP. Two blind spots in medical knowledge. *Nurs Times*. 1976;72(1):24–7.
3317. Burkitt DP. Hiatus hernia: is it preventable? *Am J Clin Nutr*. 1981;34(3):428–31.
3318. Burkitt DP. Dietary fibre and "pressure diseases." *J R Coll Physicians Lond*. 1975;9(2):138–46.
3319. Kapoor WN, Peterson J, Karpf M. Defecation syncope: a symptom with multiple etiologies. *Arch Intern Med*. 1986;146(12):2377–9.
3320. Greenfield JC, Rembert JC, Tindall GT. Transient changes in cerebral vascular resistance during the Valsalva maneuver in man. *Stroke*. 1984;15(1):76–9.
3321. Benchimol A, Wang TF, Desser KB, Gartlan JL. The Valsalva maneuver and coronary arterial blood flow velocity. Studies in man. *Ann Intern Med*. 1972;77(3):357–60.
3322. McGuire J, Green RS, Courter S, et al. Bed pan deaths. *J Lab Clin Med*. 1948;33(11):1457.
3323. Emmanuel A, Mattace-Raso F, Neri MC, Petersen KU, Rey E, Rogers J. Constipation in older people: a consensus statement. *Int J Clin Pract*. 2017;71(1):e12920.
3324. Annells M, Koch T. Faecal impaction: older people's experiences and nursing practice. *Br J Community Nurs*. 2002;7(3):118–26.
3325. Annells M, Koch T. Older people seeking solutions to constipation: the laxative mire. *J Clin Nurs*. 2002;11(5):603–12.
3326. Sakakibara R, Tsunoyama K, Hosoi H, et al. Influence of body position on defecation in humans. *Low Urin Tract Symptoms*. 2010;2(1):16–21.
3327. Isbit J. Is the porcelain throne to blame? *Tech Coloproctol*. 2015;19(3):193–4.

3328. Davies GJ, Crowder M, Reid B, Dickerson JW. Bowel function measurements of individuals with different eating patterns. *Gut*. 1986;27(2):164–9.
3329. Choi YI, Kim KO, Chung JW, et al. Effects of automatic abdominal massage device in treatment of chronic constipation patients: a prospective study. *Dig Dis Sci*. 2021;66(9):3105–12.
3330. Rao SSC, Lembo A, Chey WD, Friedenberg K, Quigley EMM. Effects of the vibrating capsule on colonic circadian rhythm and bowel symptoms in chronic idiopathic constipation. *Neurogastroenterol Motil*. 2020;32(11):e13890.
3331. Staller K, Cash BD. Myths and misconceptions about constipation: a new view for the 2020s. *Am J Gastroenterol*. 2020;115(11):1741–5.
3332. Knowles CH, Grossi U, Chapman M, et al. Surgery for constipation: systematic review and practice recommendations: Results I: colonic resection. *Colorectal Dis*. 2017;19 Suppl 3:17–36.
3333. Rao SSC, Brenner DM. Efficacy and safety of over-the-counter therapies for chronic constipation: an updated systematic review. *Am J Gastroenterol*. 2021;116(6):1156–81.
3334. Rao SSC, Brenner DM. Efficacy and safety of over-the-counter therapies for chronic constipation: an updated systematic review. *Am J Gastroenterol*. 2021;116(6):1156–81.
3335. Pont LG, Fisher M, Williams K. Appropriate use of laxatives in the older person. *Drugs Aging*. 2019;36(11):999–1005.
3336. Rao SSC, Brenner DM. Efficacy and safety of over-the-counter therapies for chronic constipation: an updated systematic review. *Am J Gastroenterol*. 2021;116(6):1156–81.
3337. Noergaard M, Traerup Andersen J, Jimenez-Solem E, Bring Christensen M. Long term treatment with stimulant laxatives—clinical evidence for effectiveness and safety? *Scand J Gastroenterol*. 2019;54(1):27–34.
3338. Riemann JF, Schmidt H, Zimmermann W. The fine structure of colonic submucosal nerves in patients with chronic laxative abuse. *Scand J Gastroenterol*. 1980;15(6):761–8.
3339. Serrano-Falcón B, Rey E. The safety of available treatments for chronic constipation. *Expert Opin Drug Saf*. 2017;16(11):1243–53.

3340. Rao SSC, Brenner DM. Efficacy and safety of over-the-counter therapies for chronic constipation: an updated systematic review. *Am J Gastroenterol*. 2021;116(6):1156–81.
3341. Leth PM, Gregersen M. Ethylene glycol poisoning. *Forensic Sci Int*. 2005;155(2–3):179–84.
3342. Serrano-Falcón B, Rey E. The safety of available treatments for chronic constipation. *Expert Opin Drug Saf*. 2017;16(11):1243–53.
3343. Lacy BE, Shea EP, Manuel M, Abel JL, Jiang H, Taylor DCA. Lessons learned: chronic idiopathic constipation patient experiences with over-the-counter medications. *PLoS One*. 2021;16(1):e0243318.
3344. Lucak S, Lunsford TN, Harris LA. Evaluation and treatment of constipation in the geriatric population. *Clin Geriatr Med*. 2021;37(1):85–102.
3345. Annells M, Koch T. Older people seeking solutions to constipation: the laxative mire. *J Clin Nurs*. 2002;11(5):603–12.
3346. Wilson PB. Associations between physical activity and constipation in adult Americans: results from the National Health and Nutrition Examination Survey. *Neurogastroenterol Motil*. 2020;32(5):e13789.
3347. Liu F, Kondo T, Toda Y. Brief physical inactivity prolongs colonic transit time in elderly active men. *Int J Sports Med*. 1993;14(8):465–7.
3348. Asnicar F, Leeming ER, Dimidi E, et al. Blue poo: impact of gut transit time on the gut microbiome using a novel marker. *Gut*. 2021;70(9):1665–74.
3349. Gao R, Tao Y, Zhou C, et al. Exercise therapy in patients with constipation: a systematic review and meta-analysis of randomized controlled trials. *Scand J Gastroenterol*. 2019;54(2):169–77.
3350. Mari A, Mahamid M, Amara H, Baker FA, Yaccob A. Chronic constipation in the elderly patient: updates in evaluation and management. *Korean J Fam Med*. 2020;41(3):139–45.
3351. Pont LG, Fisher M, Williams K. Appropriate use of laxatives in the older person. *Drugs Aging*. 2019;36(11):999–1005.
3352. Burkitt DP. A deficiency of dietary fiber may be one cause of certain colonic and venous disorders. *Am J Dig Dis*. 1976;21(2):104–8.
3353. Clemens R, Kranz S, Mobley AR, et al. Filling America's fiber intake gap: summary of a roundtable to probe realistic solutions with a focus

on grain-based foods. *J Nutr*. 2012;142(7):1390S-401S.
3354. Sanjoaquin MA, Appleby PN, Spencer EA, Key TJ. Nutrition and lifestyle in relation to bowel movement frequency: a cross-sectional study of 20630 men and women in EPIC-Oxford. *Public Health Nutr*. 2004 Feb;7(1):77–83.
3355. Schmier JK, Miller PE, Levine JA, et al. Cost savings of reduced constipation rates attributed to increased dietary fiber intakes: a decision-analytic model. *BMC Public Health*. 2014;14:374.
3356. Oh SJ, Fuller G, Patel D, et al. Chronic constipation in the United States: results from a population-based survey assessing healthcare seeking and use of pharmacotherapy. *Am J Gastroenterol*. 2020;115(6):895–905.
3357. Christodoulides S, Dimidi E, Fragkos KC, Farmer AD, Whelan K, Scott SM. Systematic review with meta-analysis: effect of fibre supplementation on chronic idiopathic constipation in adults. *Aliment Pharmacol Ther*. 2016;44(2):103–16.
3358. Staller K, Cash BD. Myths and misconceptions about constipation: a new view for the 2020s. *Am J Gastroenterol*. 2020;115(11):1741–5.
3359. Jalanka J, Major G, Murray K, et al. The effect of psyllium husk on intestinal microbiota in constipated patients and healthy controls. *Int J Mol Sci*. 2019;20(2):E433.
3360. Hefny AF, Ayad AZ, Matev N, Bashir MO. Intestinal obstruction caused by a laxative drug (Psyllium): a case report and review of the literature. *Int J Surg Case Rep*. 2018;52:59–62.
3361. Gill SK, Rossi M, Bajka B, Whelan K. Dietary fibre in gastrointestinal health and disease. *Nat Rev Gastroenterol Hepatol.* 2021;18(2):101–16.
3362. Threapleton DE, Greenwood DC, Evans CE, et al. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2013;347:f6879.
3363. Gill SK, Rossi M, Bajka B, Whelan K. Dietary fibre in gastrointestinal health and disease. *Nat Rev Gastroenterol Hepatol.* 2021;18(2):101–16.
3364. Maskarinec G, Takata Y, Pagano I, et al. Trends and dietary determinants of overweight and obesity in a multiethnic population. *Obesity* (Silver Spring). 2006;14(4):717–26.

3365. Yao B, Fang H, Xu W, et al. Dietary fiber intake and risk of type 2 diabetes: a dose-response analysis of prospective studies. *Eur J Epidemiol*. 2014;29(2):79–88.
3366. Fatahi S, Matin SS, Sohouli MH, et al. Association of dietary fiber and depression symptom: a systematic review and meta-analysis of observational studies. *Complement Ther Med*. 2021;56:102621.
3367. Kim Y, Je Y. Dietary fiber intake and total mortality: a meta-analysis of prospective cohort studies. *Am J Epidemiol*. 2014;180(6):565–73.
3368. Threapleton DE, Greenwood DC, Evans CEL, et al. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2013;347:f6879.
3369. Wolever TM, Jenkins DJ. What is a high fiber diet? *Adv Exp Med Biol*. 1997;427:35–42.
3370. Shaper AG, Jones KW. Serum-cholesterol, diet, and coronary heart-disease in Africans and Asians in Uganda: 1959. *Int J Epidemiol*. 2012;41(5):1221–5.
3371. Singh SA, Trowell HC. A case of coronary heart disease in an African. *East Afr Med J*. 1956;33(10):391–4.
3372. Ikem I, Sumpio BE. Cardiovascular disease: the new epidemic in sub-Saharan Africa. *Vascular*. 2011;19(6):301–7.
3373. Burkitt DP, Walker AR, Painter NS. Effect of dietary fibre on stools and the transit-times, and its role in the causation of disease. *Lancet*. 1972;2(7792):1408–12.
3374. Dietary fiber market to reach $3.25 billion by 2017. *Neutraceuticals World*. https://nutraceuticalsworld.com/contents/view_breaking-news/2012–10–29/dietary-fiber-market-to-reach-325-billion-by-2017. Published October 29, 2012. Accessed March 29, 2022.
3375. Eastwood M, Kritchevsky D. Dietary fiber: how did we get where we are? *Annu Rev Nutr*. 2005;25:1–8.
3376. Threapleton DE, Greenwood DC, Evans CE, et al. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2013;347:f6879.
3377. Eastwood M, Kritchevsky D. Dietary fiber: how did we get where we are? *Annu Rev Nutr*. 2005;25:1–8.
3378. McRorie JW. Evidence-based approach to fiber supplements and clinically meaningful health benefits, part 2: what to look for and

how to recommend an effective fiber therapy. *Nutr Today*. 2015;50(2):90–7.

3379. Agricultural Research Service, United States Department of Agriculture. Seeds, flaxseeds. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html#/food-details/169414/nutrients. Published April 1, 2019. Accessed February 22, 2023.

3380. Soltanian N, Janghorbani M. A randomized trial of the effects of flaxseed to manage constipation, weight, glycemia, and lipids in constipated patients with type 2 diabetes. *Nutr Metab (Lond)*. 2018;15:36.

3381. Soltanian N, Janghorbani M. Effect of flaxseed or psyllium vs. placebo on management of constipation, weight, glycemia, and lipids: a randomized trial in constipated patients with type 2 diabetes. *Clin Nutr ESPEN*. 2019;29:41–8.

3382. Sun J, Bai H, Ma J, et al. Effects of flaxseed supplementation on functional constipation and quality of life in a Chinese population: a randomized trial. *Asia Pac J Clin Nutr*. 2020;29(1):61–7.

3383. Hongisto SM, Paajanen L, Saxelin M, Korpela R. A combination of fibre-rich rye bread and yoghurt containing *Lactobacillus* GG improves bowel function in women with self-reported constipation. *Eur J Clin Nutr*. 2006;60(3):319–24.

3384. Almario CV, Almario AA, Cunningham ME, Fouladian J, Spiegel BMR. Old farts—fact or fiction? Results from a population-based survey of 16,000 Americans examining the association between age and flatus. *Clin Gastroenterol Hepatol*. 2017;15(8):1308–10.

3385. Behm RM. A special recipe to banish constipation. *Geriatr Nurs*. 1985;6(4):216–7.

3386. Hull MA, McIntire DD, Atnip SD, et al. Randomized trial comparing 2 fiber regimens for the reduction of symptoms of constipation. *Female Pelvic Med Reconstr Surg*. 2011;17(3):128–33.

3387. Lever E, Cole J, Scott SM, Emery PW, Whelan K. Systematic review: the effect of prunes on gastrointestinal function. *Aliment Pharmacol Ther*. 2014;40(7):750–8.

3388. Sanjoaquin MA, Appleby PN, Spencer EA, Key TJ. Nutrition and lifestyle in relation to bowel movement frequency: a cross-sectional

study of 20 630 men and women in EPIC–Oxford. *Public Health Nutr*. 2004;7(1):77–83.

3389. Attaluri A, Donahoe R, Valestin J, Brown K, Rao SSC. Randomised clinical trial: dried plums (prunes) vs. psyllium for constipation. *Aliment Pharmacol Ther*. 2011;33(7):822–8.

3390. Baek HI, Ha KC, Kim HM, et al. Randomized, double-blind, placebo-controlled trial of Ficus carica paste for the management of functional constipation. *Asia Pac J Clin Nutr*. 2016;25(3):487–96.

3391. Venancio VP, Kim H, Sirven MA, et al. Polyphenol-rich mango (*Mangifera indica* L.) ameliorate functional constipation symptoms in humans beyond equivalent amount of fiber. *Mol Nutr Food Res*. 2018;62(12):e1701034.

3392. Ojo B, El-Rassi GD, Payton ME, et al. Mango supplementation modulates gut microbial dysbiosis and short-chain fatty acid production independent of body weight reduction in C57BL/6 mice fed a high-fat diet. *J Nutr*. 2016;146(8):1483–91.

3393. Kim H, Venancio VP, Fang C, Dupont AW, Talcott ST, Mertens-Talcott SU. Mango (*Mangifera indica* L.) polyphenols reduce IL-8, GRO, and GM-SCF plasma levels and increase *Lactobacillus* species in a pilot study in patients with inflammatory bowel disease. *Nutr Res*. 2020;75:85–94.

3394. What are the key statistics about colorectal cancer? American Cancer Society website. http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-key-statistics. Updated January 12, 2022. Accessed March 29, 2022.

3395. American Cancer Society. Cancer Facts & Figures 2014. American Cancer Society; 2014.

3396. U.S. Preventive Services Task Force. Screening for colorectal cancer. U.S. Preventive Services Task Force website. http://www.uspreventiveservicestaskforce.org/Home/GetFile/1/467/colcancsumm/pdf. Accessed March 29, 2022.

3397. Wender RC. Colorectal cancer screening should begin at 45. *J Gastroenterol Hepatol*. 2020;35(9):1461–3.

3398. Anderson JC, Samadder JN. To screen or not to screen adults 45–49 years of age: that is the question. *Am J Gastroenterol*.

2018;113(12):1750–3.
3399. Davidson KW, Barry MJ, Mangione CM, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2021;325(19):1965–77.
3400. Mannucci A, Zuppardo RA, Rosati R, Leo MD, Perea J, Cavestro GM. Colorectal cancer screening from 45 years of age: thesis, antithesis and synthesis. *World J Gastroenterol*. 2019;25(21):2565–80.
3401. Anderson JC, Samadder JN. To screen or not to screen adults 45–49 years of age: that is the question. *Am J Gastroenterol*. 2018;113(12):1750–3.
3402. Hussan H, Patel A, Le Roux M, et al. Rising incidence of colorectal cancer in young adults corresponds with increasing surgical resections in obese patients. *Clin Transl Gastroenterol*. 2020;11(4):e00160.
3403. Dairi O, Anderson JC, Butterly LF. Why is colorectal cancer increasing in younger age groups in the United States? *Expert Rev Gastroenterol Hepatol*. 2021;15(6):623–32.
3404. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics data visualizations tool, based on 2020 submission data (1999–2018). U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. www.cdc.gov/cancer/dataviz. Published June 2021. Accessed May 11, 2022.
3405. Khan AM, Mucci LA. Concerning trends in colorectal cancer in the wake of Chadwick Boseman's death. *J Cancer Policy*. 2020;26:100260.
3406. Mueller NM, Hyams T, King-Marshall EC, Curbow BA. Colorectal cancer knowledge and perceptions among individuals below the age of 50. *Psychooncology*. 2022;31(3):436–41.
3407. Imperiale TF, Kahi CJ, Rex DK. Lowering the starting age for colorectal cancer screening to 45 years: who will come … and should they? *Clin Gastroenterol Hepatol*. 2018;16(10):1541–4.
3408. Davidson KW, Barry MJ, Mangione CM, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2021;325(19):1965–77.

3409. Yabroff KR, Klabunde CN, Yuan G, et al. Are physicians' recommendations for colorectal cancer screening guideline–consistent? *J Gen Intern Med*. 2011;26(2):177–84.
3410. Swan H, Siddiqui AA, Myers RE. International colorectal cancer screening programs: population contact strategies, testing methods and screening rates. *Pract Gastroenter*. 2012;36(8):20–9.
3411. Swan H, Siddiqui AA, Myers RE. International colorectal cancer screening programs: population contact strategies, testing methods and screening rates. *Pract Gastroenter*. 2012;36(8):20–9.
3412. Butterfield S. Changes coming for colon cancer screening. *ACP Internist*. 2014;34(7):10–11.
3413. Hoffman RM, Levy BT, Allison JE. Rising use of multitarget stool DNA testing for colorectal cancer. *JAMA Netw Open*. 2021;4(9):e2122328.
3414. Wang K, Ma W, Wu K, et al. Healthy lifestyle, endoscopic screening, and colorectal cancer incidence and mortality in the United States: a nationwide cohort study. *PLoS Med*. 2021;18(2):e1003522.
3415. Larsen IK, Grotmol T, Almendingen K, Hoff G. Impact of colorectal cancer screening on future lifestyle choices: a three-year randomized controlled trial. *Clin Gastroenterol Hepatol*. 2007;5(4):477–83.
3416. Hoff G, Thiis-Evensen E, Grotmol T, Sauar J, Vatn MH, Moen IE. Do undesirable effects of screening affect all-cause mortality in flexible sigmoidoscopy programmes? Experience from the Telemark Polyp Study 1983–1996. *Eur J Cancer Prev*. 2001;10(2):131–7.
3417. Berstad P, Løberg M, Larsen IK, et al. Long-term lifestyle changes after colorectal cancer screening: randomised controlled trial. *Gut*. 2015;64(8):1268–76.
3418. Wang K, Ma W, Wu K, et al. Healthy lifestyle, endoscopic screening, and colorectal cancer incidence and mortality in the United States: a nationwide cohort study. *PLoS Med*. 2021;18(2):e1003522.
3419. Platz EA, Willett WC, Colditz GA, Rimm EB, Spiegelman D, Giovannucci E. Proportion of colon cancer risk that might be preventable in a cohort of middle-aged US men. *Cancer Causes Control*. 2000;11(7):579–88.
3420. O'Keefe SJD, Li JV, Lahti L, et al. Fat, fiber and cancer risk in African Americans and rural Africans. *Nat Commun*. 2015;6:6342.

3421. O'Keefe SJD, Li JV, Lahti L, et al. Fat, fiber and cancer risk in African Americans and rural Africans. *Nat Commun*. 2015;6:6342.
3422. Weber C. Nutrition. Diet change alters microbiota and might affect cancer risk. *Nat Rev Gastroenterol Hepatol*. 2015;12(6):314.
3423. Zhao Y, Zhan J, Wang Y, Wang D. The relationship between plant-based diet and risk of digestive system cancers: a meta-analysis based on 3,059,009 subjects. *Front Public Health*. 2022;10.
3424. McCarty MF. Mortality from Western cancers rose dramatically among African-Americans during the 20th century: are dietary animal products to blame? *Med Hypotheses*. 2001;57(2):169–74.
3425. Milsom I, Gyhagen M. The prevalence of urinary incontinence. *Climacteric*. 2019;22(3):217–22.
3426. Wieland LS, Shrestha N, Lassi ZS, Panda S, Chiaramonte D, Skoetz N. Yoga for treating urinary incontinence in women. *Cochrane Database Syst Rev*. 2019;2:CD012668.
3427. Pearlman A, Kreder K. Evaluation and treatment of urinary incontinence in the aging male. *Postgrad Med*. 2020;132(sup4):9–17.
3428. Faleiro DJA, Menezes EC, Capeletto E, Fank F, Porto RM, Mazo GZ. Association of physical activity with urinary incontinence in older women: a systematic review. *J Aging Phys Act*. 2019;27(4):906–13.
3429. Specht JKP. 9 myths of incontinence in older adults: both clinicians and the over-65 set need to know more. *Am J Nurs*. 2005;105(6):58–68.
3430. Muller N. Myths about incontinence in aging adults. *Ostomy Wound Manage*. 2009;55(5):22.
3431. Milsom I, Gyhagen M. The prevalence of urinary incontinence. *Climacteric*. 2019;22(3):217–22.
3432. Specht JKP. 9 myths of incontinence in older adults: both clinicians and the over-65 set need to know more. *Am J Nurs*. 2005;105(6):58–68.
3433. Pizzol D, Demurtas J, Celotto S, et al. Urinary incontinence and quality of life: a systematic review and meta-analysis. *Aging Clin Exp Res*. 2021;33(1):25–35.
3434. Milsom I, Gyhagen M. The prevalence of urinary incontinence. *Climacteric*. 2019;22(3):217–22.

3435. Ashton-Miller JA, DeLancey JOL. Functional anatomy of the female pelvic floor. *Ann N Y Acad Sci*. 2007;1101:266–96.
3436. Kuh D, Cardozo L, Hardy R. Urinary incontinence in middle aged women: childhood enuresis and other lifetime risk factors in a British prospective cohort. *J Epidemiol Community Health*. 1999;53(8):453–8.
3437. Danforth KN, Townsend MK, Lifford K, Curhan GC, Resnick NM, Grodstein F. Risk factors for urinary incontinence among middle-aged women. *Am J Obstet Gynecol*. 2006;194(2):339–45.
3438. Robinson D, Giarenis I, Cardozo L. You are what you eat: the impact of diet on overactive bladder and lower urinary tract symptoms. *Maturitas*. 2014;79(1):8–13.
3439. Imamura M, Williams K, Wells M, McGrother C. Lifestyle interventions for the treatment of urinary incontinence in adults. *Cochrane Database Syst Rev*. 2015;(12):CD003505.
3440. Subak LL, Wing R, West DS, et al. Weight loss to treat urinary incontinence in overweight and obese women. *N Engl J Med*. 2009;360(5):481–90.
3441. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol*. 2003;20(6):327–36.
3442. Flore K, Fauber J, Wynn M. Drug firms helped create $3 billion overactive bladder market. *Milwaukee Journal Sentinel*. https://www.jsonline.com/story/news/investigations/2016/10/16/overactive-bladder-drug-companies-helped-create-3-billion-market/92030360/. Published October 15, 2016. Accessed August 24, 2022.
3443. Mitcheson HD, Samanta S, Muldowney K, et al. Vibegron (RVT-901/MK-4618/KRP-114V) administered once daily as monotherapy or concomitantly with tolterodine in patients with an overactive bladder: a multicenter, phase IIb, randomized, double-blind, controlled trial. *Eur Urol.* 2019;75(2):274–82.
3444. Cho A, Eidelberg A, Butler DJ, et al. Efficacy of daily intake of dried cranberry 500 mg in women with overactive bladder: a randomized, double-blind, placebo controlled study. *J Urol*. 2021;205(2):507–13.

3445. Ernst M, Gonka J, Povcher O, Kim J. Diet modification for overactive bladder: an evidence-based review. *Curr Bladder Dysfunct Rep*. 2015;10(1):25–30.
3446. Dallosso H, Matthews R, McGrother C, Donaldson M. Diet as a risk factor for the development of stress urinary incontinence: a longitudinal study in women. *Eur J Clin Nutr*. 2004;58(6):920–6.
3447. Robinson D, Giarenis I, Cardozo L. You are what you eat: the impact of diet on overactive bladder and lower urinary tract symptoms. *Maturitas*. 2014;79(1):8–13.
3448. *Urinary Incontinence and Pelvic Organ Prolapse in Women: Management*. National Institute for Health and Care Excellence (NICE); 2019.
3449. Burkhard FC, Bosch JLHR, Cruz F, et al. EAU guidelines on urinary incontinence. Vol 3. *Eur Urol*. 2011;59(3):387–400.
3450. Le Berre M, Presse N, Morin M, et al. What do we really know about the role of caffeine on urinary tract symptoms? A scoping review on caffeine consumption and lower urinary tract symptoms in adults. *Neurourol Urodyn*. 2020;39(5):1217–33.
3451. Sun S, Liu D, Jiao Z. Coffee and caffeine intake and risk of urinary incontinence: a meta-analysis of observational studies. *BMC Urol*. 2016;16(1):61.
3452. Muller N. Myths about incontinence in aging adults. *Ostomy Wound Manage*. 2009;55(5):22.
3453. Dasgupta J, Elliott RA, Doshani A, Tincello DG. Enhancement of rat bladder contraction by artificial sweeteners via increased extracellular Ca^{2+} influx. *Toxicol Appl Pharmacol*. 2006;217(2):216–24.
3454. Russo E, Caretto M, Giannini A, et al. Management of urinary incontinence in postmenopausal women: an EMAS clinical guide. *Maturitas*. 2021;143:223–30.
3455. Riemsma R, Hagen S, Kirschner-Hermanns R, et al. Can incontinence be cured? A systematic review of cure rates. *BMC Med*. 2017;15(1):63.
3456. Wagg A, Compion G, Fahey A, Siddiqui E. Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. *BJU Int*. 2012;110(11):1767–74.

3457. Hu JS, Pierre EF. Urinary incontinence in women: evaluation and management. *Am Fam Physician*. 2019;100(6):339–48.
3458. Riemsma R, Hagen S, Kirschner-Hermanns R, et al. Can incontinence be cured? A systematic review of cure rates. *BMC Med*. 2017;15(1):63.
3459. Cody JD, Jacobs ML, Richardson K, Moehrer B, Hextall A. Oestrogen therapy for urinary incontinence in post-menopausal women. *Cochrane Database Syst Rev*. 2012;2012(10):CD001405.
3460. Russo E, Caretto M, Giannini A, et al. Management of urinary incontinence in postmenopausal women: an EMAS clinical guide. *Maturitas*. 2021;143:223–30.
3461. Cody JD, Jacobs ML, Richardson K, Moehrer B, Hextall A. Oestrogen therapy for urinary incontinence in post-menopausal women. *Cochrane Database Syst Rev*. 2012;2012(10):CD001405.
3462. Russo E, Caretto M, Giannini A, et al. Management of urinary incontinence in postmenopausal women: an EMAS clinical guide. *Maturitas*. 2021;143:223–30.
3463. Kegel AH. Stress incontinence and genital relaxation; a nonsurgical method of increasing the tone of sphincters and their supporting structures. *Ciba Clin Symp*. 1952;4(2):35–51.
3464. Kegel exercises: a how-to guide for women. Mayo Clinic. https://www.mayoclinic.org/healthy-lifestyle/womens-health/in-depth/kegel-exercises/art-20045283. Published September 15, 2020. Accessed August 24, 2022.
3465. Specht JKP. 9 myths of incontinence in older adults: both clinicians and the over-65 set need to know more. *Am J Nurs*. 2005;105(6):58–68.
3466. Nazarpour S, Simbar M, Ramezani Tehrani F, Alavi Majd H. Effects of sex education and Kegel exercises on the sexual function of postmenopausal women: a randomized clinical trial. *J Sex Med*. 2017;14(7):959–67.
3467. Vaughan CP, Markland AD. Urinary incontinence in women. *Ann Intern Med*. 2020;172(3):ITC17.
3468. Kilpatrick KA, Paton P, Subbarayan S, et al. Non-pharmacological, non-surgical interventions for urinary incontinence in older persons: a

systematic review of systematic reviews. The SENATOR project ONTOP series. *Maturitas*. 2020;133:42–8.
3469. Dumoulin C, Cacciari LP, Hay-Smith EJC. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. *Cochrane Database Syst Rev*. 2018;(10).
3470. Faleiro DJA, Menezes EC, Capeletto E, Fank F, Porto RM, Mazo GZ. Association of physical activity with urinary incontinence in older women: a systematic review. *J Aging Phys Act*. 2019;27(4):906–13.
3471. Huang AJ, Chesney M, Lisha N, et al. A group-based yoga program for urinary incontinence in ambulatory women: feasibility, tolerability, and change in incontinence frequency over 3 months in a single-center randomized trial. *Am J Obstet Gynecol*. 2019;220(1):87.e1–13.
3472. Wei JT, Calhoun E, Jacobsen SJ. Urologic Diseases in America Project: benign prostatic hyperplasia. *J Urol*. 2008;179(5 Suppl):S75–80.
3473. Burnett AL, Wein AJ. Benign prostatic hyperplasia in primary care: what you need to know. *J Urol*. 2006;175(3 Pt 2):S19–24.
3474. Trumble BC, Stieglitz J, Rodriguez DE, Linares EC, Kaplan HS, Gurven MD. Challenging the inevitability of prostate enlargement: low levels of benign prostatic hyperplasia among Tsimane forager-horticulturalists. *J Gerontol A Biol Sci Med Sci*. 2015;70(10):1262–8.
3475. Taub DA, Wei JT. The economics of benign prostatic hyperplasia and lower urinary tract symptoms in the United States. *Curr Urol Rep*. 2006;7(4):272–81.
3476. Zhang AY, Xu X. Prevalence, burden, and treatment of lower urinary tract symptoms in men aged 50 and older: a systematic review of the literature. *SAGE Open Nurs*. 2018;4:2377960818811773.
3477. Traish AM, Mulgaonkar A, Giordano N. The dark side of 5α-reductase inhibitors' therapy: sexual dysfunction, high Gleason grade prostate cancer and depression. *Korean J Urol*. 2014;55(6):367–79.
3478. Cindolo L, Pirozzi L, Fanizza C, et al. Drug adherence and clinical outcomes for patients under pharmacological therapy for lower urinary tract symptoms related to benign prostatic hyperplasia: population-based cohort study. *Eur Urol*. 2015;68(3):418–25.

3479. Roehrborn CG, Bruskewitz R, Nickel JC, et al. Sustained decrease in incidence of acute urinary retention and surgery with finasteride for 6 years in men with benign prostatic hyperplasia. *J Urol.* 2004;171(3):1194–8.
3480. Irwig MS. How routine pharmacovigilance failed to identify finasteride's persistent sexual side effects. *Andrology*. 2022;10(2):207–8.
3481. Zhang AY, Xu X. Prevalence, burden, and treatment of lower urinary tract symptoms in men aged 50 and older: a systematic review of the literature. *SAGE Open Nurs*. 2018;4:2377960818811773.
3482. Metcalfe C, Poon KS. Long-term results of surgical techniques and procedures in men with benign prostatic hyperplasia. *Curr Urol Rep*. 2011;12(4):265–73.
3483. Burnett AL, Wein AJ. Benign prostatic hyperplasia in primary care: what you need to know. *J Urol*. 2006;175(3 Pt 2):S19–24.
3484. Burnett AL, Wein AJ. Benign prostatic hyperplasia in primary care: what you need to know. *J Urol*. 2006;175(3 Pt 2):S19–24.
3485. Gu F. Epidemiological survey of benign prostatic hyperplasia and prostatic cancer in China. *Chin Med J*. 2000;113(4):299–302.
3486. Kraft TS, Stieglitz J, Trumble BC, Martin M, Kaplan H, Gurven M. Nutrition transition in 2 lowland Bolivian subsistence populations. *Am J Clin Nutr*. 2018;108(6):1183–95.
3487. Trumble BC, Stieglitz J, Rodriguez DE, Linares EC, Kaplan HS, Gurven MD. Challenging the inevitability of prostate enlargement: low levels of benign prostatic hyperplasia among Tsimane forager-horticulturalists. *J Gerontol A Biol Sci Med Sci*. 2015;70(10):1262–8.
3488. Cicero AFG, Allkanjari O, Busetto GM, et al. Nutraceutical treatment and prevention of benign prostatic hyperplasia and prostate cancer. *Arch Ital Urol Androl*. 2019;91(3).
3489. Koskimäki J, Hakama M, Huhtala H, Tammela TL. Association of dietary elements and lower urinary tract symptoms. *Scand J Urol Nephrol*. 2000;34(1):46–50.
3490. Bravi F, Bosetti C, Dal Maso L, et al. Food groups and risk of benign prostatic hyperplasia. *Urology*. 2006;67(1):73–9.
3491. Galeone C, Pelucchi C, Talamini R, et al. Onion and garlic intake and the odds of benign prostatic hyperplasia. *Urology*. 2007;70(4):672–6.

3492. Bravi F, Bosetti C, Dal Maso L, et al. Food groups and risk of benign prostatic hyperplasia. *Urology*. 2006;67(1):73–9.
3493. Bhagwat S, Haytowitz DB, Holden JM. *USDA database for the isoflavone content of selected foods: release 2.0.* Agricultural Research Service, United States Department of Agriculture. numbering.xml. Published September 2008. Accessed April 15, 2022.
3494. Wong SYS, Lau WWY, Leung PC, Leung JCS, Woo J. The association between isoflavone and lower urinary tract symptoms in elderly men. *Br J Nutr*. 2007;98(6):1237–42.
3495. Zhou Z, Wang Z, Chen C, et al. Transurethral prostate vaporization using an oval electrode in 82 cases of benign prostatic hyperplasia. *Chin Med J*. 1998;111(1):52–5.
3496. Ornish D, Weidner G, Fair WR, et al. Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol*. 2005;174(3):1065–9.
3497. Barnard RJ, Gonzalez JH, Liva ME, Ngo TH. Effects of a low-fat, high-fiber diet and exercise program on breast cancer risk factors in vivo and tumor cell growth and apoptosis in vitro. *Nutr Cancer*. 2006;55(1):28–34.
3498. Barnard RJ, Kobayashi N, Aronson WJ. Effect of diet and exercise intervention on the growth of prostate epithelial cells. *Prostate Cancer Prostatic Dis*. 2008;11(4):362–6.
3499. Keehn A, Taylor J, Lowe FC. Phytotherapy for benign prostatic hyperplasia. *Curr Urol Rep*. 2016;17(7):53.
3500. Trivisonno LF, Sgarbossa N, Alvez GA, et al. *Serenoa repens* for the treatment of lower urinary tract symptoms due to benign prostatic enlargement: a systematic review and meta-analysis. *Investig Clin Urol*. 2021;62(5):520–34.
3501. Zendehdel A, Ansari M, Khatami F, Mansoursamaei S, Dialameh H. The effect of vitamin D supplementation on the progression of benign prostatic hyperplasia: a randomized controlled trial. *Clin Nutr*. 2021;40(5):3325–31.
3502. Safwat AS, Hasanain A, Shahat A, et al. Cholecalciferol for the prophylaxis against recurrent urinary tract infection among patients with benign prostatic hyperplasia: a randomized, comparative study. *World J Urol*. 2019;37(7):1347–52.

3503. Zhang W, Wang X, Liu Y, et al. Effects of dietary flaxseed lignan extract on symptoms of benign prostatic hyperplasia. *J Med Food*. 2008;11(2):207–14.
3504. Vahlensieck W, Theurer C, Pfitzer E, Patz B, Banik N, Engelmann U. Effects of pumpkin seed in men with lower urinary tract symptoms due to benign prostatic hyperplasia in the one-year, randomized, placebo-controlled GRANU study. *Urol Int*. 2015;94(3):286–95.
3505. Assessment report on *Cucurbita pepo* L., semen. European Medicines Agency. https://www.ema.europa.eu/en/documents/herbal-report/draft-assessment-report-cucurbita-pepo-l-semen_en.pdf. Published September 13, 2011. Accessed August 22, 2022.
3506. Matsuo T, Miyata Y, Sakai H. Effect of salt intake reduction on nocturia in patients with excessive salt intake. *Neurourol Urodyn*. 2019;38(3):927–33.
3507. Bradley CS, Erickson BA, Messersmith EE, et al. Evidence for the impact of diet, fluid intake, caffeine, alcohol and tobacco on lower urinary tract symptoms: a systematic review. *J Urol*. 2017;198(5):1010–20.
3508. Xue Z, Lin Y, Jiang Y, Wei N, Bi J. The evaluation of nocturia in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia and the analysis of the curative effect after medical or placebo therapy for nocturia: a randomized placebo-controlled study. *BMC Urol*. 2018;18(1):115.
3509. Johnson TM II, Sattin RW, Parmelee P, Fultz NH, Ouslander JG. Evaluating potentially modifiable risk factors for prevalent and incident nocturia in older adults. *J Am Geriatr Soc*. 2005;53(6):1011–6.
3510. Tani M, Hirayama A, Torimoto K, Matsushita C, Yamada A, Fujimoto K. Guidance on water intake effectively improves urinary frequency in patients with nocturia. *Int J Urol*. 2014;21(6):595–600.
3511. Soda T, Masui K, Okuno H, Terai A, Ogawa O, Yoshimura K. Efficacy of nondrug lifestyle measures for the treatment of nocturia. *J Urol*. 2010;184(3):1000–4.
3512. Cho SY, Lee SL, Kim IS, Koo DH, Kim HK, Oh SJ. Short-term effects of systematized behavioral modification program for nocturia: a prospective study. *Neurourol Urodyn*. 2012;31(1):64–8.

3513. Johnson TM. The chicken-or-egg dilemma with nocturia: which matters most, the water or the salt? *J Clin Hypertens*. 2020;22(4):639–41.
3514. Matsuo T, Miyata Y, Sakai H. Daily salt intake is an independent risk factor for pollakiuria and nocturia. *Int J Urol*. 2017;24(5):384–9.
3515. Alwis US, Monaghan TF, Haddad R, et al. Dietary considerations in the evaluation and management of nocturia. *F1000Res*. 2020;9(F1000 Faculty Rev):165.
3516. Matsuo T, Miyata Y, Sakai H. Effect of salt intake reduction on nocturia in patients with excessive salt intake. *Neurourol Urodyn*. 2019;38(3):927–33.
3517. Monaghan TF, Michelson KP, Wu ZD, et al. Sodium restriction improves nocturia in patients at a cardiology clinic. *J Clin Hypertens (Greenwich)*. 2020;22(4):633–8.
3518. Alwis US, Delanghe J, Dossche L, et al. Could evening dietary protein intake play a role in nocturnal polyuria? *J Clin Med*. 2020;9(8):E2532.
3519. Vidlar A, Student V, Vostalova J, et al. Cranberry fruit powder (Flowens™) improves lower urinary tract symptoms in men: a double-blind, randomized, placebo-controlled study. *World J Urol*. 2016;34(3):419–24.
3520. An YJ, Lee JY, Kim Y, Jun W, Lee YH. Cranberry powder attenuates benign prostatic hyperplasia in rats. *J Med Food*. 2020;23(12):1296–302.
3521. Vidlar A, Vostalova J, Ulrichova J, et al. The effectiveness of dried cranberries (*Vaccinium macrocarpon*) in men with lower urinary tract symptoms. *Br J Nutr*. 2010;104(8):1181–9.
3522. Vidlar A, Student V, Vostalova J, et al. Cranberry fruit powder (Flowens™) improves lower urinary tract symptoms in men: a double-blind, randomized, placebo-controlled study. *World J Urol*. 2016;34(3):419–24.
3523. Ledda A, Belcaro G, Dugall M, et al. Supplementation with high titer cranberry extract (Anthocran®) for the prevention of recurrent urinary tract infections in elderly men suffering from moderate prostatic hyperplasia: a pilot study. *Eur Rev Med Pharmacol Sci*. 2016;20(24):5205–9.

3524. Spettel S, Chughtai B, Feustel P, Kaufman A, Levin RM, De E. A prospective randomized double-blind trial of grape juice antioxidants in men with lower urinary tract symptoms. *Neurourol Urodyn*. 2013;32(3):261–5.
3525. Edinger MS, Koff WJ. Effect of the consumption of tomato paste on plasma prostate–specific antigen levels in patients with benign prostate hyperplasia. *Braz J Med Biol Res*. 2006;39(8):1115–9.
3526. Durak lker, Yilmaz E, Devrim E, Perk H, Kaçmaz M. Consumption of aqueous garlic extract leads to significant improvement in patients with benign prostate hyperplasia and prostate cancer. *Nutr Res*. 2003;23(2):199–204.
3527. Jani B, Rajkumar C. Ageing and vascular ageing. *Postgrad Med J*. 2006;82(968):357–62.
3528. Mosca L, Ferris A, Fabunmi R, Robertson RM, American Heart Association. Tracking women's awareness of heart disease: an American Heart Association national study. *Circulation*. 2004;109(5):573–9.
3529. Xu J. Mortality among centenarians in the United States, 2000–2014. *NCHS Data Brief*. 2016;(233):1–8.
3530. Cushman M, Shay CM, Howard VJ, et al. Ten-year differences in women's awareness related to coronary heart disease: results of the 2019 American Heart Association national survey: a special report from the American Heart Association. *Circulation*. 2021;143(7):e239–48.
3531. Tao J, Qiu Y. All disease stems from vessels. *Aging Med (Milton)*. 2020;3(4):224–5.
3532. Jin K. A microcirculatory theory of aging. *Aging Dis*. 2019;10(3):676–83.
3533. Möbius-Winkler S, Linke A, Adams V, Schuler G, Erbs S. How to improve endothelial repair mechanisms: the lifestyle approach. *Expert Rev Cardiovasc Ther*. 2010;8(4):573–80.
3534. Sharma S, Pandey NN, Sinha M, et al. Randomized, double-blind, placebo-controlled trial to evaluate safety and therapeutic efficacy of angiogenesis induced by intraarterial autologous bone marrow-derived stem cells in patients with severe peripheral arterial disease. *J Vasc Interv Radiol*. 2021;32(2):157–63.

3535. Altabas V, Altabas K, Kirigin L. Endothelial progenitor cells (EPCs) in ageing and age-related diseases: how currently available treatment modalities affect EPC biology, atherosclerosis, and cardiovascular outcomes. *Mech Ageing Dev*. 2016;159:49–62.
3536. Hoetzer GL, Van Guilder GP, Irmiger HM, Keith RS, Stauffer BL, DeSouza CA. Aging, exercise, and endothelial progenitor cell clonogenic and migratory capacity in men. *J Appl Physiol (1985)*. 2007;102(3):847–52.
3537. Wang M, Monticone RE, McGraw KR. Proinflammation, profibrosis, and arterial aging. *Aging Med (Milton)*. 2020;3(3):159–68.
3538. Weech M, Altowaijri H, Mayneris-Perxachs J, et al. Replacement of dietary saturated fat with unsaturated fats increases numbers of circulating endothelial progenitor cells and decreases numbers of microparticles: findings from the randomized, controlled Dietary Intervention and VAScular function (DIVAS) study. *Am J Clin Nutr*. 2018;107(6):876–82.
3539. Shi Q, Hubbard GB, Kushwaha RS, et al. Endothelial senescence after high-cholesterol, high-fat diet challenge in baboons. *Am J Physiol Heart Circ Physiol*. 2007;292(6):H2913–20.
3540. Jeong HS, Kim S, Hong SJ, et al. Black raspberry extract increased circulating endothelial progenitor cells and improved arterial stiffness in patients with metabolic syndrome: a randomized controlled trial. *J Med Food*. 2016;19(4):346–52.
3541. Choi EY, Lee H, Woo JS, et al. Effect of onion peel extract on endothelial function and endothelial progenitor cells in overweight and obese individuals. *Nutrition*. 2015;31(9):1131–5.
3542. Kim W, Jeong MH, Cho SH, et al. Effect of green tea consumption on endothelial function and circulating endothelial progenitor cells in chronic smokers. *Circ J*. 2006;70(8):1052–7.
3543. Keith M, Kuliszewski MA, Liao C, et al. A modified portfolio diet complements medical management to reduce cardiovascular risk factors in diabetic patients with coronary artery disease. *Clin Nutr*. 2015;34(3):541–8.
3544. Steinberg D, Blumenthal S, Carleton RA, et al. Lowering blood cholesterol to prevent heart disease: NIH Consensus Development Conference statement. *Nutr Rev*. 1985;43(9):283–91.

3545. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38(32):2459–72.
3546. Roberts WC. It's the cholesterol, stupid! *Am J Cardiol*. 2010;106(9):1364–6.
3547. Roberts WC. William Clifford Roberts, MD curriculum vitae. http://www.iscvdp.org/docs/WCRoberts-CV.pdf. Accessed May 13, 2022.
3548. Roberts WC. Quantitative extent of atherosclerotic plaque in the major epicardial coronary arteries in patients with fatal coronary heart disease, in coronary endarterectomy specimens, in aorta–coronary saphenous venous conduits, and means to prevent the plaques: a review after studying the coronary arteries for 50 years. *Am J Cardiol*. 2018;121(11):1413–35.
3549. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38(32):2459–72.
3550. Fernández-Friera L, Fuster V, López-Melgar B, et al. Normal LDL–cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors. *J Am Coll Cardiol*. 2017;70(24):2979–91.
3551. Nambi V, Bhatt DL. Primary prevention of atherosclerosis: time to take a selfie? *J Am Coll Cardiol*. 2017;70(24):2992–4.
3552. Hochholzer W, Giugliano RP. Lipid lowering goals: back to nature? *Ther Adv Cardiovasc Dis*. 2010;4(3):185–91.
3553. Fernández-Friera L, Fuster V, López-Melgar B, et al. Normal LDL–cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors. *J Am Coll Cardiol*. 2017;70(24):2979–91.
3554. Gitin A, Pfeffer MA, Hennekens CH. Editorial commentary: the lower the LDL the better but how and how much? *Trends Cardiovasc Med*. 2018;28(5):355–6.
3555. Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. *BMJ*. 2002;324(7353):1570–6.

3556. Hochholzer W, Giugliano RP. Lipid lowering goals: back to nature? *Ther Adv Cardiovasc Dis*. 2010;4(3):185–91.
3557. O'Keefe JH, Cordain L, Harris WH, Moe RM, Vogel R. Optimal low-density lipoprotein is 50 to 70 mg/dL: lower is better and physiologically normal. *J Am Coll Cardiol*. 2004;43(11):2142–6.
3558. Anderson JW, Konz EC, Jenkins DJ. Health advantages and disadvantages of weight-reducing diets: a computer analysis and critical review. *J Am Coll Nutr.* 2000;19(5):578–90.
3559. Hochholzer W, Giugliano RP. Lipid lowering goals: back to nature? *Ther Adv Cardiovasc Dis*. 2010;4(3):185–91.
3560. Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. *BMJ*. 2002;324(7353):1570–6.
3561. Roberts WC. Quantitative extent of atherosclerotic plaque in the major epicardial coronary arteries in patients with fatal coronary heart disease, in coronary endarterectomy specimens, in aorta–coronary saphenous venous conduits, and means to prevent the plaques: a review after studying the coronary arteries for 50 years. *Am J Cardiol*. 2018;121(11):1413–35.
3562. Packard CJ. LDL cholesterol: How low to go? *Trends Cardiovasc Med*. 2018;28(5):348–54.
3563. Packard CJ. LDL cholesterol: How low to go? *Trends Cardiovasc Med*. 2018;28(5):348–54.
3564. Nambi V, Bhatt DL. Primary prevention of atherosclerosis: time to take a selfie? *J Am Coll Cardiol*. 2017;70(24):2992–4.
3565. Hong KN, Fuster V, Rosenson RS, Rosendorff C, Bhatt DL. How low to go with glucose, cholesterol, and blood pressure in primary prevention of CVD. *J Am Coll Cardiol.* 2017;70(17):2171–85.
3566. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670–81.
3567. Guber K, Pemmasani G, Malik A, Aronow WS, Yandrapalli S, Frishman WH. Statins and higher diabetes mellitus risk: incidence, proposed mechanisms, and clinical implications. *Cardiol Rev*. 2021;29(6):314–22.

3568. Hong KN, Fuster V, Rosenson RS, Rosendorff C, Bhatt DL. How low to go with glucose, cholesterol, and blood pressure in primary prevention of CVD. *J Am Coll Cardiol.* 2017;70(17):2171–85.
3569. Glenn AJ, Li J, Lo K, et al. The Portfolio Diet and incident type 2 diabetes: findings from the Women's Health Initiative prospective cohort study. *Diabetes Care*. 2023;46(1):28–37.
3570. Sliding scale for LDL: how low should you go? The target for the safest amount of "bad" cholesterol continues to drift downward. *Harv Heart Lett*. 2011;21(12):5.
3571. How low should your cholesterol go? Even lower may be better. For those at highest risk, very low cholesterol levels may help prevent a second heart attack or stroke. *Health News*. 2004;10(10):6.
3572. De Biase SG, Fernandes SFC, Gianini RJ, Duarte JLG. Vegetarian diet and cholesterol and triglycerides levels. *Arq Bras Cardiol*. 2007;88(1):35–9.
3573. Kahleova H, Levin S, Barnard ND. Vegetarian dietary patterns and cardiovascular disease. *Prog Cardiovasc Dis*. 2018;61(1):54–61.
3574. The US Burden of Disease Collaborators, Mokdad AH, Ballestros K, et al. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319(14):1444–72.
3575. Huang Z, Xu A, Cheung BMY. The potential role of fibroblast growth factor 21 in lipid metabolism and hypertension. *Curr Hypertens Rep*. 2017;19(4):28.
3576. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies [published correction appears in *Lancet.* 2003;361(9362):1060]. *Lancet*. 2002;360(9349):1903–13.
3577. Kramer H, Cooper R. Pros and cons of intensive systolic blood pressure lowering. *Curr Hypertens Rep*. 2018;20(2):16.
3578. Kjeldsen SE, Os I, Westheim A. Could adverse events offset the benefit of intensive blood pressure lowering treatment in the Systolic Blood Pressure Intervention Trial? *J Hypertens*. 2019;37(5):902–4.
3579. Fuster V. No such thing as ideal blood pressure: a case for personalized medicine. *J Am Coll Cardiol*. 2016;67(25):3014–5.

3580. Goldhamer A, Lisle D, Parpia B, Anderson SV, Campbell TC. Medically supervised water-only fasting in the treatment of hypertension. *J Manipulative Physiol Ther*. 2001;24(5):335–9.
3581. McDougall J, Litzau K, Haver E, Saunders V, Spiller GA. Rapid reduction of serum cholesterol and blood pressure by a twelve-day, very low fat, strictly vegetarian diet. *J Am Coll Nutr*. 1995;14(5):491–6.
3582. Brown MS, Goldstein JL. Biomedicine. Lowering LDL—not only how low, but how long? *Science.* 2006;311(5768):1721–3.
3583. McGill HC, McMahan CA. Determinants of atherosclerosis in the young. *Am J Cardiol*. 1998;82(10B):30T-6T.
3584. Strong JP, Malcom GT, McMahan CA, et al. Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the Pathobiological Determinants of Atherosclerosis in Youth Study. *JAMA*. 1999;281(8):727–35.
3585. Steinberg D, Glass CK, Witztum JL. Evidence mandating earlier and more aggressive treatment of hypercholesterolemia. *Circulation*. 2008;118(6):672–7.
3586. Myerburg RJ, Junttila MJ. 2012. Sudden cardiac death caused by coronary heart disease. *Circulation*. 28;125(8):1043–52.
3587. Brown MS, Goldstein JL. Biomedicine. Lowering LDL—not only how low, but how long? *Science.* 2006;311(5768):1721–3.
3588. Steinberg D, Glass CK, Witztum JL. Evidence mandating earlier and more aggressive treatment of hypercholesterolemia. *Circulation*. 2008;118(6):672–7.
3589. Cohen J, Pertsemlidis A, Kotowski IK, Graham R, Garcia CK, Hobbs HH. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. *Nat Genet*. 2005;37(2):161–5.
3590. Cohen JC, Boerwinkle E, Mosley TH, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med*. 2006;354(12):1264–72.
3591. Robinson JG, Gidding SS. Curing atherosclerosis should be the next major cardiovascular prevention goal. *J Am Coll Cardiol*. 2014;63(25):2779–85.

3592. Brown MS, Goldstein JL. Biomedicine. Lowering LDL—not only how low, but how long? *Science.* 2006;311(5768):1721–3.
3593. Wang N, Fulcher J, Abeysuriya N, et al. Intensive LDL cholesterol–lowering treatment beyond current recommendations for the prevention of major vascular events: a systematic review and meta-analysis of randomised trials including 327 037 participants. *Lancet Diabetes Endocrinol*. 2020;8(1):36–49.
3594. Shapiro MD, Bhatt DL. "Cholesterol-years" for ASCVD risk prediction and treatment. *J Am Coll Cardiol*. 2020;76(13):1517–20.
3595. Kaplan H, Thompson RC, Trumble BC, et al. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. *Lancet*. 2017;389(10080):1730–9.
3596. Penson PE, Pirro M, Banach M. LDL-C: lower is better for longer—even at low risk. *BMC Med*. 2020;18(1):320.
3597. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38(32):2459–72.
3598. Brown MS, Goldstein JL. Biomedicine. Lowering LDL—not only how low, but how long? *Science.* 2006;311(5768):1721–3.
3599. Kahleova H, Levin S, Barnard ND. Vegetarian dietary patterns and cardiovascular disease. *Prog Cardiovasc Dis*. 2018;61(1):54–61.
3600. O'Keefe JH, Cordain L, Harris WH, Moe RM, Vogel R. Optimal low-density lipoprotein is 50 to 70 mg/dL: lower is better and physiologically normal. *J Am Coll Cardiol*. 2004;43(11):2142–6.
3601. Roberts WC. Cholesterol is the cause of atherosclerosis. *Am J Cardiol*. 2017;120(9):1696.
3602. Kataoka Y, Hammadah M, Puri R, et al. Plaque microstructures in patients with coronary artery disease who achieved very low low-density lipoprotein cholesterol levels. *Atherosclerosis*. 2015;242(2):490–5.
3603. Diamond DM, Ravnskov U. How statistical deception created the appearance that statins are safe and effective in primary and secondary prevention of cardiovascular disease. *Expert Rev Clin Pharmacol*. 2015;8(2):201–10.

3604. Trewby PN, Reddy AV, Trewby CS, Ashton VJ, Brennan G, Inglis J. Are preventive drugs preventive enough? A study of patients' expectation of benefit from preventive drugs. *Clin Med (Lond)*. 2002;2(6):527–33.
3605. Salami JA, Warraich H, Valero-Elizondo J, et al. National trends in statin use and expenditures in the US adult population from 2002 to 2013: insights from the Medical Expenditure Panel Survey. *JAMA Cardiol*. 2017;2(1):56–65.
3606. Diprose W, Verster F. The preventive-pill paradox: how shared decision making could increase cardiovascular morbidity and mortality. *Circulation*. 2016;134(21):1599–600.
3607. Ziaeian B, Fonarow GC. Statins and the prevention of heart disease. *JAMA Cardiol*. 2017;2(4):464.
3608. ASCVD Risk Estimator Plus. American College of Cardiology. https://tools.acc.org/ASCVD-Risk-Estimator/. Accessed April 3, 2022.
3609. Framingham Risk Score. Medscape. https://reference.medscape.com/calculator/framingham-cardiovascular-disease-risk. Accessed April 3, 2022.
3610. Reynolds Risk Score. https://www.reynoldsriskscore.org. Accessed April 3, 2022.
3611. Lloyd-Jones DM, Braun LT, Ndumele CE, et al. Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease: a special report from the American Heart Association and American College of Cardiology. *J Am Coll Cardiol*. 2019;73(24):3153–67.
3612. Lloyd-Jones DM, Braun LT, Ndumele CE, et al. Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease: a special report from the American Heart Association and American College of Cardiology. *J Am Coll Cardiol*. 2019;73(24):3153–67.
3613. Curry SJ, Krist AH, Owens DK, et al. Risk assessment for cardiovascular disease with nontraditional risk factors: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;320(3):272–80.

3614. Diamond DM, de Lorgeril M, Kendrick M, Ravnskov U, Rosch PJ. Formal comment on "Systematic review of the predictors of statin adherence for the primary prevention of cardiovascular disease." *PLoS One*. 2019;14(1):e0205138.
3615. Wei MY, Ito MK, Cohen JD, Brinton EA, Jacobson TA. Predictors of statin adherence, switching, and discontinuation in the USAGE survey: understanding the use of statins in America and gaps in patient education. *J Clin Lipidol*. 2013;7(5):472–83.
3616. Ward NC, Watts GF, Eckel RH. Statin toxicity: mechanistic insights and clinical implications. *Circ Res*. 2019;124(2):328–50.
3617. Zaleski AL, Taylor BA, Thompson PD. Coenzyme Q10 as treatment for statin-associated muscle symptoms—a good idea, but.… *Adv Nutr*. 2018;9(4):519S-23S.
3618. Banach M, Serban C, Sahebkar A, et al. Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials. *Mayo Clin Proc*. 2015;90(1):24–34.
3619. Armour R, Zhou L. Outcomes of statin myopathy after statin withdrawal. *J Clin Neuromuscul Dis*. 2013;14(3):103–9.
3620. Majeed A, Molokhia M. Urgent need to establish the true incidence of the side effects of statins. *BMJ*. 2014;348:g3650.
3621. Finegold JA, Manisty CH, Goldacre B, Barron AJ, Francis DP. What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice. *Eur J Prev Cardiol*. 2014;21(4):464–74.
3622. Climent E, Benaiges D, Pedro-Botet J. Statin treatment and increased diabetes risk. Possible mechanisms. *Clínica e Investigación en Arteriosclerosis*. 2019;31(5):228–32.
3623. Mansi IA, English J, Zhang S, Mortensen EM, Halm EA. Long-term outcomes of short-term statin use in healthy adults: a retrospective cohort study. *Drug Saf*. 2016;39(6):543–59.
3624. The Panel on Food Additives and Nutrient Sources, Aggett P, Aguilar F, et al. Scientific opinion on the safety of monacolins in red yeast rice. *EFSA J*. 2018;16(80):5368.
3625. Gordon RY, Cooperman T, Obermeyer W, Becker DJ. Marked variability of monacolin levels in commercial red yeast rice products:

buyer beware! *Arch Intern Med*. 2010;170(19):1722–7.
3626. Righetti L, Dall'Asta C, Bruni R. Risk assessment of RYR food supplements: perception vs. reality. *Front Nutr*. 2021;8:792529.
3627. Murphy SL, Kochanek KD, Xu J, Arias E. Mortality in the United States, 2020. NCHS Data Brief, No. 427. https://www.cdc.gov/nchs/products/databriefs/db427.htm. Published December 2021. Accessed January 3, 2023.
3628. Jukema JW, Cannon CP, de Craen AJM, Westendorp RGJ, Trompet S. The controversies of statin therapy: weighing the evidence. *J Am Coll Cardiol*. 2012;60(10):875–81.
3629. Newman CB, Preiss D, Tobert JA, et al. Statin safety and associated adverse events: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2019;39(2):e38–81.
3630. Redberg RF, Katz MH. Statins for primary prevention: the debate is intense, but the data are weak. *JAMA*. 2016;316(19):1979–81.
3631. Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease. *JAMA*. 1998;280(23):2001–7.
3632. Kelly J, Karlsen M, Steinke G. Type 2 diabetes remission and lifestyle medicine: a position statement from the American College of Lifestyle Medicine. *Am J Lifestyle Med*. 2020;14(4):406–19.
3633. Esselstyn CB Jr, Gendy G, Doyle J, Golubic M, Roizen MF. A way to reverse CAD? *J Fam Pract*. 2014;63(7):356–64b.
3634. Hochholzer W, Giugliano RP. Lipid lowering goals: back to nature? *Ther Adv Cardiovasc Dis*. 2010;4(3):185–91.
3635. Steinberg D, Witztum JL. Inhibition of PCSK9: a powerful weapon for achieving ideal LDL cholesterol levels. *Proc Natl Acad Sci U S A*. 2009;106(24):9546–7.
3636. Cohen J, Pertsemlidis A, Kotowski IK, Graham R, Garcia CK, Hobbs HH. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. *Nat Genet*. 2005;37(2):161–5.
3637. Jaworski K, Jankowski P, Kosior DA. PCSK9 inhibitors—from discovery of a single mutation to a groundbreaking therapy of lipid disorders in one decade. *Arch Med Sci*. 2017;13(4):914–29.

3638. Qamar A, Bhatt DL. Effect of low cholesterol on steroid hormones and vitamin E levels: just a theory or real concern? *Circ Res*. 2015;117(8):662–4.
3639. Blom DJ, Djedjos CS, Monsalvo ML, et al. Effects of evolocumab on vitamin E and steroid hormone levels: results from the 52-week, phase 3, double-blind, randomized, placebo-controlled DESCARTES study. *Circ Res*. 2015;117(8):731–41.
3640. Qamar A, Libby P. Low-density lipoprotein cholesterol after an acute coronary syndrome: how low to go? *Curr Cardiol Rep*. 2019;21(8):77.
3641. Hochholzer W, Giugliano RP. Lipid lowering goals: back to nature? *Ther Adv Cardiovasc Dis*. 2010;4(3):185–91.
3642. Glueck CJ, Gartside P, Fallat RW, Sielski J, Steiner PM. Longevity syndromes: familial hypobeta and familial hyperalpha lipoproteinemia. *J Lab Clin Med*. 1976;88(6):941–57.
3643. Packard CJ. LDL cholesterol: How low to go? *Trends Cardiovasc Med*. 2018;28(5):348–54.
3644. Gotto AM. Low-density lipoprotein cholesterol and cardiovascular risk reduction: how low is low enough without causing harm? *JAMA Cardiol*. 2018;3(9):802–3.
3645. Packard CJ. LDL cholesterol: How low to go? *Trends Cardiovasc Med*. 2018;28(5):348–54.
3646. Steinberg D. The cholesterol controversy is over. Why did it take so long? *Circulation*. 1989;80(4):1070–8.
3647. Morgan DJ, Dhruva SS, Coon ER, Wright SM, Korenstein D. 2018 update on medical overuse. *JAMA Intern Med*. 2019;179(2):240–6.
3648. Lyu H, Xu T, Brotman D, et al. Overtreatment in the United States. *PLoS One*. 2017;12(9):e0181970.
3649. Rothberg MB, Scherer L, Kashef MA, et al. The effect of information presentation on beliefs about the benefits of elective percutaneous coronary intervention. *JAMA Intern Med*. 2014;174(10):1623–9.
3650. Rothberg MB, Sivalingam SK, Ashraf J, et al. Summaries for patients: patients' and cardiologists' beliefs about a common heart procedure. *Ann Intern Med*. 2010;153(5):I46.
3651. Laukkanen JA, Kunutsor SK, Lavie CJ. Percutaneous coronary intervention versus medical therapy in the treatment of stable

coronary artery disease: an updated meta-analysis of contemporary randomized controlled trials. *J Invasive Cardiol*. 2021;33(8):E647–57.

3652. Harvard Heart Letter. COURAGE to make choices. *Harvard Health Publishing*. https://www.health.harvard.edu/newsletter_article/courage-to-make-choices. Published June 1, 2007. Accessed April 5, 2022.

3653. Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet*. 2018;391(10115):31–40.

3654. Kolata G. 'Unbelievable': heart stents fail to ease chest pain. *The New York Times*. https://www.nytimes.com/2017/11/02/health/heart-disease-stents.html. Published November 2, 2017. Accessed April 5, 2022.

3655. Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet*. 2018;391(10115):31–40.

3656. Doenst T, Haverich A, Serruys P, et al. PCI and CABG for treating stable coronary artery disease: *JACC* review topic of the week. *J Am Coll Cardiol*. 2019;73(8):964–76.

3657. Rothberg MB. Coronary artery disease as clogged pipes: a misconceptual model. *Circ Cardiovasc Qual Outcomes*. 2013;6(1):129–32.

3658. Trumbo PR, Shimakawa T. Tolerable upper intake levels for trans fat, saturated fat, and cholesterol. *Nutr Rev*. 2011;69(5):270–8.

3659. World Health Organization. Countdown to 2023: WHO report on global trans-fat elimination 2021. Geneva: 2021.

3660. Wanders AJ, Zock PL, Brouwer IA. Trans fat intake and its dietary sources in general populations worldwide: a systematic review. *Nutrients*. 2017;9(8):E840.

3661. Kahle L, Krebs-Smith SM, Reedy J, Rodgers AB, Signes C. Identification of top food sources of various food components. Epidemiology and Genomics Research Program. https://epi.grants.cancer.gov/diet/foodsources/top-food-sources-report-02212020.pdf. Updated November 30, 2019. Accessed April 5, 2022.

3662. Xu Z, McClure ST, Appel LJ. Dietary cholesterol intake and sources among U.S. adults: results from National Health and Nutrition Examination Surveys (NHANES), 2001–2014. *Nutrients*. 2018;10(6):E771.
3663. Kahle L, Krebs-Smith SM, Reedy J, Rodgers AB, Signes C. Identification of top food sources of various food components. Epidemiology and Genomics Research Program. https://epi.grants.cancer.gov/diet/foodsources/top-food-sources-report-02212020.pdf. Updated November 30, 2019. Accessed April 5, 2022.
3664. Riccardi G, Giosuè A, Calabrese I, Vaccaro O. Dietary recommendations for prevention of atherosclerosis. *Cardiovasc Res*. 2022;118(5):1188–204.
3665. Hooper L, Martin N, Abdelhamid A, Davey Smith G. Reduction in saturated fat intake for cardiovascular disease. *Cochrane Database Syst Rev*. 2015;(6):CD011737.
3666. Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. *Circulation*. 2017;136(3):e1–30.
3667. Hughes S. AHA issues 'Presidential Advisory' on harms of saturated fat. Medscape. https://www.medscape.com/viewarticle/881689. Published June 15, 2017. Accessed April 3, 2022.
3668. Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. *Circulation*. 2017;136(3):e1–30.
3669. Bergeron N, Chiu S, Williams PT, M King S, Krauss RM. Effects of red meat, white meat, and nonmeat protein sources on atherogenic lipoprotein measures in the context of low compared with high saturated fat intake: a randomized controlled trial. *Am J Clin Nutr*. 2019;110(1):24–33.
3670. Maki KC, Van Elswyk ME, Alexander DD, Rains TM, Sohn EL, McNeill S. A meta-analysis of randomized controlled trials that compare the lipid effects of beef versus poultry and/or fish consumption. *J Clin Lipidol*. 2012;6(4):352–61.
3671. Connor WE, Connor SL. Dietary cholesterol and coronary heart disease. *Curr Atheroscler Rep*. 2002;4(6):425–32.

3672. Khalighi Sikaroudi M, Soltani S, Kolahdouz-Mohammadi R, et al. The responses of different dosages of egg consumption on blood lipid profile: an updated systematic review and meta-analysis of randomized clinical trials. *J Food Biochem*. 2020;44(8):e13263.
3673. Barnard ND, Long MB, Ferguson JM, Flores R, Kahleova H. Industry funding and cholesterol research: a systematic review. *Am J Lifestyle Med*. 2021;15(2):165–72.
3674. Choi Y, Chang Y, Lee JE, et al. Egg consumption and coronary artery calcification in asymptomatic men and women. *Atherosclerosis*. 2015;241(2):305–12.
3675. Zhong VW, Van Horn L, Cornelis MC, et al. Associations of dietary cholesterol or egg consumption with incident cardiovascular disease and mortality. *JAMA*. 2019;321(11):1081–95.
3676. Abbasi J. Study puts eggs and dietary cholesterol back on the radar. *JAMA*. 2019;321(20):1959–61.
3677. *Physicians Comm for Responsible Med v. Vilsack*, No 16-cv-00069-LB, 2016 US Dist LEXIS 141489, 2016 WL 5930585 (ND Cal 2016).
3678. U.S. Department of Agriculture, U.S. Department of Health and Human Services. *Dietary guidelines for Americans, 2015–2020*. 8th ed. http://health.gov/dietaryguidelines/2015/guidelines/. Published December 2015. Accessed May 25, 2022
3679. U.S. Department of Agriculture, U.S. Department of Health and Human Services. *Dietary guidelines for Americans, 2020–2025*. 9th ed. https://www.dietaryguidelines.gov/sites/default/files/2020–12/Dietary_Guidelines_for_Americans_2020–2025.pdf. Published December 2020. Accessed April 5, 2022.
3680. Trumbo PR, Shimakawa T. Tolerable upper intake levels for trans fat, saturated fat, and cholesterol. *Nutr Rev*. 2011;69(5):270–8.
3681. David Spence J. Dietary cholesterol and egg yolk should be avoided by patients at risk of vascular disease. *J Transl Int Med*. 2016;4(1):20–4.
3682. Enas EA, Varkey B, Dharmarajan TS, Pare G, Bahl VK. Lipoprotein(a): an independent, genetic, and causal factor for cardiovascular disease and acute myocardial infarction. *Indian Heart J*. 2019;71(2):99–112.

3683. Kotani K, Serban MC, Penson P, Lippi G, Banach M. Evidence-based assessment of lipoprotein(a) as a risk biomarker for cardiovascular diseases—some answers and still many questions. *Crit Rev Clin Lab Sci*. 2016;53(6):370–8.
3684. Stulnig TM, Morozzi C, Reindl-Schwaighofer R, Stefanutti C. Looking at Lp(a) and related cardiovascular risk: from scientific evidence and clinical practice. *Curr Atheroscler Rep*. 2019;21(10):37.
3685. Kostner KM, Kostner GM, Wierzbicki AS. Is Lp(a) ready for prime time use in the clinic? A pros-and-cons debate. *Atherosclerosis*. 2018;274:16–22.
3686. Stender S. In equal amounts, the major ruminant *trans* fatty acid is as bad for LDL cholesterol as industrially produced *trans* fatty acids, but the latter are easier to remove from foods. *Am J Clin Nutr*. 2015;102(6):1301–2.
3687. Gebauer SK, Destaillats F, Dionisi F, Krauss RM, Baer DJ. Vaccenic acid and *trans* fatty acid isomers from partially hydrogenated oil both adversely affect LDL cholesterol: a double-blind, randomized controlled trial. *Am J Clin Nutr*. 2015;102(6):1339–46.
3688. Masarei JR, Rouse IL, Lynch WJ, Robertson K, Vandongen R, Beilin LJ. Effects of a lacto-ovo vegetarian diet on serum concentrations of cholesterol, triglyceride, HDL-C, HDL_2-C, HDL_3-C, apoprotein-B, and Lp(a). *Am J Clin Nutr*. 1984;40(3):468–78.
3689. Sahebkar A, Katsiki N, Ward N, Reiner Ž. Flaxseed supplementation reduces plasma lipoprotein(a) levels: a meta-analysis. *Altern Ther Health Med*. 2021;27(3):50–3.
3690. Biswas TK, Chakrabarti S, Pandit S, Jana U, Dey SK. Pilot study evaluating the use of *Emblica officinalis* standardized fruit extract in cardio-respiratory improvement and antioxidant status of volunteers with smoking history. J Herb Med. 2014;4(4):188–94.
3691. Najjar RS, Moore CE, Montgomery BD. Consumption of a defined, plant-based diet reduces lipoprotein(a), inflammation, and other atherogenic lipoproteins and particles within 4 weeks. *Clin Cardiol*. 2018;41(8):1062–8.
3692. Berk KA, Yahya R, Verhoeven AJM, et al. Effect of diet-induced weight loss on lipoprotein(A) levels in obese individuals with and

without type 2 diabetes. *Diabetologia*. 2017;60(6):989–97.
3693. Najjar RS, Moore CE, Montgomery BD. A defined, plant-based diet utilized in an outpatient cardiovascular clinic effectively treats hypercholesterolemia and hypertension and reduces medications. *Clin Cardiol*. 2018;41(3):307–13.
3694. Najjar RS, Moore CE, Montgomery BD. Consumption of a defined, plant-based diet reduces lipoprotein(a), inflammation, and other atherogenic lipoproteins and particles within 4 weeks. *Clin Cardiol*. 2018;41(8):1062–8.
3695. Li H, Zeng X, Wang Y, et al. A prospective study of healthful and unhealthful plant-based diet and risk of overall and cause-specific mortality. *Eur J Nutr*. 2022;61(1):387–98.
3696. Keaver L, Ruan M, Chen F, et al. Plant- and animal-based diet quality and mortality among US adults: a cohort study. *Br J Nutr*. 2021;125(12):1405–15.
3697. Spiegelhalter D. Using speed of ageing and "microlives" to communicate the effects of lifetime habits and environment. *BMJ*. 2012;345:e8223.
3698. Jafari S, Hezaveh E, Jalilpiran Y, et al. Plant-based diets and risk of disease mortality: a systematic review and meta-analysis of cohort studies. *Crit Rev Food Sci Nutr*. Published online May 6, 2021:1–13.
3699. Remde A, DeTurk SN, Almardini A, Steiner L, Wojda T. Plant-predominant eating patterns—how effective are they for treating obesity and related cardiometabolic health outcomes?—a systematic review. *Nutr Rev*. 2022;80(5):1094–104.
3700. Benatar JR, Stewart RAH. Cardiometabolic risk factors in vegans; a meta-analysis of observational studies. *PLoS One*. 2018;13(12):e0209086.
3701. Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term low-calorie low-protein vegan diet and endurance exercise are associated with low cardiometabolic risk. *Rejuvenation Res*. 2007;10(2):225–34.
3702. Chen GC, Chen PY, Su YC, et al. Vascular, cognitive, and psychomental survey on elderly recycling volunteers in Northern Taiwan. *Front Neurol*. 2018;9:1176.
3703. McDougall J, Thomas LE, McDougall C, et al. Effects of 7 days on an ad libitum low-fat vegan diet: the McDougall Program cohort.

Nutr J. 2014;13:99.
3704. Bloomer RJ, Kabir MM, Canale RE, et al. Effect of a 21 day Daniel Fast on metabolic and cardiovascular disease risk factors in men and women. *Lipids Health Dis*. 2010;9:94.
3705. Friedman SM, Barnett CH, Franki R, Pollock B, Garver B, Barnett TD. Jumpstarting health with a 15-day whole-food plant-based program. *Am J Lifestyle Med*. Published online April 8, 2021:155982762110063.
3706. Kapur NK, Musunuru K. Clinical efficacy and safety of statins in managing cardiovascular risk. *Vasc Health Risk Manag*. 2008;4(2):341–53.
3707. Friedman SM, Barnett CH, Franki R, Pollock B, Garver B, Barnett TD. Jumpstarting health with a 15-day whole-food plant-based program. *Am J Lifestyle Med*. Published online April 8, 2021:155982762110063.
3708. Paz MA, de-La-Sierra A, Sáez M, et al. Treatment efficacy of anti-hypertensive drugs in monotherapy or combination: ATOM systematic review and meta-analysis of randomized clinical trials according to PRISMA statement. *Medicine (Baltimore)*. 2016;95(30):e4071.
3709. Lin CL, Fang TC, Gueng MK. Vascular dilatory functions of ovo-lactovegetarians compared with omnivores. *Atherosclerosis*. 2001;158(1):247–51.
3710. Ernst E, Pietsch L, Matrai A, Eisenberg J. Blood rheology in vegetarians. *Br J Nutr*. 1986;56(3):555–60.
3711. McCarty MF. Favorable impact of a vegan diet with exercise on hemorheology: implications for control of diabetic neuropathy. *Med Hypotheses*. 2002;58(6):476–86.
3712. Dintenfass L. Effect of low-fat, low-protein diet on blood viscosity factors. *Med J Aust*. 1982;1(13):543.
3713. Ernst E, Franz A. Blood fluidity score during vegetarian and hypocaloric diets—a pilot study. *Complement Ther Med*. 1995;3(2):70–1.
3714. Tong TYN, Appleby PN, Bradbury KE, et al. Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians

over 18 years of follow-up: results from the prospective EPIC-Oxford study. *BMJ*. Published online September 4, 2019:l4897.
3715. Petermann-Rocha F, Parra-Soto S, Gray S, et al. Vegetarians, fish, poultry, and meat-eaters: who has higher risk of cardiovascular disease incidence and mortality? A prospective study from UK Biobank. *Eur Heart J*. 2021;42(12):1136–43.
3716. Chiu THT, Chang HR, Wang LY, Chang CC, Lin MN, Lin CL. Vegetarian diet and incidence of total, ischemic, and hemorrhagic stroke in 2 cohorts in Taiwan. *Neurology*. 2020;94(11):e1112–21.
3717. Baden MY, Shan Z, Wang F, et al. Quality of plant-based diet and risk of total, ischemic, and hemorrhagic stroke. *Neurology*. 2021;96(15):e1940–53.
3718. Lu JW, Yu LH, Tu YK, et al. Risk of incident stroke among vegetarians compared to nonvegetarians: a systematic review and meta-analysis of prospective cohort studies. *Nutrients*. 2021;13(9):3019.
3719. Jafari S, Hezaveh E, Jalilpiran Y, et al. Plant-based diets and risk of disease mortality: a systematic review and meta-analysis of cohort studies. *Crit Rev Food Sci Nutr*. Published online May 6, 2021:1–13.
3720. Mazidi M, Katsiki N, Mikhailidis DP, Sattar N, Banach M. Lower carbohydrate diets and all-cause and cause-specific mortality: a population-based cohort study and pooling of prospective studies. *Eur Heart J*. 2019;40(34):2870–9.
3721. Schutz Y, Montani JP, Dulloo AG. Low-carbohydrate ketogenic diets in body weight control: a recurrent plaguing issue of fad diets? *Obes Rev*. 2021;22 Suppl 2:e13195.
3722. Mazidi M, Katsiki N, Mikhailidis DP, Sattar N, Banach M. Lower carbohydrate diets and all-cause and cause-specific mortality: a population-based cohort study and pooling of prospective studies. *Eur Heart J*. 2019;40(34):2870–9.
3723. Fleming RM. The effect of high-protein diets on coronary blood flow. *Angiology*. 2000;51(10):817–26.
3724. Schwingshackl L, Hoffmann G. Low-carbohydrate diets impair flow-mediated dilatation: evidence from a systematic review and meta-analysis. *Br J Nutr*. 2013;110(5):969–70.

3725. Nicholls SJ, Lundman P, Harmer JA, et al. Consumption of saturated fat impairs the anti-inflammatory properties of high-density lipoproteins and endothelial function. *J Am Coll Cardiol*. 2006;48(4):715–20.
3726. Phillips SA, Jurva JW, Syed AQ, et al. Benefit of low-fat over low-carbohydrate diet on endothelial health in obesity. *Hypertension*. 2008;51(2):376–82.
3727. Schwingshackl L, Hoffmann G. Low-carbohydrate diets impair flow-mediated dilatation: evidence from a systematic review and meta-analysis. *Br J Nutr*. 2013;110(5):969–70.
3728. Mazidi M, Katsiki N, Mikhailidis DP, Sattar N, Banach M. Lower carbohydrate diets and all-cause and cause-specific mortality: a population-based cohort study and pooling of prospective studies. *Eur Heart J*. 2019;40(34):2870–9.
3729. Young NJ, Metcalfe C, Gunnell D, et al. A cross-sectional analysis of the association between diet and insulin-like growth factor (IGF)-I, IGF-II, IGF-binding protein (IGFBP)-2, and IGFBP-3 in men in the United Kingdom. *Cancer Causes Control*. 2012;23(6):907–17.
3730. Lee DH, Lee IK, Song K, et al. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999–2002. *Diabetes Care*. 2006;29(7):1638–44.
3731. Ax E, Lampa E, Lind L, et al. Circulating levels of environmental contaminants are associated with dietary patterns in older adults. *Environ Int*. 2015;75:93–102.
3732. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Arterioscler Thromb Vasc Biol*. 2003;23(2):e20–30.
3733. Shepherd CJ, Jackson AJ. Global fishmeal and fish-oil supply: inputs, outputs and markets. *J Fish Biol*. 2013;83(4):1046–66.
3734. Abdelhamid AS, Brown TJ, Brainard JS, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2018;7:CD003177.
3735. de Magalhães JP, Müller M, Rainger GEd, Steegenga W. Fish oil supplements, longevity and aging. *Aging (Albany NY)*. 2016;8(8):1578–82.

3736. Bowman L, Mafham M, Wallendszus K, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med*. 2018;379(16):1540–50.
3737. Kalstad AA, Myhre PL, Laake K, et al. Effects of n-3 fatty acid supplements in elderly patients after myocardial infarction: a randomized, controlled trial. *Circulation*. 2021;143(6):528–39.
3738. Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. *JAMA*. 2020;324(22):2268–80.
3739. Manson JE, Cook NR, Lee IM, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med*. 2019;380(1):23–32.
3740. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11–22.
3741. Park S, Lee S, Kim Y, et al. Causal effects of serum levels of n-3 or n-6 polyunsaturated fatty acids on coronary artery disease: Mendelian randomization study. *Nutrients*. 2021;13(5):1490.
3742. Nicholls SJ, Nelson AJ. The fish-oil paradox. *Curr Opin Lipidol*. 2020;31(6):356–61.
3743. Wennberg M, Tornevi A, Johansson I, Hörnell A, Norberg M, Bergdahl IA. Diet and lifestyle factors associated with fish consumption in men and women: a study of whether gender differences can result in gender-specific confounding. *Nutr J*. 2012;11:101.
3744. Mariotti F. Animal and plant protein sources and cardiometabolic health. *Adv Nutr*. 2019;10(Suppl_4):S351–66.
3745. Krittanawong C, Isath A, Hahn J, et al. Fish consumption and cardiovascular health: a systematic review. *Am J Med*. 2021;134(6):713–20.
3746. Gardner CD, Mehta T, Bernstein A, Aronson D. Three factors that need to be addressed more consistently in nutrition studies: “Instead of what?”, “In what context?”, and “For what?.” *Am J Health Promot*. 2021;35(6):881–2.

3747. Song M, Fung TT, Hu FB, et al. Association of animal and plant protein intake with all-cause and cause-specific mortality. *JAMA Intern Med*. 2016;176(10):1453–63.
3748. Rimm EB, Appel LJ, Chiuve SE, et al. Seafood long-chain n-3 polyunsaturated fatty acids and cardiovascular disease: a science advisory from the American Heart Association. *Circulation*. 2018;138(1):e35–47.
3749. Guasch-Ferré M, Satija A, Blondin SA, et al. Meta-analysis of randomized controlled trials of red meat consumption in comparison with various comparison diets on cardiovascular risk factors. *Circulation*. 2019;139(15):1828–45.
3750. Song M, Fung TT, Hu FB, et al. Association of animal and plant protein intake with all-cause and cause-specific mortality. *JAMA Intern Med*. 2016;176(10):1453–63.
3751. Sun Y, Liu B, Snetselaar LG, et al. Association of major dietary protein sources with all-cause and cause-specific mortality: prospective cohort study. *J Am Heart Assoc*. 2021;10(5):e015553.
3752. Song M, Fung TT, Hu FB, et al. Association of animal and plant protein intake with all-cause and cause-specific mortality. *JAMA Intern Med*. 2016;176(10):1453–63.
3753. Esselstyn CB. Resolving the coronary artery disease epidemic through plant-based nutrition. *Prev Cardiol*. 2001;4(4):171–7.
3754. Affairs of the Heart. Frontier profile: Bill Castelli. Scientific American Frontiers. http://www.pbs.org/saf/1104/features/castelli3.htm. Accessed February 24, 2023.
3755. Keogh EV, Walsh RJ. Rate of greying of human hair. *Nature*. 1965;207(999):877–8.
3756. Seiberg M. Age-induced hair greying—the multiple effects of oxidative stress. *Int J Cosmet Sci*. 2013;35(6):532–8.
3757. Kumar AB, Shamim H, Nagaraju U. Premature graying of hair: review with updates. *Int J Trichology*. 2018;10(5):198–203.
3758. Commo S, Gaillard O, Thibaut S, Thibaut S, Bernard BA. Absence of TRP-2 in melanogenic melanocytes of human hair. *Pigment Cell Res*. 2004;17(5):488–97.

3759. Mastore M, Kohler L, Nappi AJ. Production and utilization of hydrogen peroxide associated with melanogenesis and tyrosinase-mediated oxidations of DOPA and dopamine. *FEBS J*. 2005;272(10):2407–15.
3760. Wood JM, Decker H, Hartmann H, et al. Senile hair graying: H_2O_2-mediated oxidative stress affects human hair color by blunting methionine sulfoxide repair. *FASEB J*. 2009;23(7):2065–75.
3761. Pandhi D, Khanna D. Premature graying of hair. Indian *J Dermatol Venereol Leprol*. 2013;79(5):641–53.
3762. Tobin DJ, Paus R. Graying: gerontobiology of the hair follicle pigmentary unit. *Exp Gerontol*. 2001;36(1):29–54.
3763. Fernandez-Flores A, Saeb-Lima M, Cassarino DS. Histopathology of aging of the hair follicle. *J Cutan Pathol*. 2019;46(7):508–19.
3764. Mahendiratta S, Sarma P, Kaur H, et al. Premature graying of hair: risk factors, co-morbid conditions, pharmacotherapy and reversal—a systematic review and meta-analysis. *Dermatol Ther*. 2020;33(6):e13990.
3765. Daulatabad D, Singal A, Grover C, Sharma SB, Chhillar N. Assessment of oxidative stress in patients with premature canities. *Int J Trichology*. 2015;7(3):91–4.
3766. Babadjouni A, Foulad DP, Hedayati B, Evron E, Mesinkovska N. The effects of smoking on hair health: a systematic review. *Skin Appendage Disord*. 2021;7(4):251–64.
3767. Kumar AB, Shamim H, Nagaraju U. Premature graying of hair: review with updates. *Int J Trichology*. 2018;10(5):198–203.
3768. Acer E, Kaya Erdoğan H, İğrek A, Parlak H, Saraçoğlu ZN, Bilgin M. Relationship between diet, atopy, family history, and premature hair graying. *J Cosmet Dermatol*. 2019;18(2):665–70.
3769. Addolorato G, Leggio L, Ojetti V, Capristo E, Gasbarrini G, Gasbarrini A. Effects of short-term moderate alcohol administration on oxidative stress and nutritional status in healthy males. *Appetite*. 2008;50(1):50–6.
3770. Mahendiratta S, Sarma P, Kaur H, et al. Premature graying of hair: risk factors, co-morbid conditions, pharmacotherapy and reversal—a

systematic review and meta-analysis. *Dermatol Ther*. 2020;33(6):e13990.

3771. Acer E, Kaya Erdoğan H, İğrek A, Parlak H, Saraçoğlu ZN, Bilgin M. Relationship between diet, atopy, family history, and premature hair graying. *J Cosmet Dermatol*. 2019;18(2):665–70.

3772. Kumar AB, Shamim H, Nagaraju U. Premature graying of hair: review with updates. *Int J Trichology*. 2018;10(5):198–203.

3773. Noppakun N, Swasdikul D. Reversible hyperpigmentation of skin and nails with white hair due to vitamin B_{12} deficiency. *Arch Dermatol*. 1986;122(8):896–9.

3774. Kumar AB, Shamim H, Nagaraju U. Premature graying of hair: review with updates. *Int J Trichology*. 2018;10(5):198–203.

3775. Tobin DJ, Paus R. Graying: gerontobiology of the hair follicle pigmentary unit. *Exp Gerontol*. 2001;36(1):29–54.

3776. Tai SY, Hsieh HM, Huang SP, Wu MT. Hair dye use, regular exercise, and the risk and prognosis of prostate cancer: multicenter case-control and case-only studies. *BMC Cancer*. 2016;16:242.

3777. Towle KM, Grespin ME, Monnot AD. Personal use of hair dyes and risk of leukemia: a systematic literature review and meta-analysis. *Cancer Med*. 2017;6(10):2471–86.

3778. Odutola MK, Nnakelu E, Giles GG, van Leeuwen MT, Vajdic CM. Lifestyle and risk of follicular lymphoma: a systematic review and meta-analysis of observational studies. *Cancer Causes Control*. 2020;31(11):979–1000.

3779. Tai SY, Hsieh HM, Huang SP, Wu MT. Hair dye use, regular exercise, and the risk and prognosis of prostate cancer: multicenter case-control and case-only studies. *BMC Cancer*. 2016;16:242.

3780. Takkouche B, Regueira-Méndez C, Montes-Martínez A. Risk of cancer among hairdressers and related workers: a meta-analysis. *Int J Epidemiol*. 2009;38(6):1512–31.

3781. Qin L, Deng HY, Chen SJ, Wei W. A meta-analysis on the relationship between hair dye and the incidence of non-Hodgkin's lymphoma. *Med Princ Pract*. 2019;28(3):222–30.

3782. Park AM, Khan S, Rawnsley J. Hair biology: growth and pigmentation. *Facial Plast Surg Clin North Am*. 2018;26(4):415–24.

3783. Williams R, Pawlus AD, Thornton MJ. Getting under the skin of hair aging: the impact of the hair follicle environment. *Exp Dermatol*. 2020;29(7):588–97.
3784. Sadick NS, Callender VD, Kircik LH, Kogan S. New insight into the pathophysiology of hair loss trigger a paradigm shift in the treatment approach. *J Drugs Dermatol*. 2017;16(11):s135–40.
3785. English RS Jr. A hypothetical pathogenesis model for androgenic alopecia: clarifying the dihydrotestosterone paradox and rate-limiting recovery factors. *Med Hypotheses*. 2018;111:73–81.
3786. Carmina E, Azziz R, Bergfeld W, et al. Female pattern hair loss and androgen excess: a report from the multidisciplinary Androgen Excess and PCOS committee. *J Clin Endocrinol Metab*. 2019;104(7):2875–91.
3787. Varothai S, Bergfeld WF. Androgenetic alopecia: an evidence-based treatment update. *Am J Clin Dermatol*. 2014;15(3):217–30.
3788. Grymowicz M, Rudnicka E, Podfigurna A, et al. Hormonal effects on hair follicles. *Int J Mol Sci*. 2020;21(15):E5342.
3789. Tai T, Kochhar A. Physiology and medical treatments for alopecia. *Facial Plast Surg Clin North Am*. 2020;28(2):149–59.
3790. Hibberts NA, Howell AE, Randall VA. Balding hair follicle dermal papilla cells contain higher levels of androgen receptors than those from non-balding scalp. *J Endocrinol*. 1998;156(1):59–65.
3791. Grymowicz M, Rudnicka E, Podfigurna A, et al. Hormonal effects on hair follicles. *Int J Mol Sci*. 2020;21(15):E5342.
3792. Campo D, D'Acunzo V. Doctors and baldness: a five thousand year old challenge. *G Ital Dermatol Venereol*. 2016;151(1):93–101.
3793. English RS Jr. A hypothetical pathogenesis model for androgenic alopecia: clarifying the dihydrotestosterone paradox and rate-limiting recovery factors. *Med Hypotheses*. 2018;111:73–81.
3794. Campo D, D'Acunzo V. Doctors and baldness: a five thousand year old challenge. *G Ital Dermatol Venereol*. 2016;151(1):93–101.
3795. Hamilton JB. Effect of castration in adolescent and young adult males upon further changes in the proportions of bare and hairy scalp. *J Clin Endocrinol Metab*. 1960;20:1309–18.
3796. Collins DT. Children of sorrow: a history of the mentally retarded in Kansas. *Bull Hist Med*. 1965;39:53–78.

3797. Kempton W, Kahn E. Sexuality and people with intellectual disabilities: a historical perspective. *Sex Disabil*. 1991;9(2):93–111.
3798. Flood E. Notes on the castration of idiot children. *Am J Psychol*. 1899;10(2):296–301.
3799. Lombardo PA. Preface & acknowledgments. In: Lombardo PA, ed. *A Century of Eugenics in America: From the Indiana Experiment to the Human Genome Era*. Indiana University Press; 2011:ix.
3800. Scott ES. Sterilization of mentally retarded persons: reproductive rights and family privacy. *Duke Law J*. 1986;1986(5):806–65.
3801. Wittmann E. To what extent were ideas and beliefs about eugenics held in Nazi Germany shared in Britain and the United States prior to the Second World War? *Vesalius*. 2004;10(1):16–9.
3802. Bolland MJ, Ames RW, Grey AB, et al. Does degree of baldness influence vitamin D status? *Med J Aust*. 2008;189(11–12):674–5.
3803. Trieu N, Eslick GD. Alopecia and its association with coronary heart disease and cardiovascular risk factors: a meta-analysis. *Int J Cardiol*. 2014;176(3):687–95.
3804. Sinclair RD, English DR, Giles GG. Are bald men more virile than their well thatched contemporaries? *Med J Aust*. 2013;199(11):811–2.
3805. Jin T, Wu T, Luo Z, Duan X, Deng S, Tang Y. Association between male pattern baldness and prostate disease: a meta-analysis. *Urol Oncol*. 2018;36(2):80.e7–15.
3806. Mohammadi-Shemirani P, Chong M, Pigeyre M, Morton RW, Gerstein HC, Paré G. Effects of lifelong testosterone exposure on health and disease using Mendelian randomization. *Elife*. 2020;9:e58914.
3807. Ata Korkmaz HA. Relationship between androgenic alopecia and white matter hyperintensities in apparently healthy subjects. *Brain Imaging Behav*. 2020;14(2):527–33.
3808. Trieu N, Eslick GD. Alopecia and its association with coronary heart disease and cardiovascular risk factors: a meta-analysis. *Int J Cardiol*. 2014;176(3):687–95.
3809. Bertoli MJ, Sadoughifar R, Schwartz RA, Lotti TM, Janniger CK. Female pattern hair loss: a comprehensive review. *Dermatol Ther*. 2020;33(6):e14055.

3810. Bertoli MJ, Sadoughifar R, Schwartz RA, Lotti TM, Janniger CK. Female pattern hair loss: a comprehensive review. *Dermatol Ther*. 2020;33(6):e14055.
3811. Lin RL, Garibyan L, Kimball AB, Drake LA. Systemic causes of hair loss. *Ann Med*. 2016;48(6):393–402.
3812. van Zuuren EJ, Fedorowicz Z, Schoones J. Interventions for female pattern hair loss. *Cochrane Database Syst Rev*. 2016;(5):CD007628.
3813. Lam SM. Hair loss and hair restoration in women. *Facial Plast Surg Clin North Am*. 2020;28(2):205–23.
3814. Lam SM. Hair loss and hair restoration in women. *Facial Plast Surg Clin North Am*. 2020;28(2):205–23.
3815. Lin RL, Garibyan L, Kimball AB, Drake LA. Systemic causes of hair loss. *Ann Med*. 2016;48(6):393–402.
3816. Bauer M, Glenn T, Pilhatsch M, Pfennig A, Whybrow PC. Gender differences in thyroid system function: relevance to bipolar disorder and its treatment. *Bipolar Disord*. 2014;16(1):58–71.
3817. Lin RL, Garibyan L, Kimball AB, Drake LA. Systemic causes of hair loss. *Ann Med*. 2016;48(6):393–402.
3818. Williams R, Pawlus AD, Thornton MJ. Getting under the skin of hair aging: the impact of the hair follicle environment. *Exp Dermatol*. 2020;29(7):588–97.
3819. Chien Yin GO, Siong-See JL, Wang ECE. Telogen Effluvium—a review of the science and current obstacles. *J Dermatol Sci*. 2021;101(3):156–63.
3820. Sharquie KE, Jabbar RI. COVID-19 infection is a major cause of acute telogen effluvium. *Ir J Med Sci*. Published online August 31, 2021.
3821. Malkud S. Telogen effluvium: a review. *J Clin Diagn Res*. 2015;9(9):WE01–3.
3822. Bertoli MJ, Sadoughifar R, Schwartz RA, Lotti TM, Janniger CK. Female pattern hair loss: a comprehensive review. *Dermatol Ther*. 2020;33(6):e14055.
3823. Malkud S. Telogen effluvium: a review. *J Clin Diagn Res*. 2015;9(9):WE01–3.
3824. Sharquie KE, Jabbar RI. COVID-19 infection is a major cause of acute telogen effluvium. *Ir J Med Sci*. Published online August 31,

2021.
3825. Trieu N, Eslick GD. Alopecia and its association with coronary heart disease and cardiovascular risk factors: a meta-analysis. *Int J Cardiol*. 2014;176(3):687–95.
3826. Gatherwright J, Liu MT, Amirlak B, Gliniak C, Totonchi A, Guyuron B. The contribution of endogenous and exogenous factors to male alopecia: a study of identical twins. *Plast Reconstr Surg*. 2013;131(5):794e-801e.
3827. Lolli F, Pallotti F, Rossi A, et al. Androgenetic alopecia: a review. *Endocrine*. 2017;57(1):9–17.
3828. DiMarco G, McMichael A. Hair loss myths. *J Drugs Dermatol*. 2017;16(7):690–4.
3829. Gatherwright J, Liu MT, Gliniak C, Totonchi A, Guyuron B. The contribution of endogenous and exogenous factors to female alopecia: a study of identical twins. *Plast Reconstr Surg*. 2012;130(6):1219–26.
3830. Gatherwright J, Liu MT, Amirlak B, Gliniak C, Totonchi A, Guyuron B. The contribution of endogenous and exogenous factors to male alopecia: a study of identical twins. *Plast Reconstr Surg*. 2013;131(5):794e-801e.
3831. Gatherwright J, Liu MT, Gliniak C, Totonchi A, Guyuron B. The contribution of endogenous and exogenous factors to female alopecia: a study of identical twins. *Plast Reconstr Surg*. 2012;130(6):1219–26.
3832. D'Andrea S, Spaggiari G, Barbonetti A, Santi D. Endogenous transient doping: physical exercise acutely increases testosterone levels—results from a meta-analysis. *J Endocrinol Invest*. 2020;43(10):1349–71.
3833. Wedick NM, Mantzoros CS, Ding EL, et al. The effects of caffeinated and decaffeinated coffee on sex hormone–binding globulin and endogenous sex hormone levels: a randomized controlled trial. *Nutr J*. 2012;11:86.
3834. Gatherwright J, Liu MT, Amirlak B, Gliniak C, Totonchi A, Guyuron B. The contribution of endogenous and exogenous factors to male alopecia: a study of identical twins. *Plast Reconstr Surg*. 2013;131(5):794e–801e.

3835. Gatherwright J, Liu MT, Gliniak C, Totonchi A, Guyuron B. The contribution of endogenous and exogenous factors to female alopecia: a study of identical twins. *Plast Reconstr Surg*. 2012;130(6):1219–26.
3836. Babadjouni A, Foulad DP, Hedayati B, Evron E, Mesinkovska N. The effects of smoking on hair health: a systematic review. *Skin Appendage Disord*. 2021;7(4):251–64.
3837. Lai CH, Chu NF, Chang CW, et al. Androgenic alopecia is associated with less dietary soy, lower [corrected] blood vanadium and rs1160312 1 polymorphism in Taiwanese communities. *PLoS One*. 2013;8(12):e79789.
3838. Yu V, Juhász M, Chiang A, Atanaskova Mesinkovska N. Alopecia and associated toxic agents: a systematic review. *Skin Appendage Disord*. 2018;4(4):245–60.
3839. Clarkson TW. The three modern faces of mercury. *Environ Health Perspect*. 2002;110(Suppl 1):11–23.
3840. Ross JJ. Shakespeare's chancre: did the bard have syphilis? *Clin Infect Dis*. 2005;40(3):399–404.
3841. Centers for Disease Control and Prevention. Executive summary. *Fourth National Report on Human Exposure to Environmental Chemicals*. 2009.
3842. Peters JB, Warren MP. Reversible alopecia associated with high blood mercury levels and early menopause: a report of two cases. *Menopause*. 2019;26(8):915–8.
3843. Campo D, D'Acunzo V. Doctors and baldness: a five thousand year old challenge. *G Ital Dermatol Venereol*. 2016;151(1):93–101.
3844. Nanda S, De Bedout V, Miteva M. Alopecia as a systemic disease. *Clin Dermatol*. 2019;37(6):618–28.
3845. Park AM, Khan S, Rawnsley J. Hair biology: growth and pigmentation. *Facial Plast Surg Clin North Am*. 2018;26(4):415–24.
3846. Sadick NS, Callender VD, Kircik LH, Kogan S. New insight into the pathophysiology of hair loss trigger a paradigm shift in the treatment approach. *J Drugs Dermatol*. 2017;16(11):s135–40.
3847. Sand JP. Follicular unit transplantation. *Facial Plast Surg Clin North Am*. 2020;28(2):161–7.

3848. Stoneburner J, Shauly O, Carey J, Patel KM, Stevens WG, Gould DJ. Contemporary management of alopecia: a systematic review and meta-analysis for surgeons. *Aesthetic Plast Surg*. 2020;44(1):97–113.
3849. Vogel JE. Hair restoration complications: an approach to the unnatural-appearing hair transplant. *Facial Plast Surg*. 2008;24(4):453–61.
3850. Rose PT. Advances in hair restoration. *Dermatol Clin*. 2018;36(1):57–62.
3851. Umar S. Hair transplantation in patients with inadequate head donor supply using nonhead hair: report of 3 cases. *Ann Plast Surg*. 2011;67(4):332–5.
3852. Stoneburner J, Shauly O, Carey J, Patel KM, Stevens WG, Gould DJ. Contemporary management of alopecia: a systematic review and meta-analysis for surgeons. *Aesthetic Plast Surg*. 2020;44(1):97–113.
3853. Gatherwright J, Liu MT, Gliniak C, Totonchi A, Guyuron B. The contribution of endogenous and exogenous factors to female alopecia: a study of identical twins. *Plast Reconstr Surg*. 2012;130(6):1219–26.
3854. Nadimi S. Complications with hair transplantation. *Facial Plast Surg Clin North Am*. 2020;28(2):225–35.
3855. Gupta AK, Mays RR, Dotzert MS, Versteeg SG, Shear NH, Piguet V. Efficacy of non-surgical treatments for androgenetic alopecia: a systematic review and network meta-analysis. *J Eur Acad Dermatol Venereol*. 2018;32(12):2112–25.
3856. Lotti T, Goren A, Verner I, D'Alessio PA, Franca K. Platelet rich plasma in androgenetic alopecia: a systematic review. *Dermatol Ther*. 2019;32(3):e12837.
3857. Carloni R, Pechevy L, Postel F, Zielinski M, Gandolfi S. Is there a therapeutic effect of botulinum toxin on scalp alopecia? Physiopathology and reported cases: a systematic review of the literature. *J Plast Reconstr Aesthet Surg*. 2020;73(12):2210–6.
3858. Wang Y, Zhang H, Zheng Q, Tang K, Fang R, Sun Q. Botulinum toxin as a double-edged sword in alopecia: a systematic review. *J Cosmet Dermatol*. 2020;19(10):2560–5.
3859. Dodd EM, Winter MA, Hordinsky MK, Sadick NS, Farah RS. Photobiomodulation therapy for androgenetic alopecia: a clinician's

guide to home-use devices cleared by the Federal Drug Administration. *J Cosmet Laser Ther*. 2018;20(3):159–67.
3860. Simunovic Z, Trobonjaca T, Trobonjaca Z. Treatment of medial and lateral epicondylitis—tennis and golfer's elbow—with low level laser therapy: a multicenter double blind, placebo-controlled clinical study on 324 patients. *J Clin Laser Med Surg*. 1998;16(3):145–51.
3861. Cohen PR. A case report of scrotal rejuvenation: laser treatment of angiokeratomas of the scrotum. *Dermatol Ther (Heidelb)*. 2019;9(1):185–92.
3862. Egger A, Resnik SR, Aickara D, et al. Examining the safety and efficacy of low-level laser therapy for male and female pattern hair loss: a review of the literature. *Skin Appendage Disord*. 2020;6(5):259–67.
3863. Egger A, Resnik SR, Aickara D, et al. Examining the safety and efficacy of low-level laser therapy for male and female pattern hair loss: a review of the literature. *Skin Appendage Disord*. 2020;6(5):259–67.
3864. Egger A, Resnik SR, Aickara D, et al. Examining the safety and efficacy of low-level laser therapy for male and female pattern hair loss: a review of the literature. *Skin Appendage Disord*. 2020;6(5):259–67.
3865. Ledoux S, Flamant M, Calabrese D, Bogard C, Sami O, Coupaye M. What are the micronutrient deficiencies responsible for the most common nutritional symptoms after bariatric surgery? *Obes Surg*. 2020;30(5):1891–7.
3866. DiMarco G, McMichael A. Hair loss myths. *J Drugs Dermatol*. 2017;16(7):690–4.
3867. Thompson KG, Kim N. Dietary supplements in dermatology: a review of the evidence for zinc, biotin, vitamin D, nicotinamide, and *Polypodium*. *J Am Acad Dermatol*. 2021;84(4):1042–50.
3868. Patel DP, Swink SM, Castelo-Soccio L. A review of the use of biotin for hair loss. *Skin Appendage Disord*. 2017;3(3):166–9.
3869. FDA in brief: FDA reminds patients, health care professionals and laboratory personnel about the potential for biotin interference with certain test results, especially specific tests to aid in heart attack diagnoses. U.S. Food and Drug Administration.

https://www.fda.gov/news-events/fda-brief/fda-brief-fda-reminds-patients-health-care-professionals-and-laboratory-personnel-about-potential#:~:text=Today%2C%20the%20U.S.%20Food%20and,and%20cause%20incorrect%20results%20that. Published November 5, 2019. Accessed July 2, 2022.

3870. MacFarquhar JK, Broussard DL, Melstrom P, et al. Acute selenium toxicity associated with a dietary supplement. *Arch Intern Med*. 2010;170(3):256–61.

3871. Almohanna HM, Ahmed AA, Tsatalis JP, Tosti A. The role of vitamins and minerals in hair loss: a review. *Dermatol Ther (Heidelb)*. 2018;9(1):51–70.

3872. Guo EL, Katta R. Diet and hair loss: effects of nutrient deficiency and supplement use. *Dermatol Pract Concept*. 2017;7(1):1–10.

3873. DiMarco G, McMichael A. Hair loss myths. *J Drugs Dermatol*. 2017;16(7):690–4.

3874. Bater K, Rieder E. Over-the-counter hair loss treatments: help or hype? *J Drugs Dermatol*. 2018;17(12):1317–21.

3875. Yi Y, Qiu J, Jia J, et al. Severity of androgenetic alopecia associated with poor sleeping habits and carnivorous eating and junk food consumption—a web-based investigation of male pattern hair loss in China. *Dermatol Ther*. 2020;33(2):e13273.

3876. Fortes C, Mastroeni S, Mannooranparampil T, Abeni D, Panebianco A. Mediterranean diet: fresh herbs and fresh vegetables decrease the risk of Androgenetic Alopecia in males. *Arch Dermatol Res*. 2018;310(1):71–6.

3877. Lai CH, Chu NF, Chang CW, et al. Androgenic alopecia is associated with less dietary soy, lower [corrected] blood vanadium and rs1160312 1 polymorphism in Taiwanese communities. *PLoS One*. 2013;8(12):e79789.

3878. Daniels G, Akram S, Westgate GE, Tamburic S. Can plant-derived phytochemicals provide symptom relief for hair loss? A critical review. *Int J Cosmet Sci*. 2019;41(4):332–45.

3879. Hosking AM, Juhasz M, Atanaskova Mesinkovska N. Complementary and alternative treatments for alopecia: a comprehensive review. *Skin Appendage Disord*. 2019;5(2):72–89.

3880. Herman A, Herman AP. Topically used herbal products for the treatment of hair loss: preclinical and clinical studies. *Arch Dermatol Res*. 2017;309(8):595–610.
3881. Grothe T, Wandrey F, Schuerch C. Short communication: clinical evaluation of pea sprout extract in the treatment of hair loss. *Phytother Res*. 2020;34(2):428–31.
3882. Harada N, Okajima K, Arai M, Kurihara H, Nakagata N. Administration of capsaicin and isoflavone promotes hair growth by increasing insulin-like growth factor-I production in mice and in humans with alopecia. *Growth Horm IGF Res*. 2007;17(5):408–15.
3883. Troconis-Torres IG, Rojas-López M, Hernández-Rodríguez C, et al. Biochemical and molecular analysis of some commercial samples of chilli peppers from Mexico. *J Biomed Biotech*. 2012;2012:1–11.
3884. Cho H, Kwon Y. Development of a database of capsaicinoid contents in foods commonly consumed in Korea. *Food Sci Nutr*. 2020;8(8):4611–24.
3885. Harada N, Okajima K, Arai M, Kurihara H, Nakagata N. Administration of capsaicin and isoflavone promotes hair growth by increasing insulin-like growth factor-I production in mice and in humans with alopecia. *Growth Horm IGF Res*. 2007;17(5):408–15.
3886. Bhagwat S, Haytowitz DB, Holden JM. USDA database for the isoflavone content of selected foods: release 2.0. Agricultural Research Service, United States Department of Agriculture. https://www.ars.usda.gov/arsuserfiles/80400525/data/isoflav/isoflav_r2.pdf. Published September 2008. Accessed April 15, 2022.
3887. Cho YH, Lee SY, Jeong DW, et al. Effect of pumpkin seed oil on hair growth in men with androgenetic alopecia: a randomized, double-blind, placebo-controlled trial. *Evid Based Complement Alternat Med*. 2014;2014:549721.
3888. Octa Sabal Plus. tradeKorea.com. https://www.tradekorea.com/product/detail/P291943/Octa-Sabal-Plus-.html. Accessed July 5, 2022.
3889. Hajhashemi V, Rajabi P, Mardani M. Beneficial effects of pumpkin seed oil as a topical hair growth promoting agent in a mice model. *Avicenna J Phytomed*. 2019;9(6):499–504.

3890. Ibrahim IM, Hasan MS, Elsabaa KI, Elsaie ML. Pumpkin seed oil vs. minoxidil 5% topical foam for the treatment of female pattern hair loss: a randomized comparative trial. *J Cosmet Dermatol*. 2021;20(9):2867–73.
3891. Dhurat R, Chitallia J, May TW, et al. An open-label randomized multicenter study assessing the noninferiority of a caffeine-based topical liquid 0. 2% versus minoxidil 5% solution in male androgenetic alopecia. *Skin Pharmacol Physiol*. 2017;30(6):298–305.
3892. Daniels G, Akram S, Westgate GE, Tamburic S. Can plant-derived phytochemicals provide symptom relief for hair loss? A critical review. *Int J Cosmet Sci*. 2019;41(4):332–45.
3893. Randall VA, Ebling FJ. Seasonal changes in human hair growth. *Br J Dermatol*. 1991;124(2):146–51.
3894. Fischer TW, Herczeg-Lisztes E, Funk W, Zillikens D, Bíró T, Paus R. Differential effects of caffeine on hair shaft elongation, matrix and outer root sheath keratinocyte proliferation, and transforming growth factor-β2/insulin-like growth factor-1-mediated regulation of the hair cycle in male and female human hair follicles *in vitro*. *Br J Dermatol*. 2014;171(5):1031–43.
3895. Dressler C, Blumeyer A, Rosumeck S, Arayesh A, Nast A. Efficacy of topical caffeine in male androgenetic alopecia. *J Dtsch Dermatol Ges*. 2017;15(7):734–41.
3896. Bussoletti C, Tolaini MV, Celleno L. Efficacy of a cosmetic phyto-caffeine shampoo in female androgenetic alopecia. *G Ital Dermatol Venereol*. 2020;155(4):492–9.
3897. Dressler C, Blumeyer A, Rosumeck S, Arayesh A, Nast A. Efficacy of topical caffeine in male androgenetic alopecia. *J Dtsch Dermatol Ges*. 2017;15(7):734–41.
3898. Kwon OS, Han JH, Yoo HG, et al. Human hair growth enhancement in vitro by green tea epigallocatechin-3-gallate (EGCG). *Phytomedicine*. 2007;14(7–8):551–5.
3899. Liao S, Hiipakka RA. Selective inhibition of steroid 5 α-reductase isozymes by tea epicatechin-3-gallate and epigallocatechin-3-gallate. *Biochem Biophys Res Commun*. 1995;214(3):833–8.
3900. Kim YY, Up No S, Kim MH, et al. Effects of topical application of EGCG on testosterone-induced hair loss in a mouse model. *Exp*

Dermatol. 2011;20(12):1015–7.
3901. Berger RS, Fu JL, Smiles KA, et al. The effects of minoxidil, 1% pyrithione zinc and a combination of both on hair density: a randomized controlled trial. *Br J Dermatol*. 2003;149(2):354–62.
3902. Miao Y, Sun Y, Wang W, et al. 6-gingerol inhibits hair shaft growth in cultured human hair follicles and modulates hair growth in mice. *PLoS One*. 2013;8(2):e57226.
3903. Li Y, Han M, Lin P, He Y, Yu J, Zhao R. Hair growth promotion activity and its mechanism of *Polygonum multiflorum*. *Evid Based Complement Alternat Med*. 2015;2015:517901.
3904. Shin JY, Choi YH, Kim J, et al. *Polygonum multiflorum* extract support hair growth by elongating anagen phase and abrogating the effect of androgen in cultured human dermal papilla cells. *BMC Complement Med Ther*. 2020;20(1):144.
3905. Teka T, Wang L, Gao J, et al. *Polygonum multiflorum*: recent updates on newly isolated compounds, potential hepatotoxic compounds and their mechanisms. *J Ethnopharmacol.* 2021;271:113864.
3906. Hay IC, Jamieson M, Ormerod AD. Randomized trial of aromatherapy: successful treatment for alopecia areata. *Arch Dermatol*. 1998;134(11):1349–52.
3907. Sharquie KE, Al-Obaidi HK. Onion juice (Allium cepa L.), a new topical treatment for alopecia areata. *J Dermatol*. 2002;29(6):343–6.
3908. Hajheydari Z, Jamshidi M, Akbari J, Mohammadpour R. Combination of topical garlic gel and betamethasone valerate cream in the treatment of localized alopecia areata: a double-blind randomized controlled study. *Indian J Dermatol Venereol Leprol*. 2007;73(1):29–32.
3909. Panahi Y, Taghizadeh M, Marzony ET, Sahebkar A. Rosemary oil vs minoxidil 2% for the treatment of androgenetic alopecia: a randomized comparative trial. *Skinmed*. 2015;13(1):15–21.
3910. Ajmani GS, Suh HH, Wroblewski KE, Pinto JM. Smoking and olfactory dysfunction: a systematic literature review and meta-analysis. *Laryngoscope*. 2017;127(8):1753–61.
3911. Desiato VM, Levy DA, Byun YJ, Nguyen SA, Soler ZM, Schlosser RJ. The prevalence of olfactory dysfunction in the general

population: a systematic review and meta-analysis. *Am J Rhinol Allergy*. 2021;35(2):195–205.
3912. Stevens JC, Cain WS, Demarque A, Ruthruff AM. On the discrimination of missing ingredients: aging and salt flavor. *Appetite*. 1991;16(2):129–40.
3913. Schäfer L, Schriever VA, Croy I. Human olfactory dysfunction: causes and consequences. *Cell Tissue Res*. 2021;383(1):569–79.
3914. Nolan LS. Age-related hearing loss: why we need to think about sex as a biological variable. *J Neurosci Res*. 2020;98(9):1705–20.
3915. Mao Z, Zhao L, Pu L, Wang M, Zhang Q, He DZZ. How well can centenarians hear? *PLoS One*. 2013;8(6):e65565.
3916. Committee on Accessible and Affordable Hearing Health Care for Adults. Blazer DG, Domnitz S, Liverman CT, eds. *Hearing Health Care for Adults: Priorities for Improving Access and Affordability*. National Academies Press; 2016.
3917. Goman AM, Lin FR. Prevalence of hearing loss by severity in the United States. *Am J Public Health*. 2016;106(10):1820–2.
3918. Mao Z, Zhao L, Pu L, Wang M, Zhang Q, He DZZ. How well can centenarians hear? *PLoS One*. 2013;8(6):e65565.
3919. Wattamwar K, Qian ZJ, Otter J, et al. Increases in the rate of age-related hearing loss in the older old. *JAMA Otolaryngol Head Neck Surg*. 2017;143(1):41–5.
3920. Shukla A, Harper M, Pedersen E, et al. Hearing loss, loneliness, and social isolation: a systematic review. *Otolaryngol Head Neck Surg*. 2020;162(5):622–33.
3921. Lawrence BJ, Jayakody DMP, Bennett RJ, Eikelboom RH, Gasson N, Friedland PL. Hearing loss and depression in older adults: a systematic review and meta-analysis. *Gerontologist*. 2020;60(3):e137–54.
3922. Wattamwar K, Qian ZJ, Otter J, et al. Increases in the rate of age-related hearing loss in the older old. *JAMA Otolaryngol Head Neck Surg*. 2017;143(1):41–5.
3923. Goman AM, Lin FR. Hearing loss in older adults—from epidemiological insights to national initiatives. *Hear Res*. 2018;369:29–32.

3924. Brennan-Jones CG, Weeda E, Ferguson M. Cochrane corner: hearing aids for mild to moderate hearing loss in adults. *Int J Audiol*. 2018;57(7):479–82.
3925. Mahmoudi E, Basu T, Langa K, et al. Can hearing aids delay time to diagnosis of dementia, depression, or falls in older adults? *J Am Geriatr Soc*. 2019;67(11):2362–9.
3926. Goman AM, Lin FR. Hearing loss in older adults—from epidemiological insights to national initiatives. *Hear Res*. 2018;369:29–32.
3927. Franck KH, Rathi VK. Regulation of over-the-counter hearing aids—deafening silence from the FDA. *N Engl J Med*. 2020;383(21):1997–2000.
3928. Fact Sheet: cheaper hearing aids now in stores thanks to Biden-Harris administration competition agenda. WhiteHouse.gov. https://www.whitehouse.gov/briefing-room/statements-releases/2022/10/17/fact-sheet-cheaper-hearing-aids-now-in-stores-thanks-to-biden-harris-administration-competition-agenda/. Published October 17, 2022. Accessed January 3, 2023.
3929. Michaud HN, Duchesne L. Aural rehabilitation for older adults with hearing loss: impacts on quality of life—a systematic review of randomized controlled trials. *J Am Acad Audiol*. 2017;28(7):596–609.
3930. Ferguson MA, Kitterick PT, Chong LY, Edmondson-Jones M, Barker F, Hoare DJ. Hearing aids for mild to moderate hearing loss in adults. *Cochrane Database Syst Rev*. 2017;2017(9):CD012023.
3931. Brennan-Jones CG, Weeda E, Ferguson M. Cochrane corner: hearing aids for mild to moderate hearing loss in adults. *Int J Audiol*. 2018;57(7):479–82.
3932. Lerner S. Limitations of conventional hearing aids: examining common complaints and issues that can and cannot be remedied. *Otolaryngol Clin North Am*. 2019;52(2):211–20.
3933. Davis A, McMahon CM, Pichora-Fuller KM, et al. Aging and hearing health: the life-course approach. *Gerontologist*. 2016;56 Suppl 2:S256–67.
3934. McCormack A, Fortnum H. Why do people fitted with hearing aids not wear them? *Int J Audiol*. 2013;52(5):360–8.

3935. Blustein J, Weinstein BE, Chodosh J. Marketing claims about using hearing aids to forestall or prevent dementia. *JAMA Otolaryngol Head Neck Surg*. 2020;146(8):765–6.
3936. World Health Organization. *Risk Reduction of Cognitive Decline and Dementia: WHO Guidelines*. World Health Organization; 2019.
3937. Schwartz SR, Magit AE, Rosenfeld RM, et al. Clinical practice guideline (update): earwax (cerumen impaction). *Otolaryngol Head Neck Surg*. 2017;156(1_suppl):S1–29.
3938. Nagala S, Singh P, Tostevin P. Extent of cotton-bud use in ears. *Br J Gen Pract*. 2011;61(592):662–3.
3939. Baxter P. Association between use of cotton tipped swabs and cerumen plugs. *BMJ*. 1983;287(6401):1260.
3940. Barton RT. Q-tip otalgia. *JAMA*. 1972;220(12):1619.
3941. Schwartz SR, Magit AE, Rosenfeld RM, et al. Clinical practice guideline (update): earwax (cerumen impaction). *Otolaryngol Head Neck Surg*. 2017;156(1_suppl):S1–29.
3942. Oron Y, Zwecker-Lazar I, Levy D, Kreitler S, Roth Y. Cerumen removal: comparison of cerumenolytic agents and effect on cognition among the elderly. *Arch Gerontol Geriatr*. 2011;52(2):228–32.
3943. Schwartz SR, Magit AE, Rosenfeld RM, et al. Clinical practice guideline (update): earwax (cerumen impaction). *Otolaryngol Head Neck Surg*. 2017;156(1_suppl):S1–29.
3944. Lee LM, Govindaraju R, Hon SK. Cotton bud and ear cleaning—a loose tip cotton bud? *Med J Malaysia*. 2005;60(1):85–8.
3945. Schwartz SR, Magit AE, Rosenfeld RM, et al. Clinical practice guideline (update): earwax (cerumen impaction). *Otolaryngol Head Neck Surg*. 2017;156(1_suppl):S1–29.
3946. Goldman SA, Ankerstjerne JK, Welker KB, Chen DA. Fatal meningitis and brain abscess resulting from foreign body-induced otomastoiditis. *Otolaryngol Head Neck Surg*. 1998;118(1):6–8.
3947. Aaron K, Cooper TE, Warner L, Burton MJ. Ear drops for the removal of ear wax. Cochrane ENT Group, ed. *Cochrane Database of Systematic Reviews*. 2018;7(CD012171).
3948. Schwartz SR, Magit AE, Rosenfeld RM, et al. Clinical practice guideline (update): earwax (cerumen impaction). *Otolaryngol Head Neck Surg*. 2017;156(1_suppl):S1–29.

3949. Schwartz SR, Magit AE, Rosenfeld RM, et al. Clinical practice guideline (update): earwax (cerumen impaction). *Otolaryngol Head Neck Surg*. 2017;156(1_suppl):S1–29.
3950. Coppin R, Wicke D, Little P. Managing earwax in primary care: efficacy of self-treatment using a bulb syringe. *Br J Gen Pract*. 2008;58(546):44–9.
3951. Coppin R, Wicke D, Little P. Randomized trial of bulb syringes for earwax: impact on health service utilization. *Ann Fam Med*. 2011;9(2):110–4.
3952. Nieman CL, Oh ES. Hearing loss. *Ann Intern Med*. 2020;173(11):ITC81–96.
3953. Dinsdale RC, Roland PS, Manning SC, Meyerhoff WL. Catastrophic otologic injury from oral jet irrigation of the external auditory canal. *Laryngoscope*. 1991;101(1 Pt 1):75–8.
3954. Seely DR, Quigley SM, Langman AW. Ear candles—efficacy and safety. *Laryngoscope*. 1996;106(10):1226–9.
3955. Seely DR, Quigley SM, Langman AW. Ear candles—efficacy and safety. *Laryngoscope*. 1996;106(10):1226–9.
3956. Schwartz SR, Magit AE, Rosenfeld RM, et al. Clinical practice guideline (update): earwax (cerumen impaction). *Otolaryngol Head Neck Surg*. 2017;156(1_suppl):S1–29.
3957. Mao Z, Zhao L, Pu L, Wang M, Zhang Q, He DZZ. How well can centenarians hear? *PLoS One*. 2013;8(6):e65565.
3958. Donnison CP. Blood pressure in the African native. *Lancet*. 1929;213(5497):6–7.
3959. Morse WR, McGill MD, Beh YT. Blood pressure amongst aboriginal ethnic groups of Szechwan Province, West China. *Lancet*. 1937;229(5929):966–8.
3960. Mueller NT, Noya-Alarcon O, Contreras M, Appel LJ, Dominguez-Bello MG. Association of age with blood pressure across the lifespan in isolated Yanomami and Yekwana villages. *JAMA Cardiol*. 2018;3(12):1247–9.
3961. Rosen S, Bergman M, Plester D, El-Mofty A, Satti MH. Presbycusis study of a relatively noise-free population in the Sudan. *Ann Otol Rhinol Laryngol*. 1962;71:727–43.

3962. Goycoolea MV, Goycoolea HG, Farfan CR, Rodriguez LG, Martinez GC, Vidal R. Effect of life in industrialized societies on hearing in natives of Easter Island. *Laryngoscope*. 1986;96(12):1391–6.
3963. Wu PZ, O'Malley JT, de Gruttola V, Liberman MC. Age-related hearing loss is dominated by damage to inner ear sensory cells, not the cellular battery that powers them. *J Neurosci*. 2020;40(33):6357–66.
3964. Nieman CL, Oh ES. Hearing loss. *Ann Intern Med*. 2020;173(11):ITC81–96.
3965. Momi SK, Wolber LE, Fabiane SM, MacGregor AJ, Williams FMK. Genetic and environmental factors in age-related hearing impairment. *Twin Res Hum Genet*. 2015;18(4):383–92.
3966. Mao Z, Zhao L, Pu L, Wang M, Zhang Q, He DZZ. How well can centenarians hear? *PLoS One*. 2013;8(6):e65565.
3967. Wang J, Puel JL. Presbycusis: an update on cochlear mechanisms and therapies. *J Clin Med*. 2020;9(1):E218.
3968. Attarha M, Bigelow J, Merzenich MM. Unintended consequences of white noise therapy for tinnitus—otolaryngology's cobra effect: a review. *JAMA Otolaryngol Head Neck Surg*. 2018;144(10):938–43.
3969. Attarha M, Bigelow J, Merzenich MM. No evidence of broadband noise having any harmful effect on hearing. *JAMA Otolaryngol Head Neck Surg*. 2019;145(3):292–3.
3970. Nieman CL, Oh ES. Hearing loss. *Ann Intern Med*. 2020;173(11):ITC81–96.
3971. Joo Y, Cruickshanks KJ, Klein BEK, Klein R, Hong O, Wallhagen MI. The contribution of ototoxic medications to hearing loss among older adults. *J Gerontol A Biol Sci Med Sci*. 2020;75(3):561–6.
3972. Panda NK, Modi R, Munjal S, Virk RS. Auditory changes in mobile users: is evidence forthcoming? *Otolaryngol Head Neck Surg*. 2011;144(4):581–5.
3973. Alsanosi AA, Al-Momani MO, Hagr AA, Almomani FM, Shami IM, Al-Habeeb SF. The acute auditory effects of exposure for 60 minutes to mobile's electromagnetic field. *Saudi Med J*. 2013;34(2):142–6.
3974. Mandalà M, Colletti V, Sacchetto L, et al. Effect of Bluetooth headset and mobile phone electromagnetic fields on the human auditory nerve. *Laryngoscope*. 2014;124(1):255–9.

3975. Rosen S, Olin P. Hearing loss and coronary heart disease. *Arch Otolaryngol*. 1965;82:236–43.
3976. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71(6):1269–324.
3977. Rosen S, Olin P. Hearing loss and coronary heart disease. *Arch Otolaryngol*. 1965;82:236–43.
3978. Rosen S, Bergman M, Plester D, El-Mofty A, Satti MH. Presbycusis study of a relatively noise-free population in the Sudan. *Ann Otol Rhinol Laryngol*. 1962;71:727–43.
3979. Curhan SG, Halpin C, Wang M, Eavey RD, Curhan GC. Prospective study of dietary patterns and hearing threshold elevation. *Am J Epidemiol*. 2020;189(3):204–14.
3980. Rosen S, Bergman M, Plester D, El-Mofty A, Satti MH. Presbycusis study of a relatively noise-free population in the Sudan. *Ann Otol Rhinol Laryngol*. 1962;71:727–43.
3981. Gopinath B, Flood VM, McMahon CM, Burlutsky G, Brand-Miller J, Mitchell P. Dietary glycemic load is a predictor of age-related hearing loss in older adults. *J Nutr*. 2010;140(12):2207–12.
3982. Samocha-Bonet D, Wu B, Ryugo DK. Diabetes mellitus and hearing loss: a review. *Ageing Res Rev*. 2021;71:101423.
3983. Prasad MPR, Rao BD, Kalpana K, Rao MV, Patil JV. Glycaemic index and glycaemic load of sorghum products. *J Sci Food Agric*. 2015;95(8):1626–30.
3984. Poquette NM, Gu X, Lee SO. Grain sorghum muffin reduces glucose and insulin responses in men. *Food Funct*. 2014;5(5):894–9.
3985. Honkura Y, Matsuo H, Murakami S, et al. NRF2 is a key target for prevention of noise-induced hearing loss by reducing oxidative damage of cochlea. *Sci Rep*. 2016;6:19329.
3986. Yang JR, Hidayat K, Chen CL, Li YH, Xu JY, Qin LQ. Body mass index, waist circumference, and risk of hearing loss: a meta-analysis

and systematic review of observational study. *Environ Health Prev Med*. 2020;25(1):25.

3987. Wang J, Puel JL. Presbycusis: an update on cochlear mechanisms and therapies. *J Clin Med*. 2020;9(1):E218.

3988. de Rivera C, Shukitt-Hale B, Joseph JA, Mendelson JR. The effects of antioxidants in the senescent auditory cortex. *Neurobiol Aging*. 2006;27(7):1035–44.

3989. Seidman MD, Khan MJ, Bai U, Shirwany N, Quirk WS. Biologic activity of mitochondrial metabolites on aging and age-related hearing loss. *Am J Otol*. 2000;21(2):161–7.

3990. Sanz-Fernández R, Sánchez-Rodriguez C, Granizo JJ, Durio-Calero E, Martín-Sanz E. Accuracy of auditory steady state and auditory brainstem responses to detect the preventive effect of polyphenols on age-related hearing loss in Sprague-Dawley rats. *Eur Arch Otorhinolaryngol*. 2016;273(2):341–7.

3991. Polanski JF, Cruz OL. Evaluation of antioxidant treatment in presbyacusis: prospective, placebo-controlled, double-blind, randomised trial. *J Laryngol Otol*. 2013;127(2):134–41.

3992. Durga J, Verhoef P, Anteunis LJC, Schouten E, Kok FJ. Effects of folic acid supplementation on hearing in older adults: a randomized, controlled trial. *Ann Intern Med*. 2007;146(1):1–9.

3993. Agricultural Research Service, United States Department of Agriculture. Lentils, mature seeds, cooked, boiled, without salt. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html?query=kale&utf8=%E2%9C%93&affiliate=usda&commit=Search#/food-details/172421/nutrients. Published April 1, 2019. Accessed April 21, 2022.

3994. Agricultural Research Service, United States Department of Agriculture. Edamame, frozen, prepared. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html#/food-details/168411/nutrients. Published April 1, 2019. Accessed February 21, 2023.

3995. Rodrigo L, Campos-Asensio C, Rodríguez MÁ, Crespo I, Olmedillas H. Role of nutrition in the development and prevention of age-related hearing loss: a scoping review. *J Formos Med Assoc*. 2021;120(1 Pt 1):107–20.

3996. Pillsbury HC. Hypertension, hyperlipoproteinemia, chronic noise exposure: is there synergism in cochlear pathology? *Laryngoscope*. 1986;96(10):1112–38.
3997. Sikora MA, Morizono T, Ward WD, Paparella MM, Leslie K. Diet-induced hyperlipidemia and auditory dysfunction. *Acta Oto-Laryngologica*. 1986;102(5–6):372–81.
3998. Momi SK, Wolber LE, Fabiane SM, MacGregor AJ, Williams FMK. Genetic and environmental factors in age-related hearing impairment. *Twin Res Hum Genet*. 2015;18(4):383–92.
3999. Gopinath B, Flood VM, Teber E, McMahon CM, Mitchell P. Dietary intake of cholesterol is positively associated and use of cholesterol-lowering medication is negatively associated with prevalent age-related hearing loss. *J Nutr*. 2011;141(7):1355–61.
4000. Erkan AF, Beriat GK, Ekici B, Doğan C, Kocatürk S, Töre HF. Link between angiographic extent and severity of coronary artery disease and degree of sensorineural hearing loss. *Herz*. 2015;40(3):481–6.
4001. Croll PH, Bos D, Vernooij MW, et al. Carotid atherosclerosis is associated with poorer hearing in older adults. *J Am Med Dir Assoc*. 2019;20(12):1617–22.e1.
4002. Fischer ME, Schubert CR, Nondahl DM, et al. Subclinical atherosclerosis and increased risk of hearing impairment. *Atherosclerosis*. 2015;238(2):344–9.
4003. Fischer ME, Schubert CR, Nondahl DM, et al. Subclinical atherosclerosis and increased risk of hearing impairment. *Atherosclerosis*. 2015;238(2):344–9.
4004. Erkan AF, Beriat GK, Ekici B, Doğan C, Kocatürk S, Töre HF. Link between angiographic extent and severity of coronary artery disease and degree of sensorineural hearing loss. *Herz*. 2015;40(3):481–6.
4005. Sikora MA, Morizono T, Ward WD, Paparella MM, Leslie K. Diet-induced hyperlipidemia and auditory dysfunction. *Acta Oto-Laryngologica*. 1986;102(5–6):372–81.
4006. Saito T, Sato K, Saito H. An experimental study of auditory dysfunction associated with hyperlipoproteinemia. *Arch Otorhinolaryngol*. 1986;243(4):242–5.
4007. Turpeinen O, Roine P, Pekkarinen M, et al. Effect on serum-cholesterol level of replacement of dietary milk fat by soybean oil.

Lancet. January 23, 1960;196–9.
4008. Hearing loss and coronary heart disease. *JAMA*. 1965;194(4):452
4009. Puga AM, Pajares MA, Varela-Moreiras G, Partearroyo T. Interplay between nutrition and hearing loss: state of art. *Nutrients*. 2018;11(1):E35.
4010. Hearing loss and coronary heart disease. *JAMA*. 1965;194(4):452.
4011. Rosen S, Olin P, Rosen HV. Dietary prevention of hearing loss. *Acta Oto-Laryngologica*. 1970;70(4):242–7.
4012. Nobus D. The madness of Princess Alice: Sigmund Freud, Ernst Simmel and Alice of Battenberg at Kurhaus Schloß Tegel. *Hist Psychiatry*. 2020;31(2):147–62.
4013. Brown-Séquard. Note on the effects produced on man by subcutaneous injections of a liquid obtained from the testicles of animals. *Lancet*. 1889;134(3438):105–7.
4014. Kahn A. Regaining lost youth: the controversial and colorful beginnings of hormone replacement therapy in aging. *J Gerontol A Biol Sci Med Sci*. 2005;60(2):142–7.
4015. Blue E. The strange career of Leo Stanley: remaking manhood and medicine at San Quentin State Penitentiary, 1913–1951. *Pac Hist Rev*. 2009;78(2):210–41.
4016. Perls TT. Anti-aging quackery: human growth hormone and tricks of the trade—more dangerous than ever. *J Gerontol A Biol Sci Med Sci*. 2004;59(7):682–91.
4017. Irwig MS, Fleseriu M, Jonklaas J, et al. Off-label use and misuse of testosterone, growth hormone, thyroid hormone, and adrenal supplements: risks and costs of a growing problem. *Endocr Pract*. 2020;26(3):340–53.
4018. Regelson W. Growth hormone use. *Science*. 1987;235(4784):14c-5c.
4019. Barkan AL. Growth hormone as an anti-aging therapy—do the benefits outweigh the risks? *Nat Clin Pract Endocrinol Metab*. 2007;3(7):508–9.
4020. Irwig MS, Fleseriu M, Jonklaas J, et al. Off-label use and misuse of testosterone, growth hormone, thyroid hormone, and adrenal supplements: risks and costs of a growing problem. *Endocr Pract*. 2020;26(3):340–53.

4021. Mullur RS. Making a difference in adrenal fatigue. *Endocr Pract*. 2018;24(12):1103–5.
4022. Cadegiani FA, Kater CE. Adrenal fatigue does not exist: a systematic review. *BMC Endocr Disord*. 2016;16(1):48.
4023. Nippoldt T. Mayo Clinic office visit. Adrenal fatigue: an interview with Todd Nippoldt, M.D. *Mayo Clin Womens Healthsource*. 2010;14(3):6.
4024. Chimote BN, Chimote NM. Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) in mammalian reproduction: known roles and novel paradigms. *Vitam Horm*. 2018;108:223–50.
4025. Kim MJ, Morley JE. The hormonal fountains of youth: myth or reality? *J Endocrinol Invest*. 2005;28(11 Suppl Proceedings):5–14.
4026. Peixoto C, Carrilho CG, Barros JA, et al. The effects of dehydroepiandrosterone on sexual function: a systematic review. *Climacteric*. 2017;20(2):129–37.
4027. Rutkowski K, Sowa P, Rutkowska-Talipska J, Kuryliszyn-Moskal A, Rutkowski R. Dehydroepiandrosterone (DHEA): hypes and hopes. *Drugs*. 2014;74(11):1195–207.
4028. ConsumerLab.com tests DHEA supplements, warns of differences in dose and price. ConsumerLab.com. https://www.consumerlab.com/news/dhea-dose-price/07–22–2015/. Published July 22, 2015. Accessed May 5, 2022.
4029. Celec P, Stárka L. Dehydroepiandrosterone—is the fountain of youth drying out? *Physiol Res*. 2003;52(4):397–407.
4030. Peixoto C, Carrilho CG, Barros JA, et al. The effects of dehydroepiandrosterone on sexual function: a systematic review. *Climacteric*. 2017;20(2):129–37.
4031. Wiser A, Gonen O, Ghetler Y, Shavit T, Berkovitz A, Shulman A. Addition of dehydroepiandrosterone (DHEA) for poor-responder patients before and during IVF treatment improves the pregnancy rate: a randomized prospective study. *Hum Reprod*. 2010;25(10):2496–500.
4032. Tartagni M, Cicinelli MV, Baldini D, et al. Dehydroepiandrosterone decreases the age-related decline of the in vitro fertilization outcome in women younger than 40 years old. *Reprod Biol Endocrinol*. 2015;13:18.

4033. Thompson RD, Carlson M. Liquid chromatographic determination of dehydroepiandrosterone (DHEA) in dietary supplement products. *J AOAC Int*. 2000;83(4):847–57.
4034. Trichopoulou A, Bamia C, Kalapothaki V, Spanos E, Naska A, Trichopoulos D. Dehydroepiandrosterone relations to dietary and lifestyle variables in a general population sample. *Ann Nutr Metab*. 2003;47(3–4):158–64.
4035. Remer T, Pietrzik K, Manz F. The short-term effect of dietary pectin on plasma levels and renal excretion of dehydroepiandrosterone sulfate. *Z Ernahrungswiss*. 1996;35(1):32–8.
4036. Remer T, Pietrzik K, Manz F. Short-term impact of a lactovegetarian diet on adrenocortical activity and adrenal androgens. *J Clin Endocrinol Metab*. 1998;83(6):2132–7.
4037. Hill P, Wynder EL, Garbaczewski L, Walker AR. Effect of diet on plasma and urinary hormones in South African black men with prostatic cancer. *Cancer Res*. 1982;42(9):3864–9.
4038. Hill P, Garbaczewski L, Helman P, Huskisson J, Sporangisa E, Wynder EL. Diet, lifestyle, and menstrual activity. *Am J Clin Nut*r. 1980;33(6):1192–8.
4039. Remer T, Pietrzik K, Manz F. Short-term impact of a lactovegetarian diet on adrenocortical activity and adrenal androgens. *J Clin Endocrinol Metab*. 1998;83(6):2132–7.
4040. Grande M, Borobio V, Jimenez JM, et al. Antral follicle count as a marker of ovarian biological age to reflect the background risk of fetal aneuploidy. *Hum Reprod*. 2014;29(6):1337–43.
4041. Bozdag G, Calis P, Zengin D, Tanacan A, Karahan S. Age related normogram for antral follicle count in general population and comparison with previous studies. *Eur J Obstet Gynecol Reprod Biol*. 2016;206:120–4.
4042. Souter I, Chiu YH, Batsis M, et al. The association of protein intake (amount and type) with ovarian antral follicle counts among infertile women: results from the EARTH prospective study cohort. *BJOG*. 2017;124(10):1547–55.
4043. Hartmann S, Lacorn M, Steinhart H. Natural occurrence of steroid hormones in food. *Food Chem (Oxf)*. 1998;62(1):7–20.

4044. Brinkman MT, Baglietto L, Krishnan K, et al. Consumption of animal products, their nutrient components and postmenopausal circulating steroid hormone concentrations. *Eur J Clin Nutr*. 2010;64(2):176–83.
4045. Andersson AM, Skakkebaek NE. Exposure to exogenous estrogens in food: possible impact on human development and health. *Eur J Endocrinol*. 1999;140(6):477–85.
4046. Souter I, Chiu YH, Batsis M, et al. The association of protein intake (amount and type) with ovarian antral follicle counts among infertile women: results from the EARTH prospective study cohort. *BJOG*. 2017;124(10):1547–55.
4047. Lumsden MA, Sassarini J. The evolution of the human menopause. *Climacteric*. 2019;22(2):111–6.
4048. National Center for Health Statistics. *Health, United States, 2010: With Special Feature on Death and Dying*. https://www.cdc.gov/nchs/data/hus/hus10.pdf. Published February 2011. Accessed May 5, 2022.
4049. Llarena N, Hine C. Reproductive longevity and aging: geroscience approaches to maintain long-term ovarian fitness. *J Gerontol A Biol Sci Med Sci*. 2021;76(9):1551–60.
4050. Gagnon A. Natural fertility and longevity. *Fertil Steril*. 2015;103(5):1109–16.
4051. Giri R, Vincent AJ. Prevalence and risk factors of premature ovarian insufficiency/early menopause. *Semin Reprod Med*. 2020;38(4–05):237–46.
4052. Stanford JL, Hartge P, Brinton LA, Hoover RN, Brookmeyer R. Factors influencing the age at natural menopause. *J Chronic Dis*. 1987;40(11):995–1002.
4053. Boutot ME, Purdue-Smithe A, Whitcomb BW, et al. Dietary protein intake and early menopause in the Nurses' Health Study II. *Am J Epidemiol*. 2018;187(2):270–7.
4054. Conway F. Menopause matters: attending to the vitality of older women. *J Women Aging*. 2020;32(5):489–90.
4055. Minkin MJ. Menopause: hormones, lifestyle, and optimizing aging. *Obstet Gynecol Clin North Am*. 2019;46(3):501–14.
4056. Johnson A, Roberts L, Elkins G. Complementary and alternative medicine for menopause. *J Evid Based Integr Med*.

2019;24:2515690X19829380.
4057. Minkin MJ. Menopause: hormones, lifestyle, and optimizing aging. *Obstet Gynecol Clin North Am*. 2019;46(3):501–14.
4058. Pirhadi R, Sinai Talaulikar V, Onwude J, Manyonda I. It is all in the name: the importance of correct terminology in hormone replacement therapy. *Post Reprod Health*. 2020;26(3):142–6.
4059. Hunter MM, Huang AJ, Wallhagen MI. "I'm going to stay young": belief in anti-aging efficacy of menopausal hormone therapy drives prolonged use despite medical risks. *PLoS One*. 2020;15(5):e0233703.
4060. Wilson RA, Wilson TA. The fate of the nontreated postmenopausal woman: a plea for the maintenance of adequate estrogen from puberty to the grave. *J Am Geriatr Soc*. 1963;11:347–62.
4061. Wilson RA, Wilson TA. The basic philosophy of estrogen maintenance. *J Am Geriatr Soc*.1972;20(11):521–3.
4062. Chew F, Wu X. Sources of information influencing the state-of-the-science gap in hormone replacement therapy usage. *PLoS One*. 2017;12(2):e0171189.
4063. Fugh-Berman A. The science of marketing: how pharmaceutical companies manipulated medical discourse on menopause. *Women's Reprod Health*. 2015;2(1):18–23.
4064. Rubinstein H. Defining what is normal at menopause: how women's and clinician's different understandings may lead to a lack of provision for those in most need. *Hum Fertil (Camb)*. 2014;17(3):218–22.
4065. Tatsioni A, Siontis GCM, Ioannidis JPA. Partisan perspectives in the medical literature: a study of high frequency editorialists favoring hormone replacement therapy. *J Gen Intern Med*. 2010;25(9):914–9.
4066. Rubinstein H. Defining what is normal at menopause: how women's and clinician's different understandings may lead to a lack of provision for those in most need. *Hum Fertil (Camb)*. 2014;17(3):218–22.
4067. Minkin MJ. Menopause: hormones, lifestyle, and optimizing aging. *Obstet Gynecol Clin North Am*. 2019;46(3):501–14.
4068. Verkooijen HM, Bouchardy C, Vinh-Hung V, Rapiti E, Hartman M. The incidence of breast cancer and changes in the use of hormone

replacement therapy: a review of the evidence. *Maturitas*. 2009;64(2):80–5.
4069. Auchincloss H, Haagensen CD. Cancer of the breast possibly induced by estrogenic substance. *JAMA*. 1940;114(16):1517–23.
4070. Anderson G, Cummings S, Freedman LS, et al. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19(1):61–109.
4071. Cummings SR. Evaluating the benefits and risks of postmenopausal hormone therapy. *Am J Med*. 1991;91(5B):14S-8S.
4072. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321–33.
4073. Marsden J. Hormone replacement therapy and female malignancy: what has the Million Women Study added to our knowledge? *J Fam Plann Reprod Health Care.* 2007;33(4):237–43.
4074. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291(14):1701–12.
4075. Fugh-Berman A, Pearson C. The overselling of hormone replacement therapy. *Pharmacotherapy*. 2002;22(9):1205–8.
4076. Katz A. Observations and advertising: controversies in the prescribing of hormone replacement therapy. *Health Care Women Int*. 2003;24(10):927–39.
4077. Majumdar SR, Almasi EA, Stafford RS. Promotion and prescribing of hormone therapy after report of harm by the Women's Health Initiative. *JAMA*. 2004;292(16):1983–8.
4078. Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med*. 2007;356(16):1670–4.
4079. Fugh-Berman A. The science of marketing: how pharmaceutical companies manipulated medical discourse on menopause. *Women's Reprod Health*. 2015;2(1):18–23.
4080. Roth JA, Etzioni R, Waters TM, et al. Economic return from the Women's Health Initiative estrogen plus progestin clinical trial: a

modeling study. *Ann Intern Med*. 2014;160(9):594–602.
4081. Majumdar SR, Almasi EA, Stafford RS. Promotion and prescribing of hormone therapy after report of harm by the Women's Health Initiative. *JAMA*. 2004;292(16):1983–8.
4082. Carstens AJ. HRT prescriptions linked to 25% of breast cancers in California. *S Afr Med J*. 2009;99(5):280.
4083. Fugh-Berman AJ. The haunting of medical journals: how ghostwriting sold "HRT." *PLoS Med*. 2010;7(9):e1000335.
4084. Fugh-Berman A, Scialli AR. Gynecologists and estrogen: an affair of the heart. *Perspect Biol Med*. 2006;49(1):115–30.
4085. Fugh-Berman AJ. The haunting of medical journals: how ghostwriting sold "HRT." *PLoS Med*. 2010;7(9):e1000335.
4086. Egilman AC, Kesselheim AS, Krumholz HM, Ross JS, Kim J, Kapczynski A. Confidentiality orders and public interest in drug and medical device litigation. *JAMA Intern Med*. 2020;180(2):292–9.
4087. Fugh-Berman A, Scialli AR. Gynecologists and estrogen: an affair of the heart. *Perspect Biol Med*. 2006;49(1):115–30.
4088. Tatsioni A, Siontis GCM, Ioannidis JPA. Partisan perspectives in the medical literature: a study of high frequency editorialists favoring hormone replacement therapy. *J Gen Intern Med*. 2010;25(9):914–9.
4089. Fugh-Berman A, Pearson C. The overselling of hormone replacement therapy. *Pharmacotherapy*. 2002;22(9):1205–8.
4090. Akesson A, Weismayer C, Newby PK, Wolk A. Combined effect of low-risk dietary and lifestyle behaviors in primary prevention of myocardial infarction in women. *Arch Intern Med*. 2007;167(19):2122–7.
4091. American Academy of Family Physicians. Clinical preventative service recommendation: hormone replacement therapy. https://www.aafp.org/family-physician/patient-care/clinical-recommendations/all-clinical-recommendations/hrt.html. Accessed Aug 2, 2022.
4092. Fick DM, Semla TP, Steinman M, et al. American Geriatrics Society 2019 updated AGS Beers criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67(4):674–94.
4093. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update.

J Am Coll Cardiol. 2011;57(12):1404–23.
4094. Grossman DC, Curry SJ, Owens DK, et al. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: US Preventive Services Task Force recommendation statement. *JAMA*. 2017;318(22):2224–33.
4095. ACOG Committee Opinion No. 565: Hormone therapy and heart disease. *Obstet Gynecol*. 2013;121(6):1407–10.
4096. Maclennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database Syst Rev*. 2004;(4):CD002978.
4097. Santoro N, Allshouse A, Neal-Perry G, et al. Longitudinal changes in menopausal symptoms comparing women randomized to low-dose oral conjugated estrogens or transdermal estradiol plus micronized progesterone versus placebo: the Kronos Early Estrogen Prevention Study (KEEPS). *Menopause*. 2017;24(3):238–46.
4098. Marjoribanks J, Farquhar CM, Roberts H, Lethaby A. Cochrane corner: long-term hormone therapy for perimenopausal and postmenopausal women. *Heart*. 2018;104(2):93–5.
4099. Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J. Long-term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev*. 2017;1:CD004143.
4100. Marjoribanks J, Farquhar CM, Roberts H, Lethaby A. Cochrane corner: long-term hormone therapy for perimenopausal and postmenopausal women. *Heart*. 2018;104(2):93–5.
4101. Manson JE, Bassuk SS, Kaunitz AM, Pinkerton JV. The Women's Health Initiative trials of menopausal hormone therapy: lessons learned. *Menopause*. 2020;27(8):918–28.
4102. Kim JJ, Chapman-Davis E. Role of progesterone in endometrial cancer. *Semin Reprod Med*. 2010;28(1):81–90.
4103. Maclennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database Syst Rev*. 2004;(4):CD002978.
4104. Marjoribanks J, Farquhar CM, Roberts H, Lethaby A. Cochrane corner: long-term hormone therapy for perimenopausal and postmenopausal women. *Heart*. 2018;104(2):93–5.

4105. Pinkerton JV. Hormone therapy for postmenopausal women. *N Engl J Med*. 2020;382(5):446–5.
4106. Chew F, Wu X. Sources of information influencing the state-of-the-science gap in hormone replacement therapy usage. *PLoS One*. 2017;12(2):e0171189.
4107. Bhavnani BR, Stanczyk FZ. Pharmacology of conjugated equine estrogens: efficacy, safety and mechanism of action. *J Steroid Biochem Mol Biol*. 2014;142:16–29.
4108. ClinCalc DrugStats database. The top 300 of 2019. ClinCalc.com. https://clincalc.com/DrugStats/Top300Drugs.aspx. Updated September 12, 2021. Accessed May 5, 2022.
4109. Kling J. The strange case of Premarin. *Mod Drug Discov*. 2000;3(8):46–52.
4110. Pinkerton JV. Hormone therapy for postmenopausal women. *N Engl J Med*. 2020;382(5):446–5.
4111. ACOG Practice Bulletin No. 141: management of menopausal symptoms. *Obstet Gynecol*. 2014;123(1):202–16.
4112. Pinkerton JV. Hormone therapy for postmenopausal women. *N Engl J Med*. 2020;382(5):446–5.
4113. Brawley OW, O'Regan RM. Breast cancer screening: time for rational discourse. *Cancer*. 2014;120(18):2800–2.
4114. Biller-Andorno N, Jüni P. Abolishing mammography screening programs? A view from the Swiss Medical Board. *N Engl J Med*. 2014;370(21):1965–7.
4115. Nelson AL. Controversies regarding mammography, breast self-examination, and clinical breast examination. *Obstet Gynecol Clin North Am*. 2013;40(3):413–27.
4116. Loh KP, Stefan MS, Friderici J, et al. Healthcare professionals' perceptions and knowledge of the USPSTF guidelines on breast self-examination. *South Med J*. 2015;108(8):459–62.
4117. Welch HG. Screening mammography—a long run for a short slide? *N Engl J Med*. 2010;363(13):1276–8.
4118. Gigerenzer G. Women's perception of the benefit of breast cancer screening. *Maturitas*. 2010;67(1):5–6.
4119. Atkins CD. Potential hazards of mammography. *J Clin Oncol*. 2007;25(5):604.

4120. Barratt A. Overdiagnosis in mammography screening: a 45 year journey from shadowy idea to acknowledged reality. *BMJ*. 2015;350:h867.
4121. Gøtzsche PC, Jørgensen KJ, Zahl PH, Mæhlen J. Why mammography screening has not lived up to expectations from the randomised trials. *Cancer Causes Control*. 2012;23(1):15–21.
4122. Pace LE, Keating NL. A systematic assessment of benefits and risks to guide breast cancer screening decisions. *JAMA*. 2014;311(13):1327–35.
4123. Gøtzsche PC, Jørgensen KJ, Zahl PH, Mæhlen J. Why mammography screening has not lived up to expectations from the randomised trials. *Cancer Causes Control*. 2012;23(1):15–21.
4124. Sohn E. Screening: don't look now. *Nature*. 2015;527(7578):S118–9.
4125. Gotzsche P. Commentary: screening: a seductive paradigm that has generally failed us. *Int J Epidemiol*. 2015;44(1):278–80.
4126. Derbyshire SWG. Second opinion: doctors, diseases and decisions in modern medicine. *BMJ*. 2003;327(7411):399.
4127. Jørgensen KJ, Gøtzsche PC. The background review for the USPSTF recommendation on screening for breast cancer. *Ann Intern Med*. 2010;152(8):538; author reply 538–9.
4128. Domenighetti G, D'Avanzo B, Egger M, et al. Women's perception of the benefits of mammography screening: population-based survey in four countries. *Int J Epidemiol*. 2003;32(5):816–21.
4129. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. *Circulation*. 2021;143(8):e254–743.
4130. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer stat facts: female breast cancer. https://seer.cancer.gov/statfacts/html/breast.html. Accessed May 5, 2022.
4131. Parise CA, Caggiano V. Breast cancer survival defined by the ER/PR/HER2 subtypes and a surrogate classification according to tumor grade and immunohistochemical biomarkers. *J Cancer Epidemiol*. 2014;2014:469251.
4132. Romanos-Nanclares A, Willett WC, Rosner BA, et al. Healthful and unhealthful plant-based diets and risk of breast cancer in U.S.

women: results from the Nurses' Health Studies. *Cancer Epidemiol Biomarkers Prev*. 2021;30(10):1921–31.

4133. Link LB, Canchola AJ, Bernstein L, et al. Dietary patterns and breast cancer risk in the California Teachers Study cohort. *Am J Clin Nutr*. 2013;98(6):1524–32.

4134. Hankinson SE. Circulating levels of sex steroids and prolactin in premenopausal women and risk of breast cancer. In: Li JJ, Li SA, Mohla S, Rochefort H, Maudelonde T, eds. *Hormonal Carcinogenesis V*. Springer; 2008:161–9.

4135. Key T, Appleby P, Barnes I, et al. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst*. 2002;94(8):606–16.

4136. Hankinson SE. Circulating levels of sex steroids and prolactin in premenopausal women and risk of breast cancer. In: Li JJ, Li SA, Mohla S, Rochefort H, Maudelonde T, eds. *Hormonal Carcinogenesis V*. Springer; 2008:161–9.

4137. Cleary MP, Grossmann ME. Minireview: obesity and breast cancer: the estrogen connection. *Endocrinology*. 2009;150(6):2537–42.

4138. Shultz TD, Leklem JE. Nutrient intake and hormonal status of premenopausal vegetarian Seventh-day Adventists and premenopausal nonvegetarians. *Nutr Cancer*. 1983;4(4):247–59.

4139. Barbosa JC, Shultz TD, Filley SJ, Nieman DC. The relationship among adiposity, diet, and hormone concentrations in vegetarian and nonvegetarian postmenopausal women. *Am J Clin Nutr*. 1990;51(5):798–803.

4140. Shultz TD, Howie BJ. In vitro binding of steroid hormones by natural and purified fibers. *Nutr Cancer*. 1986;8(2):141–7.

4141. Goldin BR, Woods MN, Spiegelman DL, et al. The effect of dietary fat and fiber on serum estrogen concentrations in premenopausal women under controlled dietary conditions. *Cancer*. 1994;74(3 Suppl):1125–31.

4142. Jew S, AbuMweis SS, Jones PJH. Evolution of the human diet: linking our ancestral diet to modern functional foods as a means of chronic disease prevention. *J Med Food*. 2009;12(5):925–34.

4143. Goldin BR, Adlercreutz H, Dwyer JT, Swenson L, Warram JH, Gorbach SL. Effect of diet on excretion of estrogens in pre- and

postmenopausal women. *Cancer Res*. 1981;41(9 Pt 2):3771–3.
4144. Goldin BR, Adlercreutz H, Gorbach SL, et al. Estrogen excretion patterns and plasma levels in vegetarian and omnivorous women. *N Engl J Med*. 1982;307(25):1542–7.
4145. Beezhold B, Radnitz C, McGrath RE, Feldman A. Vegans report less bothersome vasomotor and physical menopausal symptoms than omnivores. *Maturitas*. 2018;112:12–7.
4146. Beezhold B, Radnitz C, McGrath RE, Feldman A. Vegans report less bothersome vasomotor and physical menopausal symptoms than omnivores. *Maturitas*. 2018;112:12–7.
4147. Noll PRES, Campos CAS, Leone C, et al. Dietary intake and menopausal symptoms in postmenopausal women: a systematic review. *Climacteric*. 2021;24(2):128–38.
4148. Cagnacci A, Cannoletta M, Palma F, Bellafronte M, Romani C, Palmieri B. Relation between oxidative stress and climacteric symptoms in early postmenopausal women. *Climacteric*. 2015;18(4):631–6.
4149. Aslani Z, Abshirini M, Heidari-Beni M, et al. Dietary inflammatory index and dietary energy density are associated with menopausal symptoms in postmenopausal women: a cross-sectional study. *Menopause*. 2020;27(5):568–78.
4150. Minkin MJ. Menopause: hormones, lifestyle, and optimizing aging. *Obstet Gynecol Clin North Am*. 2019;46(3):501–14.
4151. Woyka J. Consensus statement for non-hormonal-based treatments for menopausal symptoms. *Post Reprod Health*. 2017;23(2):71–5.
4152. Prentice RL, Howard BV, Van Horn L, et al. Nutritional epidemiology and the Women's Health Initiative: a review. *Am J Clin Nutr*. 2021;113(5):1083–92.
4153. Patterson RE, Kristal A, Rodabough R, et al. Changes in food sources of dietary fat in response to an intensive low-fat dietary intervention: early results from the Women's Health Initiative. *J Am Diet Assoc*. 2003;103(4):454–60.
4154. Patterson RE, Prentice RL, Beresford S, et al. Dietary adherence in the Women's Health Initiative dietary modification trial. *J Am Diet Assoc*. 2004;104(4):654–8.

4155. Kroenke CH, Caan BJ, Stefanick ML, et al. Effects of a dietary intervention and weight change on vasomotor symptoms in the Women's Health Initiative. *Menopause*. 2012;19(9):980–8.
4156. Rotolo O, Zinzi I, Veronese N, et al. Women in LOVe: lacto-ovo-vegetarian diet rich in omega-3 improves vasomotor symptoms in postmenopausal women. An exploratory randomized controlled trial. *Endocr Metab Immune Disord Drug Targets*. 2019;19(8):1232–9.
4157. Cetisli NE, Saruhan A, Kivcak B. The effects of flaxseed on menopausal symptoms and quality of life. *Holist Nurs Pract*. 2015;29(3):151–7.
4158. Messina M. Soy and health update: evaluation of the clinical and epidemiologic literature. *Nutrients*. 2016;8(12):E754.
4159. Thomas AJ, Ismail R, Taylor-Swanson L, et al. Effects of isoflavones and amino acid therapies for hot flashes and co-occurring symptoms during the menopausal transition and early postmenopause: a systematic review. *Maturitas*. 2014;78(4):263–76.
4160. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med*. 2015;175(4):531–9.
4161. Avis NE, Kaufert PA, Lock M, McKinlay SM, Vass K. The evolution of menopausal symptoms. *Baillieres Clin Endocrinol Metab*. 1993;7(1):17–32.
4162. Thomas AJ, Ismail R, Taylor-Swanson L, et al. Effects of isoflavones and amino acid therapies for hot flashes and co-occurring symptoms during the menopausal transition and early postmenopause: a systematic review. *Maturitas*. 2014;78(4):263–76.
4163. Lock M. Contested meanings of the menopause. *Lancet*. 1991;337(8752):1270–2.
4164. Avis NE, Kaufert PA, Lock M, McKinlay SM, Vass K. The evolution of menopausal symptoms. *Baillieres Clin Endocrinol Metab*. 1993;7(1):17–32.
4165. Lock M. Contested meanings of the menopause. *Lancet*. 1991;337(8752):1270–2.
4166. Lock M. Ambiguities of aging: Japanese experience and perceptions of menopause. *Cult Med Psychiatry*. 1986;10(1):23–46.

4167. Avis NE, Stellato R, Crawford S, et al. Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. *Soc Sci Med*. 2001;52(3):345–56.
4168. Taku K, Melby MK, Kronenberg F, Kurzer MS, Messina M. Extracted or synthesized soybean isoflavones reduce menopausal hot flash frequency and severity: systematic review and meta-analysis of randomized controlled trials. *Menopause*. 2012;19(7):776–90.
4169. Ghazanfarpour M, Sadeghi R, Roudsari RL. The application of soy isoflavones for subjective symptoms and objective signs of vaginal atrophy in menopause: a systematic review of randomised controlled trials. *J Obstet Gynaecol*. 2016;36(2):160–71.
4170. Lambert MNT, Hu LM, Jeppesen PB. A systematic review and meta-analysis of the effects of isoflavone formulations against estrogen-deficient bone resorption in peri- and postmenopausal women. *Am J Clin Nutr*. 2017;106(3):801–11.
4171. Su BYW, Tung TH, Chien WH. Effects of phytoestrogens on depressive symptoms in climacteric women: a meta-analysis of randomized controlled trials. *J Altern Complement Med*. 2018;24(8):850–1.
4172. Cheng PF, Chen JJ, Zhou XY, et al. Do soy isoflavones improve cognitive function in postmenopausal women? A meta-analysis. *Menopause*. 2015;22(2):198–206.
4173. Schmidt M, Arjomand-Wölkart K, Birkhäuser MH, et al. Consensus: soy isoflavones as a first-line approach to the treatment of menopausal vasomotor complaints. *Gynecol Endocrinol*. 2016;32(6):427–30.
4174. Welty FK, Lee KS, Lew NS, Nasca M, Zhou JR. The association between soy nut consumption and decreased menopausal symptoms. *J Womens Health (Larchmt)*. 2007;16(3):361–9.
4175. Barnard ND, Kahleova H, Holtz DN, et al. A dietary intervention for vasomotor symptoms of menopause: a randomized, controlled trial. *Menopause*. 2023;30(1):80–7.
4176. Barnard ND, Kahleova H, Holtz DN, et al. The Women's Study for the Alleviation of Vasomotor Symptoms (WAVS): a randomized, controlled trial of a plant-based diet and whole soybeans for postmenopausal women. *Menopause*. 2021;28(10):1150–6.

4177. Buja A, Pierbon M, Lago L, Grotto G, Baldo V. Breast cancer primary prevention and diet: an umbrella review. *Int J Environ Res Public Health*. 2020;17(13):E4731.
4178. Messina M, Messina VL. Exploring the soyfood controversy. *Nutr Today*. 2013;48(2):68.
4179. Nachvak SM, Moradi S, Anjom-Shoae J, et al. Soy, soy isoflavones, and protein intake in relation to mortality from all causes, cancers, and cardiovascular diseases: a systematic review and dose-response meta-analysis of prospective cohort studies. *J Acad Nutr Diet*. 2019;119(9):1483–1500.e17.
4180. Kelsey JL. A review of the epidemiology of human breast cancer. *Epidemiol Rev*. 1979;1:74–109.
4181. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7–33.
4182. Fraser GE, Jaceldo-Siegl K, Orlich M, Mashchak A, Sirirat R, Knutsen S. Dairy, soy, and risk of breast cancer: those confounded milks. *Int J Epidemiol*. 2020;49(5):1526–37.
4183. Shu XO, Zheng Y, Cai H, et al. Soy food intake and breast cancer survival. *JAMA*. 2009;302(22):2437–43.
4184. Guha N, Kwan ML, Quesenberry CP, Weltzien EK, Castillo AL, Caan BJ. Soy isoflavones and risk of cancer recurrence in a cohort of breast cancer survivors: the Life After Cancer Epidemiology study. *Breast Cancer Res Treat*. 2009;118(2):395–405.
4185. Kang X, Zhang Q, Wang S, Huang X, Jin S. Effect of soy isoflavones on breast cancer recurrence and death for patients receiving adjuvant endocrine therapy. *CMAJ*. 2010;182(17):1857–62.
4186. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012;62(4):243–74.
4187. Caan BJ, Natarajan L, Parker B, et al. Soy food consumption and breast cancer prognosis. *Cancer Epidemiol Biomarkers Prev*. 2011;20(5):854–8.
4188. Zhang YF, Kang HB, Li BL, Zhang RM. Positive effects of soy isoflavone food on survival of breast cancer patients in China. *Asian Pac J Cancer* Prev. 2012;13(2):479–82.

4189. Chi F, Wu R, Zeng YC, Xing R, Liu Y, Xu ZG. Post-diagnosis soy food intake and breast cancer survival: a meta-analysis of cohort studies. *Asian Pac J Cancer Prev*. 2013;14(4):2407–12.
4190. Chi F, Wu R, Zeng YC, Xing R, Liu Y, Xu ZG. Post-diagnosis soy food intake and breast cancer survival: a meta-analysis of cohort studies. *Asian Pac J Cancer Prev*. 2013;14(4):2407–12.
4191. Kang HB, Zhang YF, Yang JD, Lu KL. Study on soy isoflavone consumption and risk of breast cancer and survival. *Asian Pac J Cancer Prev*. 2012;13(3):995–8.
4192. Buck K, Zaineddin AK, Vrieling A, Linseisen J, Chang-Claude J. Meta-analyses of lignans and enterolignans in relation to breast cancer risk. *Am J Clin Nutr*. 2010;92(1):141–53.
4193. McCann SE, Thompson LU, Nie J, et al. Dietary lignan intakes in relation to survival among women with breast cancer: the Western New York Exposures and Breast Cancer (WEB) Study. *Breast Cancer Res Treat*. 2010;122(1):229–35.
4194. Thompson LU, Chen JM, Li T, Strasser-Weippl K, Goss PE. Dietary flaxseed alters tumor biological markers in postmenopausal breast cancer. *Clin Cancer Res*. 2005;11(10):3828–35.
4195. Calado A, Neves PM, Santos T, Ravasco P. The effect of flaxseed in breast cancer: a literature review. *Front Nutr*. 2018;5:4.
4196. Hadi A, Askarpour M, Salamat S, Ghaedi E, Symonds ME, Miraghajani M. Effect of flaxseed supplementation on lipid profile: an updated systematic review and dose-response meta-analysis of sixty-two randomized controlled trials. *Pharmacol Res*. 2020;152:104622.
4197. Khandouzi N, Zahedmehr A, Mohammadzadeh A, Sanati HR, Nasrollahzadeh J. Effect of flaxseed consumption on flow-mediated dilation and inflammatory biomarkers in patients with coronary artery disease: a randomized controlled trial. *Eur J Clin Nutr*. 2019;73(2):258–65.
4198. Ursoniu S, Sahebkar A, Andrica F, et al. Effects of flaxseed supplements on blood pressure: a systematic review and meta-analysis of controlled clinical trial. *Clin Nutr*. 2016;35(3):615–25.
4199. Khandouzi N, Zahedmehr A, Mohammadzadeh A, Sanati HR, Nasrollahzadeh J. Effect of flaxseed consumption on flow-mediated

dilation and inflammatory biomarkers in patients with coronary artery disease: a randomized controlled trial. *Eur J Clin Nutr*. 2019;73(2):258–65.

4200. Hadi A, Askarpour M, Ziaei R, Venkatakrishnan K, Ghaedi E, Ghavami A. Impact of flaxseed supplementation on plasma lipoprotein(A) concentrations: a systematic review and meta-analysis of randomized controlled trials. *Phytother Res*. 2020;34(7):1599–608.

4201. Almehmadi A, Lightowler H, Chohan M, Clegg ME. The effect of a split portion of flaxseed on 24-h blood glucose response. *Eur J Nutr*. 2021;60(3):1363–73.

4202. Ghazanfarpour M, Sadeghi R, Latifnejad Roudsari R, et al. Effects of flaxseed and *Hypericum perforatum* on hot flash, vaginal atrophy and estrogen-dependent cancers in menopausal women: a systematic review and meta-analysis. *Avicenna J Phytomed*. 2016;6(3):273–83.

4203. Franco OH, Chowdhury R, Troup J, et al. Use of plant-based therapies and menopausal symptoms: a systematic review and meta-analysis. *JAMA*. 2016;315(23):2554–63.

4204. Milligan SR, Kalita JC, Heyerick A, Rong H, De Cooman L, De Keukeleire D. Identification of a potent phytoestrogen in hops (*Humulus lupulus* L.) and beer. *J Clin Endocrinol Metab.* 1999;84(6):2249–52.

4205. Milligan S, Kalita J, Pocock V, et al. Oestrogenic activity of the hop phyto-oestrogen, 8-prenylnaringenin. *Reproduction*. 2002;123(2):235–42.

4206. Bradbury RB, White DE. 761. The chemistry of subterranean clover. Part I. Isolation of formononetin and genistein. *J Chem Soc*. 1951; (0):3447–9.

4207. Gavaler JS, Rosenblum ER, Deal SR, Bowie BT. The phytoestrogen congeners of alcoholic beverages: current status. *Proc Soc Exp Biol Med*. 1995;208(1):98–102.

4208. Pedrera-Zamorano JD, Lavado-Garcia JM, Roncero-Martin R, Calderon-Garcia JF, Rodriguez-Dominguez T, Canal-Macias ML. Effect of beer drinking on ultrasound bone mass in women. *Nutrition*. 2009;25(10):1057–63.

4209. Aghamiri V, Mirghafourvand M, Mohammad-Alizadeh-Charandabi S, Nazemiyeh H. The effect of Hop (*Humulus lupulus* L.) on early

menopausal symptoms and hot flashes: a randomized placebo-controlled trial. *Complement Ther Clin Pract*. 2016;23:130–5.

4210. Schaefer O, Hümpel M, Fritzemeier KH, Bohlmann R, Schleuning WD. 8-Prenyl naringenin is a potent ERα selective phytoestrogen present in hops and beer. *J Steroid Biochem Mol Biol*. 2003;84(2–3):359–60.

4211. Fugh-Berman A. "Bust enhancing" herbal products. *Obstet Gynecol*. 2003;101(6):1345–9.

4212. Lê MG, Hill C, Kramar A, Flamanti R. Alcoholic beverage consumption and breast cancer in a French case-control study. *Am J Epidemiol*. 1984;120(3):350–7.

4213. Salehi-Pourmehr H, Ostadrahimi A, Ebrahimpour-Mirzarezaei M, Farshbaf-Khalili A. Does aromatherapy with lavender affect physical and psychological symptoms of menopausal women? A systematic review and meta-analysis. *Complement Ther Clin Pract*. 2020;39:101150.

4214. Kazemzadeh R, Nikjou R, Rostamnegad M, Norouzi H. Effect of lavender aromatherapy on menopause hot flushing: a crossover randomized clinical trial. *J Chin Med Assoc*. 2016;79(9):489–92.

4215. Nikjou R, Kazemzadeh R, Asadzadeh F, Fathi R, Mostafazadeh F. The effect of lavender aromatherapy on the symptoms of menopause. *J Natl Med Assoc*. 2018;110(3):265–9.

4216. Dos Reis Lucena L, Dos Santos-Junior JG, Tufik S, Hachul H. Lavender essential oil on postmenopausal women with insomnia: double-blind randomized trial. *Complement Ther Med*. 2021;59:102726.

4217. Donelli D, Antonelli M, Bellinazzi C, Gensini GF, Firenzuoli F. Effects of lavender on anxiety: a systematic review and meta-analysis. *Phytomedicine*. 2019;65:153099.

4218. Farshbaf-Khalili A, Kamalifard M, Namadian M. Comparison of the effect of lavender and bitter orange on anxiety in postmenopausal women: a triple-blind, randomized, controlled clinical trial. *Complement Ther Clin Pract*. 2018;31:132–8.

4219. Kamalifard M, Farshbaf-Khalili A, Namadian M, Ranjbar Y, Herizchi S. Comparison of the effect of lavender and bitter orange on sleep

quality in postmenopausal women: a triple-blind, randomized, controlled clinical trial. *Women Health*. 2018;58(8):851–65.

4220. Latiff LA, Parhizkar S, Dollah MA, Hassan STS. Alternative supplement for enhancement of reproductive health and metabolic profile among perimenopausal women: a novel role of *Nigella sativa*. *Iran J Basic Med Sci*. 2014;17(12):980–5.

4221. Rahimi Kian F, Bekhradi R, Rahimi R, Golzareh P, Mehran A. Evaluating the effect of fennel soft capsules on the quality of life and its different aspects in menopausal women: a randomized clinical trial. *Nurs Pract Today*. 2017;4(2):87–95.

4222. Khan TM, Wu DBC, Dolzhenko AV. Effectiveness of fenugreek as a galactagogue: a network meta-analysis. *Phytother Res*. 2018;32(3):402–12.

4223. Hakimi S, Charandabi SMA, Shadbad MRS, et al. Effect of Fenugreek seed on early menopausal symptoms. *Pharm Sci*. 2005; (2):83–90.

4224. Tariq SH, Haren MT, Kim MJ, Morley JE. Andropause: is the emperor wearing any clothes? *Rev Endocr Metab Disord*. 2005;6(2):77–84.

4225. Saad F, Gooren LJ. Late onset hypogonadism of men is not equivalent to the menopause. *Maturitas*. 2014;79(1):52–7.

4226. Tariq SH, Haren MT, Kim MJ, Morley JE. Andropause: is the emperor wearing any clothes? *Rev Endocr Metab Disord*. 2005;6(2):77–84.

4227. Swee DS, Gan EH. Late-onset hypogonadism as primary testicular failure. *Front Endocrinol (Lausanne)*. 2019;10:372.

4228. Vitry AI, Mintzes B. Disease mongering and low testosterone in men: the tale of two regulatory failures. *Med J Aust*. 2012;196(10):619–21.

4229. Schwartz LM, Woloshin S. Low “T” as in “template”: how to sell disease. *JAMA Intern Med*. 2013;173(15):1460–2.

4230. Perls T, Handelsman DJ. Disease mongering of age-associated declines in testosterone and growth hormone levels. *J Am Geriatr Soc*. 2015;63(4):809–11.

4231. Eder S. Many players in the concerto of sex. *Science*. 2007;315(5817):1370.

4232. Shomali ME. The use of anti-aging hormones. Melatonin, growth hormone, testosterone, and dehydroepiandrosterone: consumer enthusiasm for unproven therapies. *Md Med J*. 1997;46(4):181–6.
4233. Rengachary SS, Colen C, Guthikonda M. Charles-Édouard Brown-Séquard: an eccentric genius. *Neurosurgery*. 2008;62(4):954–64.
4234. Kim MJ, Morley JE. The hormonal fountains of youth: myth or reality? *J Endocrinol Invest*. 2005;28(11 Suppl Proceedings):5–14.
4235. Swee DS, Gan EH. Late-onset hypogonadism as primary testicular failure. *Front Endocrinol (Lausanne)*. 2019;10:372.
4236. Sartorius G, Spasevska S, Idan A, et al. Serum testosterone, dihydrotestosterone and estradiol concentrations in older men self-reporting very good health: the healthy man study. *Clin Endocrinol (Oxf)*. 2012;77(5):755–63.
4237. Saad F, Gooren LJ. Late onset hypogonadism of men is not equivalent to the menopause. *Maturitas*. 2014;79(1):52–7.
4238. Busnelli A, Somigliana E, Vercellini P. 'Forever young'—testosterone replacement therapy: a blockbuster drug despite flabby evidence and broken promises. *Human Reproduction*. 2017;32(4):719–24.
4239. Handelsman DJ. Irrational exuberance in testosterone prescribing: when will the bubble burst? *Med Care*. 2015;53(9):743–5.
4240. Perls T, Handelsman DJ. Disease mongering of age-associated declines in testosterone and growth hormone levels. *J Am Geriatr Soc*. 2015;63(4):809–11.
4241. Vitry AI, Mintzes B. Disease mongering and low testosterone in men: the tale of two regulatory failures. *Med J Aust*. 2012;196(10):619–21.
4242. Mintzes B. The marketing of testosterone treatments for age-related low testosterone or "Low T." *Curr Opin Endocrinol Diabetes Obes*. 2018;25(3):224–30.
4243. Morley JE, Perry HM III, Kevorkian RT, Patrick P. Comparison of screening questionnaires for the diagnosis of hypogonadism. *Maturitas*. 2006;53(4):424–9.
4244. Vitry AI, Mintzes B. Disease mongering and low testosterone in men: the tale of two regulatory failures. *Med J Aust*. 2012;196(10):619–21.
4245. Dunn M, Mulrooney KJ, Forlini C, van de Ven K, Underwood M. The pharmaceuticalisation of "healthy" ageing: testosterone enhancement for longevity. *Int J Drug Policy*. 2021;95:103159.

4246. Fugh-Berman A, Hogenmiller A. CME stands for commercial medical education: and ACCME still won't address the issue. *J Med Ethics*. 2016;42(3):172–3.
4247. Handelsman DJ. Irrational exuberance in testosterone prescribing: when will the bubble burst? *Med Care*. 2015;53(9):743–5.
4248. Shores MM, Matsumoto AM. Testosterone, aging and survival: biomarker or deficiency. *Curr Opin Endocrinol Diabetes Obes*. 2014;21(3):209–16.
4249. Perls T, Handelsman DJ. Disease mongering of age-associated declines in testosterone and growth hormone levels. *J Am Geriatr Soc*. 2015;63(4):809–11.
4250. Al-Sharefi A, Quinton R. Current national and international guidelines for the management of male hypogonadism: helping clinicians to navigate variation in diagnostic criteria and treatment recommendations. *Endocrinol Metab (Seoul)*. 2020;35(3):526–40.
4251. Mok SF, Fennell C, Savkovic S, et al. Testosterone for androgen deficiency–like symptoms in men without pathologic hypogonadism: a randomized, placebo-controlled cross-over with masked choice extension clinical trial. *J Gerontol A Biol Sci Med Sci*. 2020;75(9):1723–31.
4252. Bandari J, Ayyash OM, Emery SL, Wessel CB, Davies BJ. Marketing and testosterone treatment in the USA: a systematic review. *Eur Urol Focus*. 2017;3(4–5):395–402.
4253. Huo S, Scialli AR, McGarvey S, et al. Treatment of men for "low testosterone": a systematic review. *PLoS One*. 2016;11(9):e0162480.
4254. Bandari J, Ayyash OM, Emery SL, Wessel CB, Davies BJ. Marketing and testosterone treatment in the USA: a systematic review. *Eur Urol Focus*. 2017;3(4–5):395–402.
4255. Irwig MS, Fleseriu M, Jonklaas J, et al. Off-label use and misuse of testosterone, growth hormone, thyroid hormone, and adrenal supplements: risks and costs of a growing problem. *Endocr Pract*. 2020;26(3):340–53.
4256. Wu FCW, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med*. 2010;363(2):123–35.

4257. Miner M, Barkin J, Rosenberg MT. Testosterone deficiency: myth, facts, and controversy. *Can J Urol*. 2014;21(Suppl 2):39–54.
4258. Salter CA, Mulhall JP. Guideline of guidelines: testosterone therapy for testosterone deficiency. *BJU Int*. 2019;124(5):722–9.
4259. Grossmann M. Serum testosterone concentrations in older men: one size does not fit all. *J Clin Endocrinol Metab*. 2020;105(8):dgaa400.
4260. Giagulli VA, Castellana M, Lisco G, Triggiani V. Critical evaluation of different available guidelines for late-onset hypogonadism. *Andrology*. 2020;8(6):1628–41.
4261. Bandari J, Ayyash OM, Emery SL, Wessel CB, Davies BJ. Marketing and testosterone treatment in the USA: a systematic review. *Eur Urol Focus*. 2017;3(4–5):395–402.
4262. Fugh-Berman A. Treating aging with testosterone. *Am Fam Physician*. 2017;96(7):428–30.
4263. The truth about testosterone replacement therapy. Fountain of youth —or harbinger of health woes? *Johns Hopkins Med Lett Health After 50*. 2014;29(5):1–2.
4264. Sansone A, Sansone M, Lenzi A, Romanelli F. Testosterone replacement therapy: the emperor's new clothes. *Rejuvenation Res*. 2017;20(1):9–14.
4265. Layton JB, Li D, Meier CR, et al. Testosterone lab testing and initiation in the United Kingdom and the United States, 2000 to 2011. *J Clin Endocrinol Metab*. 2014;99(3):835–42.
4266. Bandari J, Ayyash OM, Emery SL, Wessel CB, Davies BJ. Marketing and testosterone treatment in the USA: a systematic review. *Eur Urol Focus*. 2017;3(4–5):395–402.
4267. Busnelli A, Somigliana E, Vercellini P. 'Forever young'—testosterone replacement therapy: a blockbuster drug despite flabby evidence and broken promises. *Human Reproduction*. 2017;32(4):719–24.
4268. Tariq SH, Haren MT, Kim MJ, Morley JE. Andropause: is the emperor wearing any clothes? *Rev Endocr Metab Disord*. 2005;6(2):77–84.
4269. Mok SF, Fennell C, Savkovic S, et al. Testosterone for androgen deficiency–like symptoms in men without pathologic hypogonadism: a randomized, placebo-controlled cross-over with masked choice

extension clinical trial. *J Gerontol A Biol Sci Med Sci*. 2020;75(9):1723–31.
4270. Fox CA, Ismail AA, Love DN, Kirkham KE, Loraine JA. Studies on the relationship between plasma testosterone levels and human sexual activity. *J Endocrinol*. 1972;52(1):51–8.
4271. Effects of sexual activity on beard growth in man. *Nature*. 1970;226(5248):869–70.
4272. Jannini EA, Screponi E, Carosa E, et al. Lack of sexual activity from erectile dysfunction is associated with a reversible reduction in serum testosterone. *Int J Androl*. 1999;22(6):385–92.
4273. Dabbs JM, Mohammed S. Male and female salivary testosterone concentrations before and after sexual activity. *Physiol Behav*. 1992;52(1):195–7.
4274. Mok SF, Fennell C, Savkovic S, et al. Testosterone for androgen deficiency–like symptoms in men without pathologic hypogonadism: a randomized, placebo-controlled cross-over with masked choice extension clinical trial. *J Gerontol A Biol Sci Med Sci*. 2020;75(9):1723–31.
4275. Handelsman DJ. Testosterone and male aging: faltering hope for rejuvenation. *JAMA*. 2017;317(7):699–701.
4276. Corona G, Guaraldi F, Rastrelli G, Sforza A, Maggi M. Testosterone deficiency and risk of cognitive disorders in aging males. *World J Mens Health*. 2021;39(1):9–18.
4277. Zhang Z, Kang D, Li H. Testosterone and cognitive impairment or dementia in middle-aged or aging males: causation and intervention, a systematic review and meta-analysis. *J Geriatr Psychiatry Neurol*. 2021;34(5):405–17.
4278. Sari Motlagh R, Quhal F, Mori K, et al. The risk of new onset dementia and/or Alzheimer disease among patients with prostate cancer treated with androgen deprivation therapy: a systematic review and meta-analysis. *J Urol*. 2021;205(1):60–7.
4279. Resnick SM, Matsumoto AM, Stephens-Shields AJ, et al. Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. *JAMA*. 2017;317(7):717–27.

4280. Corona G, Guaraldi F, Rastrelli G, Sforza A, Maggi M. Testosterone deficiency and risk of cognitive disorders in aging males. *World J Mens Health*. 2021;39(1):9–18.
4281. Handelsman DJ. Testosterone and male aging: faltering hope for rejuvenation. *JAMA*. 2017;317(7):699–701.
4282. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of testosterone treatment in older men. *N Engl J Med*. 2016;374(7):611–24.
4283. Diem SJ, Greer NL, MacDonald R, et al. Efficacy and safety of testosterone treatment in men: an evidence report for a clinical practice guideline by the American College of Physicians. *Ann Intern Med*. 2020;172(2):105–18.
4284. Bandari J, Ayyash OM, Emery SL, Wessel CB, Davies BJ. Marketing and testosterone treatment in the USA: a systematic review. *Eur Urol Focus*. 2017;3(4–5):395–402.
4285. Huo S, Scialli AR, McGarvey S, et al. Treatment of men for "low testosterone": a systematic review. *PLoS One*. 2016;11(9):e0162480.
4286. Snyder PJ, Kopperdahl DL, Stephens-Shields AJ, et al. Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone: a controlled clinical trial. *JAMA Intern Med*. 2017;177(4):471–9.
4287. Zhang Z, Kang D, Li H. The effects of testosterone on bone health in males with testosterone deficiency: a systematic review and meta-analysis. *BMC Endocr Disord*. 2020;20(1):33.
4288. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of testosterone treatment in older men. *N Engl J Med*. 2016;374(7):611–24.
4289. Huo S, Scialli AR, McGarvey S, et al. Treatment of men for "low testosterone": a systematic review. *PLoS One*. 2016;11(9):e0162480.
4290. Maggi M, Filippi S, Vignozzi L, Rastrelli G. Controversial aspects of testosterone in the regulation of sexual function in late-onset hypogonadism. *Andrology*. 2020;8(6):1580–9.
4291. Corona G, Rastrelli G, Morgentaler A, Sforza A, Mannucci E, Maggi M. Meta-analysis of results of testosterone therapy on sexual function based on international index of erectile function scores. *Eur Urol*. 2017;72(6):1000–11.
4292. Maggi M, Filippi S, Vignozzi L, Rastrelli G. Controversial aspects of testosterone in the regulation of sexual function in late-onset

hypogonadism. *Andrology*. 2020;8(6):1580–9.
4293. Kwan M, Greenleaf WJ, Mann J, Crapo L, Davidson JM. The nature of androgen action on male sexuality: a combined laboratory-self-report study on hypogonadal men. *J Clin Endocrinol Metab*. 1983;57(3):557–62.
4294. Maggi M, Filippi S, Vignozzi L, Rastrelli G. Controversial aspects of testosterone in the regulation of sexual function in late-onset hypogonadism. *Andrology*. 2020;8(6):1580–9.
4295. Adlin EV. Age-related low testosterone. *Ann Intern Med*. 2020;172(2):151–2.
4296. Lang PO, Samaras D, Samaras N. Testosterone replacement therapy in reversing "andropause": what is the proof-of-principle? *Rejuvenation Res*. 2012;15(5):453–65.
4297. Corona G, Isidori AM, Buvat J, et al. Testosterone supplementation and sexual function: a meta-analysis study. *J Sex Med*. 2014;11(6):1577–92.
4298. Adlin EV. Age-related low testosterone. *Ann Intern Med*. 2020;172(2):151–2.
4299. Lang PO, Samaras D, Samaras N. Testosterone replacement therapy in reversing "andropause": what is the proof-of-principle? *Rejuvenation Res*. 2012;15(5):453–65.
4300. Fisher AD, Corona G, Bandini E, et al. Psychobiological correlates of extramarital affairs and differences between stable and occasional infidelity among men with sexual dysfunctions. *J Sex Med*. 2009;6(3):866–75.
4301. Wagels L, Votinov M, Kellermann T, Eisert A, Beyer C, Habel U. Exogenous testosterone enhances the reactivity to social provocation in males. *Front Behav Neurosci*. 2018;12:37.
4302. Handelsman DJ. Pharmacoepidemiology of testosterone: impact of reimbursement policy on curbing off-label prescribing. *Pharmacoepidemiol Drug Saf*. 2020;29(9):1030–6.
4303. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103(5):1715–44.
4304. Shin YS, Park JK. The optimal indication for testosterone replacement therapy in late onset hypogonadism. *J Clin Med*.

2019;8(2):209.
4305. Roy CN, Snyder PJ, Stephens-Shields AJ, et al. Association of testosterone levels with anemia in older men: a controlled clinical trial. *JAMA Intern Med*. 2017;177(4):480–90.
4306. Swee DS, Gan EH. Late-onset hypogonadism as primary testicular failure. *Front Endocrinol (Lausanne)*. 2019;10:372.
4307. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med*. 2010;363(2):109–22.
4308. Information update—possible cardiovascular problems associated with testosterone products. Government of Canada. https://recalls-rappels.canada.ca/en/alert-recall/information-update-possible-cardiovascular-problems-associated-testosterone-products. Published July 15, 2014. Accessed May 5, 2022.
4309. Warren CJ, Wisener J, Ward B, et al. YouTube as a patient education resource for male hypogonadism and testosterone therapy. *Sex Med*. 2021;9(2):100324.
4310. Sansone A, Sansone M, Lenzi A, Romanelli F. Testosterone replacement therapy: the emperor's new clothes. *Rejuvenation Res*. 2017;20(1):9–14.
4311. Warren CJ, Wisener J, Ward B, et al. YouTube as a patient education resource for male hypogonadism and testosterone therapy. *Sex Med*. 2021;9(2):100324.
4312. Huo S, Scialli AR, McGarvey S, et al. Treatment of men for "low testosterone": a systematic review. *PLoS One*. 2016;11(9):e0162480.
4313. Kohn TP, Mata DA, Ramasamy R, Lipshultz LI. Effects of testosterone replacement therapy on lower urinary tract symptoms: a systematic review and meta-analysis. *Eur Urol*. 2016;69(6):1083–90.
4314. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res*. 1941;1(4):293–7.
4315. Perlmutter MA, Lepor H. Androgen deprivation therapy in the treatment of advanced prostate cancer. *Rev Urol*. 2007;9(Suppl 1):S3–8.

4316. Miner M, Barkin J, Rosenberg MT. Testosterone deficiency: myth, facts, and controversy. *Can J Urol*. 2014;21(Suppl 2):39–54.
4317. Nelson WG, De Marzo AM, Isaacs WB. Prostate cancer. *N Engl J Med*. 2003;349(4):366–81.
4318. Salter CA, Mulhall JP. Guideline of guidelines: testosterone therapy for testosterone deficiency. *BJU Int*. 2019;124(5):722–9.
4319. Nelson WG, De Marzo AM, Isaacs WB. Prostate cancer. *N Engl J Med*. 2003;349(4):366–81.
4320. Grossman DC, Curry SJ, Owens DK, et al. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;319(18):1901–13.
4321. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst*. 2009;101(6):374–83.
4322. Division of Cancer Prevention and Control, Centers for Disease Control and Prevention. Prostate cancer statistics. CDC.gov. http://www.cdc.gov/cancer/prostate/statistics/index.htm. Updated September 2, 2014. Accessed May 15, 2022.
4323. Grossman DC, Curry SJ, Owens DK, et al. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;319(18):1901–13.
4324. Moyer VA, LeFevre ML, Sui AL, et al. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012;157(2):120–34.
4325. Livingston CJ, Freeman RJ, Mohammad A, et al. Choosing Wisely® in preventive medicine. *Am J Prev Med*. 2016;51(1):141–9.
4326. Mulhem E, Fulbright N, Duncan N. Prostate cancer screening. *Am Fam Physician*. 2015;92(8):683–8.
4327. Ivlev I, Jerabkova S, Mishra M, Cook LA, Eden KB. Prostate cancer screening patient decision aids: a systematic review and meta-analysis. *Am J Prev Med*. 2018;55(6):896–907.
4328. Grossman DC, Curry SJ, Owens DK, et al. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;319(18):1901–13.
4329. Carter HB. American Urological Association (AUA) guideline on prostate cancer detection: process and rationale. *BJU Int*.

2013;112(5):543–7.
4330. Wilt TJ, Harris RP, Qaseem A, et al. Screening for cancer: advice for high-value care from the American College of Physicians. *Ann Intern Med*. 2015;162(10):718–25.
4331. American Cancer Society recommendations for prostate cancer early detection. American Cancer Society. https://www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/acs-recommendations.html. Updated April 23, 2021. Accessed May 5, 2022.
4332. Grossman DC, Curry SJ, Owens DK, et al. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;319(18):1901–13.
4333. Tikkinen KAO, Dahm P, Lytvyn L, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a clinical practice guideline. *BMJ*. 2018;362:k3581.
4334. Gigerenzer G, Mata J, Frank R. Public knowledge of benefits of breast and prostate cancer screening in Europe. *J Natl Cancer Inst*. 2009;101(17):1216–20.
4335. Grossman DC, Curry SJ, Owens DK, et al. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;319(18):1901–13.
4336. Tikkinen KAO, Dahm P, Lytvyn L, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a clinical practice guideline. *BMJ*. 2018;362:k3581.
4337. Grossman DC, Curry SJ, Owens DK, et al. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;319(18):1901–13.
4338. Grossman DC, Curry SJ, Owens DK, et al. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;319(18):1901–13.
4339. Early detection of prostate cancer. Harding Center for Risk Literacy. https://www.hardingcenter.de/sites/default/files/2021–11/fact%20%20box_PSA_EN_new_design_20201123_final.pdf. Updated November 2020. Accessed May 4, 2022.
4340. Early detection of prostate cancer. Harding Center for Risk Literacy. https://www.hardingcenter.de/sites/default/files/2021–

11/fact%20%20box_PSA_EN_new_design_20201123_final.pdf. Updated November 2020. Accessed May 4, 2022.

4341. Our History. Endocrine Society. https://www.endocrine.org/our-community/advancing-endocrinology-and-public-health/history. Accessed May 5, 2022.

4342. Al-Sharefi A, Quinton R. Current national and international guidelines for the management of male hypogonadism: helping clinicians to navigate variation in diagnostic criteria and treatment recommendations. *Endocrinol Metab (Seoul)*. 2020;35(3):526–40.

4343. Swee DS, Gan EH. Late-onset hypogonadism as primary testicular failure. *Front Endocrinol (Lausanne)*. 2019;10:372.

4344. Rastrelli G, Carter EL, Ahern T, et al. Development of and recovery from secondary hypogonadism in aging men: prospective results from the EMAS. *J Clin Endocrinol Metab*. 2015;100(8):3172–82.

4345. Davidson LM, Millar K, Jones C, Fatum M, Coward K. Deleterious effects of obesity upon the hormonal and molecular mechanisms controlling spermatogenesis and male fertility. *Hum Fertil (Camb)*. 2015;18(3):184–93.

4346. Camacho EM, Huhtaniemi IT, O'Neill TW, et al. Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study. *Eur J Endocrinol*. 2013;168(3):445–55.

4347. Corona G, Rastrelli G, Monami M, et al. Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis. *Eur J Endocrinol*. 2013;168(6):829–43.

4348. Armamento-Villareal R, Aguirre LE, Qualls C, Villareal DT. Effect of lifestyle intervention on the hormonal profile of frail, obese older men. *J Nutr Health Aging*. 2016;20(3):334–40.

4349. Hayes LD, Elliott BT. Short-term exercise training inconsistently influences basal testosterone in older men: a systematic review and meta-analysis. *Front Physiol*. 2018;9:1878.

4350. Fukui H, Yamashita M. The effects of music and visual stress on testosterone and cortisol in men and women. *Neuro Endocrinol Lett*. 2003;24(3–4):173–80.

4351. Fukui H. Music and testosterone. A new hypothesis for the origin and function of music. *Ann N Y Acad Sci*. 2001;930:448–51.
4352. Leproult R, Van Cauter E. Effect of 1 week of sleep restriction on testosterone levels in young healthy men. *JAMA*. 2011;305(21):2173–4.
4353. Sarkola T, Eriksson CJP. Testosterone increases in men after a low dose of alcohol. *Alcohol Clin Exp Res*. 2003;27(4):682–5.
4354. Sierksma A, Sarkola T, Eriksson CJP, van der Gaag MS, Grobbee DE, Hendriks HFJ. Effect of moderate alcohol consumption on plasma dehydroepiandrosterone sulfate, testosterone, and estradiol levels in middle-aged men and postmenopausal women: a diet-controlled intervention study. *Alcohol Clin Exp Res*. 2004;28(5):780–5.
4355. Hang D, Kværner AS, Ma W, et al. Coffee consumption and plasma biomarkers of metabolic and inflammatory pathways in US health professionals. *Am J Clin Nutr*. 2019;109(3):635–47.
4356. Wedick NM, Mantzoros CS, Ding EL, et al. The effects of caffeinated and decaffeinated coffee on sex hormone–binding globulin and endogenous sex hormone levels: a randomized controlled trial. *Nutr J*. 2012;11:86.
4357. Balasubramanian A, Thirumavalavan N, Srivatsav A, Yu J, Lipshultz LI, Pastuszak AW. Testosterone imposters: an analysis of popular online testosterone boosting supplements. *J Sex Med*. 2019;16(2):203–12.
4358. Clemesha CG, Thaker H, Samplaski MK. 'Testosterone boosting' supplements composition and claims are not supported by the academic literature. *World J Mens Health*. 2020;38(1):115–22.
4359. Park HJ, Lee KS, Lee EK, Park NC. Efficacy and safety of a mixed extract of *Trigonella foenum-graecum* seed and *Lespedeza cuneata* in the treatment of testosterone deficiency syndrome: a randomized, double-blind, placebo-controlled clinical trial. *World J Mens Health*. 2018;36(3):230–8.
4360. Idris S, Mishra A, Khushtar M. Recent therapeutic interventions of fenugreek seed: a mechanistic approach. *Drug Res (Stuttg)*. 2021;71(4):180–92.
4361. Khodamoradi K, Khosropanah MH, Ayati Z, et al. The effects of fenugreek on cardiometabolic risk factors in adults: a systematic

review and meta-analysis. *Complement Ther Med*. 2020;52:102416.
4362. Askarpour M, Alami F, Campbell MS, Venkatakrishnan K, Hadi A, Ghaedi E. Effect of fenugreek supplementation on blood lipids and body weight: a systematic review and meta-analysis of randomized controlled trials. *J Ethnopharmacol*. 2020;253:112538.
4363. Mansoori A, Hosseini S, Zilaee M, Hormoznejad R, Fathi M. Effect of fenugreek extract supplement on testosterone levels in male: a meta-analysis of clinical trials. *Phytother Res*. 2020;34(7):1550–5.
4364. Rao A, Steels E, Inder WJ, Abraham S, Vitetta L. Testofen, a specialised *Trigonella foenum-graecum* seed extract reduces age-related symptoms of androgen decrease, increases testosterone levels and improves sexual function in healthy aging males in a double-blind randomised clinical study. *The Aging Male*. 2016;19(2):134–42.
4365. Askarpour M, Alami F, Campbell MS, Venkatakrishnan K, Hadi A, Ghaedi E. Effect of fenugreek supplementation on blood lipids and body weight: a systematic review and meta-analysis of randomized controlled trials. *J Ethnopharmacol*. 2020;253:112538.
4366. Khodamoradi K, Khosropanah MH, Ayati Z, et al. The effects of fenugreek on cardiometabolic risk factors in adults: a systematic review and meta-analysis. *Complement Ther Med*. 2020;52:102416.
4367. Mebazaa R, Rega B, Camel V. Analysis of human male armpit sweat after fenugreek ingestion: characterisation of odour active compounds by gas chromatography coupled to mass spectrometry and olfactometry. *Food Chem*. 2011;128(1):227–35.
4368. Pearce KL, Tremellen K. The effect of macronutrients on reproductive hormones in overweight and obese men: a pilot study. *Nutrients*. 2019;11(12):3059.
4369. Tremellen K, Hill A, Pearce K. Mechanistic insights into the aetiology of post-prandial decline in testosterone in reproductive-aged men. *Andrologia*. 2019;51(10):e13418.
4370. Tremellen K, McPhee N, Pearce K, Benson S, Schedlowski M, Engler H. Endotoxin-initiated inflammation reduces testosterone production in men of reproductive age. *Am J Physiol Endocrinol Metab*. 2018;314(3):E206–13.
4371. Lehtihet M, Arver S, Bartuseviciene I, Pousette A. S-testosterone decrease after a mixed meal in healthy men independent of SHBG

and gonadotrophin levels. *Andrologia*. 2012;44(6):405–10.
4372. Tremellen K, Hill A, Pearce K. Mechanistic insights into the aetiology of post-prandial decline in testosterone in reproductive-aged men. *Andrologia*. 2019;51(10):e13418.
4373. Lindgren O, Carr RD, Deacon CF, et al. Incretin hormone and insulin responses to oral *versus* intravenous lipid administration in humans. *J Clin Endocrinol Metab*. 2011;96(8):2519–24.
4374. Jeibmann A, Zahedi S, Simoni M, Nieschlag E, Byrne MM. Glucagon-like peptide-1 reduces the pulsatile component of testosterone secretion in healthy males. *Eur J Clin Invest*. 2005;35(9):565–72.
4375. Tremellen K, Hill A, Pearce K. Mechanistic insights into the aetiology of post-prandial decline in testosterone in reproductive-aged men. *Andrologia*. 2019;51(10):e13418.
4376. Anderson KE, Rosner W, Khan MS, et al. Diet-hormone interactions: protein/carbohydrate ratio alters reciprocally the plasma levels of testosterone and cortisol and their respective binding globulins in man. *Life Sci*. 1987;40(18):1761–8.
4377. Cook TM, Russell JM, Barker ME. Dietary advice for muscularity, leanness and weight control in *Men's Health* magazine: a content analysis. *BMC Public Health*. 2014;14:1062.
4378. Schwartz A, Hunschede S, Lacombe RJS, et al. Acute decrease in plasma testosterone and appetite after either glucose or protein beverages in adolescent males. *Clin Endocrinol (Oxf)*. 2019;91(2):295–303.
4379. Whittaker J, Harris M. Low-carbohydrate diets and men's cortisol and testosterone: systematic review and meta-analysis. *Nutr Health*. 2022;28(4):543–54.
4380. Schwartz A, Hunschede S, Lacombe RJS, et al. Acute decrease in plasma testosterone and appetite after either glucose or protein beverages in adolescent males. *Clin Endocrinol (Oxf)*. 2019;91(2):295–303.
4381. Messina M. Soybean isoflavone exposure does not have feminizing effects on men: a critical examination of the clinical evidence. *Fertil Steril*. 2010;93(7):2095–104.

4382. Hamilton-Reeves JM, Vazquez G, Duval SJ, Phipps WR, Kurzer MS, Messina MJ. Clinical studies show no effects of soy protein or isoflavones on reproductive hormones in men: results of a meta-analysis. *Fertil Steril*. 2010;94(3):997–1007.
4383. Shultz TD, Bonorden WR, Seaman WR. Effect of short-term flaxseed consumption on lignan and sex hormone metabolism in men. *Nutr Res*. 1991;11(10):1089–100.
4384. Takenaka T, Nagano M, Yamashita K, Kikuchi K. Flaxseed oil stimulates gynecomastia. *BMJ Case Rep*. 2020;13(12):e237948.
4385. Schwartz LM, Woloshin S. Low "T" as in "template": how to sell disease. *JAMA Intern Med*. 2013;173(15):1460–2.
4386. Shores MM, Matsumoto AM. Testosterone, aging and survival: biomarker or deficiency. *Curr Opin Endocrinol Diabetes Obes*. 2014;21(3):209–16.
4387. Fugh-Berman A. Treating aging with testosterone. *Am Fam Physician*. 2017;96(7):428–30.
4388. Lee JH, Shah PH, Uma D, Salvi DJ, Rabbani R, Hamid P. Testosterone replacement therapy in hypogonadal men and myocardial infarction risk: systematic review & meta-analysis. *Cureus*. 2021;13(8):e17475.
4389. Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA*. 2013;310(17):1829–36.
4390. Regan JC, Partridge L. Gender and longevity: why men die earlier than women? Comparative and experimental evidence. *Best Pract Res Clin Endocrinol Metab*. 2013;27(4):467–79.
4391. Tremellen K. Gut Endotoxin Leading to a Decline IN Gonadal function (GELDING)—a novel theory for the development of late onset hypogonadism in obese men. *Basic Clin Androl*. 2016;26:7.
4392. Lang PO, Samaras D, Samaras N. Testosterone replacement therapy in reversing "andropause": what is the proof-of-principle? *Rejuvenation Res*. 2012;15(5):453–65.
4393. Regan JC, Partridge L. Gender and longevity: why men die earlier than women? Comparative and experimental evidence. *Best Pract Res Clin Endocrinol Metab*. 2013;27(4):467–79.

4394. Tremellen K. Gut Endotoxin Leading to a Decline IN Gonadal function (GELDING)—a novel theory for the development of late onset hypogonadism in obese men. *Basic Clin Androl*. 2016;26:7.
4395. Garratt M, Stout MB. Hormone actions controlling sex-specific life-extension. *Aging (Albany NY)*. 2018;10(3):293–4.
4396. Drori D, Folman Y. Interactive environmental and genetic effects on longevity in the male rat: litter size, exercise, electric shocks and castration. *Exp Aging Res*. 1986;12(2):59–64.
4397. Min KJ, Lee CK, Park HN. The lifespan of Korean eunuchs. *Curr Biol*. 2012;22(18):R792–3.
4398. Le Bourg É. No ground for advocating that Korean eunuchs lived longer than intact men. *Gerontology*. 2015;62(1):69–70.
4399. Nieschlag E, Nieschlag S, Behre HM. Lifespan and testosterone. *Nature*. 1993;366(6452):215.
4400. Spiegel AM. The Jeremiah Metzger lecture: a brief history of eugenics in America: implications for medicine in the 21st century. *Trans Am Clin Climatol Assoc*. 2019;130:216–34.
4401. *Buck v Bell*, 274 US 200 (1927).
4402. Hamilton JB, Mestler GE. Mortality and survival: comparison of eunuchs with intact men and women in a mentally retarded population. *J Gerontol*. 1969;24(4):395–411.
4403. Handelsman DJ. Testosterone and male aging: faltering hope for rejuvenation. *JAMA*. 2017;317(7):699–701.
4404. Montecino-Rodriguez E, Berent-Maoz B, Dorshkind K. Causes, consequences, and reversal of immune system aging. *J Clin Invest*. 2013;123(3):958–65.
4405. Alam I, Almajwal AM, Alam W, et al. The immune-nutrition interplay in aging—facts and controversies. *Nutr Healthy Aging*. 2019;5(2):73–95.
4406. Xu W, Wong G, Hwang YY, Larbi A. The untwining of immunosenescence and aging. *Semin Immunopathol*. 2020;42(5):559–72.
4407. Crooke SN, Ovsyannikova IG, Poland GA, Kennedy RB. Immunosenescence and human vaccine immune responses. *Immun Ageing*. 2019;16:25.

4408. Fagiolo U, Cossarizza A, Scala E, et al. Increased cytokine production in mononuclear cells of healthy elderly people. *Eur J Immunol*. 1993;23(9):2375–8.
4409. Cevenini E, Monti D, Franceschi C. Inflamm-ageing. *Curr Opin Clin Nutr Metab Care*. 2013;16(1):14–20.
4410. Crimmins EM. Age-related vulnerability to coronavirus disease 2019 (COVID-19): biological, contextual, and policy-related factors. *Public Policy Aging Rep*. 2020;30(4):142–6.
4411. Painter SD, Ovsyannikova IG, Poland GA. The weight of obesity on the human immune response to vaccination. *Vaccine*. 2015;33(36):4422–9.
4412. Neidich SD, Green WD, Rebeles J, et al. Increased risk of influenza among vaccinated adults who are obese. *Int J Obes (Lond)*. 2017;41(9):1324–30.
4413. Sjöström L. Review of the key results from the Swedish Obese Subjects (SOS) trial—a prospective controlled intervention study of bariatric surgery. *J Intern Med*. 2013;273(3):219–34.
4414. Jahn J, Spielau M, Brandsch C, et al. Decreased NK cell functions in obesity can be reactivated by fat mass reduction. *Obesity (Silver Spring)*. 2015;23(11):2233–41.
4415. Walsh NP, Gleeson M, Shephard RJ, et al. Position statement. Part one: immune function and exercise. *Exerc Immunol Rev*. 2011;17:6–63.
4416. Nieman DC. Moderate exercise improves immunity and decreases illness rates. *Am J Lifestyle Med*. 2011;5(4):338–45.
4417. Bigley AB, Rezvani K, Chew C, et al. Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells. *Brain Behav Immun*. 2014;39:160–71.
4418. McTiernan A, Friedenreich CM, Katzmarzyk PT, et al. Physical activity in cancer prevention and survival: a systematic review. *Med Sci Sports Exerc*. 2019;51(6):1252–61.
4419. Kohut ML, Arntson BA, Lee W, et al. Moderate exercise improves antibody response to influenza immunization in older adults. *Vaccine*. 2004;22(17–18):2298–306.

4420. Ranadive SM, Cook M, Kappus RM, et al. Effect of acute aerobic exercise on vaccine efficacy in older adults. *Med Sci Sports Exerc*. 2014;46(3):455–61.
4421. Long JE, Ring C, Drayson M, et al. Vaccination response following aerobic exercise: can a brisk walk enhance antibody response to pneumococcal and influenza vaccinations? *Brain Behav Immun*. 2012;26(4):680–7.
4422. Antonelli M, Barbieri G, Donelli D. Effects of forest bathing (shinrin-yoku) on levels of cortisol as a stress biomarker: a systematic review and meta-analysis. *Int J Biometeorol*. 2019;63(8):1117–34.
4423. Li Q, Kawada T. Effect of forest environments on human natural killer (NK) activity. *Int J Immunopathol Pharmacol*. 2011;24(1 Suppl):39S-44S.
4424. Li Q, Morimoto K, Kobayashi M, et al. Visiting a forest, but not a city, increases human natural killer activity and expression of anti-cancer proteins. *Int J Immunopathol Pharmacol*. 2008;21(1):117–27.
4425. Sumitomo K, Akutsu H, Fukuyama S, et al. Conifer-derived monoterpenes and forest walking. *Mass Spectrom (Tokyo)*. 2015;4(1):A0042.
4426. Li Q, Nakadai A, Matsushima H, et al. Phytoncides (wood essential oils) induce human natural killer cell activity. *Immunopharmacol Immunotoxicol*. 2006;28(2):319–33.
4427. Shibata H, Fujiwara R, Iwamoto M, Matsuoka H, Yokoyama MM. Immunological and behavioral effects of fragrance in mice. *Int J Neurosci*. 1991;57(1–2):151–9.
4428. Li Q, Kobayashi M, Wakayama Y, et al. Effect of phytoncide from trees on human natural killer cell function. *Int J Immunopathol Pharmacol*. 2009;22(4):951–9.
4429. Fujimori H, Hisama M, Shibayama H, Iwaki M. Protecting effect of phytoncide solution, on normal human dermal fibroblasts against reactive oxygen species. *J Oleo Sci*. 2009;58(8):429–36.
4430. Li Q, Kobayashi M, Kawada T. Relationships between percentage of forest coverage and standardized mortality ratios (SMR) of cancers in all prefectures in Japan. *Open Public Health J*. 2008;1(1):1–7.
4431. Ahmadi F, Ahmadi N. Nature as the most important coping strategy among cancer patients: a Swedish survey. *J Relig Health*.

2015;54(4):1177–90.
4432. Brown R, Pang G, Husband AJ, King MG. Suppression of immunity to influenza virus infection in the respiratory tract following sleep disturbance. *Reg Immunol*. 1989;2(5):321–5.
4433. Toth LA, Rehg JE. Effects of sleep deprivation and other stressors on the immune and inflammatory responses of influenza-infected mice. *Life Sci*. 1998;63(8):701–9.
4434. Renegar KB, Floyd RA, Krueger JM. Effects of short-term sleep deprivation on murine immunity to influenza virus in young adult and senescent mice. *Sleep*. 1998;21(3):241–8.
4435. Besedovsky L, Lange T, Born J. Sleep and immune function. *Pflugers Arch*. 2012;463(1):121–37.
4436. Prather AA, Hall M, Fury JM, et al. Sleep and antibody response to hepatitis B vaccination. *Sleep*. 2012;35(8):1063–9.
4437. Prather AA, Pressman SD, Miller GE, Cohen S. Temporal links between self-reported sleep and antibody responses to the influenza vaccine. *Int J Behav Med*. 2021;28(1):151–8.
4438. Lange T, Perras B, Fehm HL, Born J. Sleep enhances the human antibody response to hepatitis A vaccination. *Psychosom Med*. 2003;65(5):831–5.
4439. Lange T, Dimitrov S, Bollinger T, Diekelmann S, Born J. Sleep after vaccination boosts immunological memory. *J Immunol*. 2011;187(1):283–90.
4440. Spiegel K, Sheridan JF, Van Cauter E. Effect of sleep deprivation on response to immunization. *JAMA*. 2002;288(12):1471–2.
4441. Irwin M, McClintick J, Costlow C, Fortner M, White J, Gillin JC. Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. *FASEB J*. 1996;10(5):643–53.
4442. Irwin M, Mascovich A, Gillin JC, Willoughby R, Pike J, Smith TL. Partial sleep deprivation reduces natural killer cell activity in humans. *Psychosom Med*. 1994;56(6):493–8.
4443. Patel SR, Malhotra A, Gao X, Hu FB, Neuman MI, Fawzi WW. A prospective study of sleep duration and pneumonia risk in women. *Sleep*. 2012;35(1):97–101.
4444. Cohen S, Doyle WJ, Alper CM, Janicki-Deverts D, Turner RB. Sleep habits and susceptibility to the common cold. *Arch Intern Med*.

2009;169(1):62–7.
4445. Prather AA, Janicki-Deverts D, Hall MH, Cohen S. Behaviorally assessed sleep and susceptibility to the common cold. *Sleep*. 2015;38(9):1353–9.
4446. Besedovsky L, Born J. Sleep, don't sneeze: longer sleep reduces the risk of catching a cold. *Sleep*. 2015;38(9):1341–2.
4447. Fulop T, Larbi A, Dupuis G, et al. Immunosenescence and inflamm-aging as two sides of the same coin: friends or foes? *Front Immunol*. 2018;8:1960.
4448. Lesourd B. Nutritional factors and immunological ageing. *Proc Nutr Soc*. 2006;65(3):319–25.
4449. Xu W, Wong G, Hwang YY, Larbi A. The untwining of immunosenescence and aging. *Semin Immunopathol*. 2020;42(5):559–72.
4450. Averill HM, Averill JE. The effect of daily apple consumption on dental caries experience, oral hygiene status and upper respiratory infections. *N Y State Dent J*. 1968;34(7):403–9.
4451. Charland KM, Buckeridge DL, Hoen AG, et al. Relationship between community prevalence of obesity and associated behavioral factors and community rates of influenza-related hospitalizations in the United States. *Influenza Other Respir Viruses*. 2013;7(5):718–28.
4452. U.S. Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 1997;46(RR-08):1–24.
4453. Gibson A, Edgar J, Neville C et al. Effect of fruit and vegetable consumption on immune function in older people: a randomized controlled trial. *Am J Clin Nutr*. 2012;96(6):1429–36.
4454. Skinner MA. Gold kiwifruit for immune support and reducing symptoms of cold and influenza. *J Food Drug Anal*. 2012;20:261–4.
4455. Orhan F, Karakas T, Cakir M, Aksoy A, Baki A, Gedik Y. Prevalence of immunoglobulin E–mediated food allergy in 6–9-year-old urban schoolchildren in the eastern Black Sea region of Turkey. *Clin Exp Allergy.* 2009;39(7):1027–35.
4456. Rancé F, Grandmottet X, Grandjean H. Prevalence and main characteristics of schoolchildren diagnosed with food allergies in France. *Clin Exp Allergy.* 2005;35(2):167–72.

4457. Hunter DC, Skinner MA, Wolber FM, et al. Consumption of gold kiwifruit reduces severity and duration of selected upper respiratory tract infection symptoms and increases plasma vitamin C concentration in healthy older adults. *Br J Nutr.* 2012;108(7):1235–45.
4458. Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ*. 2014;348:g2545.
4459. van der Gaag EJ, Hummel TZ. Food or medication? The therapeutic effects of food on the duration and incidence of upper respiratory tract infections: a review of the literature. *Crit Rev Food Sci Nutr*. 2021;61(16):2691–704.
4460. Hawkins J, Baker C, Cherry L, Dunne E. Black elderberry (*Sambucus nigra*) supplementation effectively treats upper respiratory symptoms: a meta-analysis of randomized, controlled clinical trials. *Complement Ther Med*. 2019;42:361–5.
4461. Macknin M, Wolski K, Negrey J, Mace S. Elderberry extract outpatient influenza treatment for emergency room patients ages 5 and above: a randomized, double-blind, placebo-controlled trial. *J Gen Intern Med*. 2020;35(11):3271–7.
4462. Rothberg MB. Influenza, like COVID-19, needs randomized trials. *J Gen Intern Med*. 2021;36(6):1490–1.
4463. David S, Cunningham R. Echinacea for the prevention and treatment of upper respiratory tract infections: a systematic review and meta-analysis. *Complement Ther Med*. 2019;44:18–26.
4464. Weissman S, Lo A, Patel R, et al. An unusual culprit of drug-induced pancreatitis. *Dig Dis Sci*. 2020;65(5):1549–52.
4465. Elderberry for influenza. *Med Lett Drugs Ther*. 2019;61(1566):32.
4466. Pogorzelski E. Formation of cyanide as a product of decomposition of cyanogenic glucosides in the treatment of elderberry fruit (*Sambucus nigra*). *J Sci Food Agric*. 1982;33(5):496–8.
4467. Centers for Disease Control. Poisoning from elderberry juice—California. *MMWR Morb Mortal Wkly Rep*. 1984;33(13):173–4.
4468. McAnulty LS, Collier SR, Landram MJ, et al. Six weeks daily ingestion of whole blueberry powder increases natural killer cell

counts and reduces arterial stiffness in sedentary males and females. *Nutr Res*. 2014;34(7):577–84.

4469. Majdalawieh AF, Carr RI. In vitro investigation of the potential immunomodulatory and anti-cancer activities of black pepper (*Piper nigrum*) and cardamom (*Elettaria cardamomum*). *J Med Food*. 2010;13(2):371–81.

4470. Pan P, Kang S, Wang Y, et al. Black raspberries enhance natural killer cell infiltration into the colon and suppress the progression of colorectal cancer. *Front Immunol*. 2017;8:997.

4471. Huang YW, Lin CW, Pan P, et al. Black raspberries suppress colorectal cancer by enhancing Smad4 expression in colonic epithelium and natural killer cells. *Front Immunol*. 2020;11:570683.

4472. Wang H, Gao T, Du Y, et al. Anticancer and immunostimulating activities of a novel homogalacturonan from *Hippophae rhamnoides* L. berry. *Carbohydr Polym*. 2015;131:288–96.

4473. Larmo P, Alin J, Salminen E, Kallio H, Tahvonen R. Effects of sea buckthorn berries on infections and inflammation: a double-blind, randomized, placebo-controlled trial. *Eur J Clin Nutr*. 2008;62(9):123–30.

4474. Agricultural Research Service, United States Department of Agriculture. Gogi berries, dried. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html?query=goji&utf8=%E2%9C%93&affiliate=usda&commit=Search#/food-details/173032/nutrients. Published April 1, 2019. Accessed May 20, 2022.

4475. Vidal K, Bucheli P, Gao Q, et al. Immunomodulatory effects of dietary supplementation with a milk-based wolfberry formulation in healthy elderly: a randomized, double-blind, placebo-controlled trial. *Rejuvenation Res*. 2012;15(1):89–97.

4476. Mostafalou S, Abdollahi M. Pesticides: an update of human exposure and toxicity. *Arch Toxicol*. 2017;91(2):549–99.

4477. Kapeleka JA, Sauli E, Ndakidemi PA. Pesticide exposure and genotoxic effects as measured by DNA damage and human monitoring biomarkers. *Int J Environ Health Res*. 2021;31(7):805–22.

4478. Hemler EC, Chavarro JE, Hu FB. Organic foods for cancer prevention—worth the investment? *JAMA Intern Med*. 2018;178(12):1606–7.
4479. Hemler EC, Chavarro JE, Hu FB. Organic foods for cancer prevention—worth the investment? *JAMA Intern Med*. 2018;178(12):1606–7.
4480. Juraske R, Mutel CL, Stoessel F, Hellweg S. Life cycle human toxicity assessment of pesticides: comparing fruit and vegetable diets in Switzerland and the United States. *Chemosphere*. 2009;77(7):939–45.
4481. Watzl B, Bub A, Brandstetter BR, Rechkemmer G. Modulation of human T-lymphocyte functions by the consumption of carotenoid-rich vegetables. *Br J Nutr*. 1999;82(5):383–9.
4482. Watzl B, Bub A, Briviba K, Rechkemmer G. Supplementation of a low-carotenoid diet with tomato or carrot juice modulates immune functions in healthy men. *Ann Nutr Metab*. 2003;47(6):255–61.
4483. Briviba K, Kulling SE, Möseneder J, Watzl B, Rechkemmer G, Bub A. Effects of supplementing a low-carotenoid diet with a tomato extract for 2 weeks on endogenous levels of DNA single strand breaks and immune functions in healthy non-smokers and smokers. *Carcinogenesis*. 2004;25(12):2373–8.
4484. Watzl B, Bub A, Blockhaus M, et al. Prolonged tomato juice consumption has no effect on cell-mediated immunity of well-nourished elderly men and women. *J Nutr*. 2000;130(7):1719–23.
4485. Müller L, Meyer M, Bauer RN, et al. Effect of broccoli sprouts and live attenuated influenza virus on peripheral blood natural killer cells: a randomized, double-blind study. *PLoS One*. 2016;11(1):e0147742.
4486. Lord SJ, Rajotte RV, Korbutt GS, Bleackley RC. Granzyme B: a natural born killer. *Immunol Rev*. 2003;193:31–8.
4487. Noah TL, Zhang H, Zhou H, et al. Effect of broccoli sprouts on nasal response to live attenuated influenza virus in smokers: a randomized, double-blind study. *PLoS One*. 2014;9(6):e98671.
4488. Cho HY, Imani F, Miller-DeGraff L, et al. Antiviral activity of Nrf2 in a murine model of respiratory syncytial virus disease. *Am J Respir Crit Care Med*. 2009;179(2):138–50.

4489. Wu CC, Chuang HY, Lin CY, et al. Inhibition of Epstein-Barr virus reactivation in nasopharyngeal carcinoma cells by dietary sulforaphane. *Mol Carcinog*. 2013;52(12):946–58.
4490. Harvey CJ, Thimmulappa RK, Sethi S, et al. Targeting Nrf2 signaling improves bacterial clearance by alveolar macrophages in patients with COPD and in a mouse model. *Sci Transl Med*. 2011;3(78):78ra32.
4491. Gasper AV, Al-janobi A, Smith JA, et al. Glutathione *S*-transferase *M1* polymorphism and metabolism of sulforaphane from standard and high-glucosinolate broccoli. *Am J Clin Nutr*. 2005;82(6):1283–91.
4492. Ritz T, Trueba AF, Vogel PD, Auchus RJ, Rosenfield D. Exhaled nitric oxide and vascular endothelial growth factor as predictors of cold symptoms after stress. *Biol Psychol*. 2018;132:116–24.
4493. Sanders SP, Siekierski ES, Richards SM, Porter JD, Imani F, Proud D. Rhinovirus infection induces expression of type 2 nitric oxide synthase in human respiratory epithelial cells in vitro and in vivo. *J Allergy Clin Immunol*. 2001;107(2):235–43.
4494. Domínguez R, Cuenca E, Maté-Muñoz JL, et al. Effects of beetroot juice supplementation on cardiorespiratory endurance in athletes. A systematic review. *Nutrients*. 2017;9(1):43.
4495. Swathi Krishna S, Thennavan A, Kanthlal SK. Dietary foods containing nitric oxide donors can be early curators of SARS-CoV-2 infection: a possible role in the immune system. *J Food Biochem*. 2022;46(3):e13884.
4496. Ritz T, Werchan CA, Kroll JL, Rosenfield D. Beetroot juice supplementation for the prevention of cold symptoms associated with stress: a proof-of-concept study. *Physiol Behav*. 2019;202:45–51.
4497. Brown ES, Allsopp PJ, Magee PJ, et al. Seaweed and human health. *Nutr Rev*. 2014;72(3):205–16.
4498. Tamama K. Potential benefits of dietary seaweeds as protection against COVID-19. *Nutr Rev*. 2021;79(7):814–23.
4499. Miyake Y, Sasaki S, Ohya Y, et al. Dietary intake of seaweed and minerals and prevalence of allergic rhinitis in Japanese pregnant females: baseline data from the Osaka Maternal and Child Health Study. *Ann Epidemiol*. 2006;16(8):614–21.

4500. Shan BE, Yoshida Y, Kuroda E, Yamashita U. Immunomodulating activity of seaweed extract on human lymphocytes in vitro. *Int J Immunopharmacol*. 1999;21(1):59–70.
4501. Cooper R, Dragar C, Elliot K, Fitton JH, Godwin J, Thompson K. GFS, a preparation of Tasmanian *Undaria pinnatifida* is associated with healing and inhibition of reactivation of Herpes. *BMC Complement Altern Med*. 2002;2:11.
4502. Ryan-Borchers TA, Park JS, Chew BP, McGuire MK, Fournier LR, Beerman KA. Soy isoflavones modulate immune function in healthy postmenopausal women. *Am J Clin Nutr*. 2006;83(5):1118–25.
4503. Messina M, Nagata C, Wu AH. Estimated Asian adult soy protein and isoflavone intakes. *Nutr Cancer*. 2006;55(1):1–12.
4504. Teas J, Hebert JR, Fitton JH, Zimba PV. Algae—a poor man's HAART? *Med Hypotheses*. 2004;62(4):507–10.
4505. Tamama K. Potential benefits of dietary seaweeds as protection against COVID-19. *Nutr Rev*. 2021;79(7):814–23.
4506. Jung SJ, Jang HY, Jung ES, et al. Effects of *Porphyra tenera* supplementation on the immune system: a randomized, double-blind, and placebo-controlled clinical trial. *Nutrients*. 2020;12(6):E1642.
4507. Agricultural Research Service, United States Department of Agriculture. Seaweed, laver, raw. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html?query=nori&utf8=%E2%9C%93&affiliate=usda&commit=Search#/food-details/168458/nutrients. Published April 1, 2019. Accessed May 20, 2022.
4508. Jung SJ, Jang HY, Jung ES, et al. Effects of *Porphyra tenera* supplementation on the immune system: a randomized, double-blind, and placebo-controlled clinical trial. *Nutrients*. 2020;12(6):E1642.
4509. Ishihara K, Oyamada C, Sato Y, et al. Relationships between quality parameters and content of glycerol galactoside and porphyra-334 in dried laver nori *Porphyra yezoensis*. *Fisheries Sci*. 2008;74(1):167–73.
4510. Neville V, Gleeson M, Folland JP. Salivary IgA as a risk factor for upper respiratory infections in elite professional athletes. *Med Sci Sports Exerc*. 2008 Jul;40(7):1228–36.

4511. Mak TW, Saunders ME. 20-Mucosal and cutaneous immunity. In: Mak TW, Saunders ME, eds. *The Immune Response*. Academic Press; 2006:583–609.
4512. Dietzen DJ. Amino acids, peptides, and proteins. In: *Principles and Applications of Molecular Diagnostics*. Elsevier; 2018:345–80.
4513. Otsuki T, Shimizu K, Iemitsu M, Kono I. Salivary secretory immunoglobulin A secretion increases after 4-weeks ingestion of chlorella-derived multicomponent supplement in humans: a randomized cross over study. *Nutr J*. 2011 Sep 9;10:91.
4514. Nakano S, Takekoshi H, Nakano M. Chlorella (*Chlorella pyrenoidosa*) supplementation decreases dioxin and increases immunoglobulin a concentrations in breast milk. *J Med Food*. 2007;10(1):134–42.
4515. Halperin SA, Smith B, Nolan C, Shay J, Kralovec J. Safety and immunoenhancing effect of a Chlorella-derived dietary supplement in healthy adults undergoing influenza vaccination: randomized, double-blind, placebo-controlled trial. *CMAJ*. 2003;169(2):111–7.
4516. Otsuki T, Shimizu K, Iemitsu M, Kono I. Salivary secretory immunoglobulin A secretion increases after 4-weeks ingestion of chlorella-derived multicomponent supplement in humans: a randomized cross over study. *Nutr J*. 2011;10:91.
4517. Kwak JH, Baek SH, Woo Y, et al. Beneficial immunostimulatory effect of short-term *Chlorella* supplementation: enhancement of *Natural Killer* cell activity and early inflammatory response (randomized, double-blinded, placebo-controlled trial). *Nutr J*. 2012;11:53.
4518. Azocar J, Diaz A. Efficacy and safety of Chlorella supplementation in adults with chronic hepatitis C virus infection. *World J Gastroenterol*. 2013;19(7):1085–90.
4519. Fallah AA, Sarmast E, Habibian Dehkordi S, et al. Effect of *Chlorella* supplementation on cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Clin Nutr*. 2018;37(6 Pt A):1892–901.
4520. Selvaraj V, Singh H, Ramaswamy S. Chlorella-induced psychosis. *Psychosomatics*. 2013;54(3):303–4.
4521. Petrovska BB, Cekovska S. Extracts from the history and medical properties of garlic. *Pharmacogn Rev*. 2010;4(7):106–10.

4522. Darooghegi Mofrad M, Milajerdi A, Koohdani F, Surkan PJ, Azadbakht L. Garlic supplementation reduces circulating C-reactive protein, tumor necrosis factor, and interleukin-6 in adults: a systematic review and meta-analysis of randomized controlled trials. *J Nutr*. 2019;149(4):605–18.
4523. Louca P, Murray B, Klaser K, et al. Modest effects of dietary supplements during the COVID-19 pandemic: insights from 445 850 users of the COVID-19 Symptom Study app. *BMJ Nutr Prev Health*. 2021;4(1):149–57.
4524. Lawson LD, Hunsaker SM. Allicin bioavailability and bioequivalence from garlic supplements and garlic foods. *Nutrients*. 2018;10(7):812.
4525. Locatelli DA, Altamirano JC, González RE, Camargo AB. Home-cooked garlic remains a healthy food. *J Funct Food*. 2015;16:1–8.
4526. Lawson LD, Hunsaker SM. Allicin bioavailability and bioequivalence from garlic supplements and garlic foods. *Nutrients*. 2018;10(7):812.
4527. Wong A, Townley S. Herbal medicines and anaesthesia. *Cont Educ Anaesth Crit Care Pain*. 2011;11(1):14–7.
4528. Gadkari JV, Joshi VD. Effect of ingestion of raw garlic on serum cholesterol level, clotting time and fibrinolytic activity in normal subjects. *J Postgrad Med*. 1991;37(3):128–31.
4529. Scharbert G, Kalb ML, Duris M, Marschalek C, Kozek-Langenecker SA. Garlic at dietary doses does not impair platelet function. *Anesth Analg*. 2007;105(5):1214–8.
4530. Munch R, Barringer SA. Deodorization of garlic breath volatiles by food and food components. *J Food Sci*. 2014;79(4):C526–33.
4531. Jeong SC, Koyyalamudi SR, Pang G. Dietary intake of *Agaricus bisporus* white button mushroom accelerates salivary immunoglobulin A secretion in healthy volunteers. *Nutrition*. 2012;28(5):527–31.
4532. Jesenak M, Hrubisko M, Majtan J, Rennerova Z, Banovcin P. Anti-allergic effect of Pleuran (β-glucan from *Pleurotus ostreatus*) in children with recurrent respiratory tract infections. *Phytother Res*. 2014;28(3):471–4.
4533. Dai X, Stanilka JM, Rowe CA, et al. Consuming *Lentinula edodes* (shiitake) mushrooms daily improves human immunity: a randomized

dietary intervention in healthy young adults. *J Am Coll Nutr.* 2015;34(6):478–87.

4534. Xu Y, Na L, Ren Z, et al. Effect of dietary supplementation with white button mushrooms on host resistance to influenza infection and immune function in mice. *Br J Nutr*. 2013;109(6):1052–61.

4535. Bobovčák M, Kuniaková R, Gabriž J, Majtán J. Effect of Pleuran (β-glucan from *Pleurotus ostreatus*) supplementation on cellular immune response after intensive exercise in elite athletes. *Appl Physiol Nutr Metab*. 2010;35(6):755–62.

4536. Cerletti C, Esposito S, Iacoviello L. Edible mushrooms and beta-glucans: impact on human health. *Nutrients*. 2021;13(7):2195.

4537. Bergendiova K, Tibenska E, Majtan J. Pleuran (β-glucan from *Pleurotus ostreatus*) supplementation, cellular immune response and respiratory tract infections in athletes. *Eur J Appl Physiol*. 2011;111(9):2033–40.

4538. Lehne G, Haneberg B, Gaustad P, Johansen PW, Preus H, Abrahamsen TG. Oral administration of a new soluble branched β-1,3-D-glucan is well tolerated and can lead to increased salivary concentrations of immunoglobulin A in healthy volunteers. *Clin Exp Immunol*. 2006;143(1):65–9.

4539. Zhong K, Liu Z, Lu Y, Xu X. Effects of yeast β-glucans for the prevention and treatment of upper respiratory tract infection in healthy subjects: a systematic review and meta-analysis. *Eur J Nutr*. 2021;60(8):4175–87.

4540. Kohl A, Gögebakan O, Möhlig M, et al. Increased interleukin-10 but unchanged insulin sensitivity after 4 weeks of (1, 3)(1, 6)-β-glycan consumption in overweight humans. *Nutr Res*. 2009;29(4):248–54.

4541. Yenidogan E, Akgul GG, Gulcelik MA, Dinc S, Colakoglu MK, Kayaoglu HA. Effect of β-glucan on drain fluid and amount of drainage following modified radical mastectomy. *Adv Ther*. 2014;31(1):130–9.

4542. Koray M, Ak G, Kürklü E, et al. The effect of β-glucan on recurrent aphthous stomatitis. *J Altern Complement Med*. 2009;15(2):111–2.

4543. Mosikanon K, Arthan D, Kettawan A, Tungtrongchitr R, Prangthip P. Yeast β-glucan modulates inflammation and waist circumference in overweight and obese subjects. *J Diet Suppl*. 2017;14(2):173–85.

4544. Santas J, Lázaro E, Cuñé J. Effect of a polysaccharide-rich hydrolysate from *Saccharomyces cerevisiae* (LipiGo®) in body weight loss: randomised, double-blind, placebo-controlled clinical trial in overweight and obese adults. *J Sci Food Agric*. 2017;97(12):4250–7.
4545. Vlassopoulou M, Yannakoulia M, Pletsa V, Zervakis GI, Kyriacou A. Effects of fungal beta-glucans on health—a systematic review of randomized controlled trials. *Food Funct*. 2021;12(8):3366–80.
4546. Barclay GR, McKenzie H, Pennington J, Parratt D, Pennington CR. The effect of dietary yeast on the activity of stable chronic Crohn's disease. *Scand J Gastroenterol*. 1992;27(3):196–200.
4547. Cannistrà C, Finocchi V, Trivisonno A, Tambasco D. New perspectives in the treatment of hidradenitis suppurativa: surgery and brewer's yeast–exclusion diet. *Surgery*. 2013;154(5):1126–30.
4548. Stier H, Ebbeskotte V, Gruenwald J. Immune-modulatory effects of dietary Yeast Beta-1,3/1,6-D-glucan. *Nutr J*. 2014;13:38.
4549. van Steenwijk HP, Bast A, de Boer A. Immunomodulating effects of fungal beta-glucans: from traditional use to medicine. *Nutrients*. 2021;13(4):1333.
4550. Stier H, Ebbeskotte V, Gruenwald J. Immune-modulatory effects of dietary Yeast Beta-1,3/1,6-D-glucan. *Nutr J*. 2014;13:38.
4551. Kamath AB, Wang L, Das H, Li L, Reinhold VN, Bukowski JF. Antigens in tea-beverage prime human Vγ2Vδ2 T cells *in vitro* and *in vivo* for memory and nonmemory antibacterial cytokine responses. *Proc Natl Acad Sci U S A*. 2003;100(10):6009–14.
4552. Bukowski JF, Morita CT, Brenner MB. Human γδ T cells recognize alkylamines derived from microbes, edible plants, and tea: implications for innate immunity. *Immunity.* 1999;11(1):57–65.
4553. Hartmann T. Nachweis von *n*-butylamin in äpfeln. *Experientia*. 1967;23(8):680–1.
4554. Ibe A, Saito K, Nakazato M, Kikuchi Y, Fujinuma K, Nishima T. Quantitative determination of amines in wine by liquid chromatography. *J Assoc Off Anal Chem*. 1991;74(4):695–8.
4555. Jones BM, Al-Fattani M, Gooch H. The determination of amines in the vaginal secretions of women in health and disease. *Int J STD AIDS*. 1994;5(1):52–5.

4556. Rowe CA, Nantz MP, Bukowski JF, Percival SS. Specific formulation of *Camellia sinensis* prevents cold and flu symptoms and enhances gamma,delta T cell function: a randomized, double-blind, placebo-controlled study. *J Am Coll Nutr*. 2007;26(5):445–52.
4557. Kamath AB, Wang L, Das H, Li L, Reinhold VN, Bukowski JF. Antigens in tea-beverage prime human Vγ2Vδ2 T cells *in vitro* and *in vivo* for memory and nonmemory antibacterial cytokine responses. *Proc Natl Acad Sci U S A*. 2003;100(10):6009–14.
4558. Park M, Yamada H, Matsushita K, et al. Green tea consumption is inversely associated with the incidence of influenza infection among schoolchildren in a tea plantation area of Japan. *J Nutr*. 2011;141(10):1862–70.
4559. Watanabe I, Kuriyama S, Kakizaki M, et al. Green tea and death from pneumonia in Japan: the Ohsaki cohort study. *Am J Clin Nutr.* 2009;90(3):672–9.
4560. Rowe CA, Nantz MP, Bukowski JF, Percival SS. Specific formulation of *Camellia sinensis* prevents cold and flu symptoms and enhances γδ T cell function: a randomized, double-blind, placebo-controlled study. *J Am Coll Nutr*. 2007;26(5):445–52.
4561. Rawangkan A, Kengkla K, Kanchanasurakit S, Duangjai A, Saokaew S. Anti-influenza with green tea catechins: a systematic review and meta-analysis. *Molecules*. 2021;26(13):4014.
4562. Matsumoto K, Yamada H, Takuma N, Niino H, Sagesaka YM. Effects of green tea catechins and theanine on preventing influenza infection among healthcare workers: a randomized controlled trial. *BMC Complement Altern Med*. 2011;11:15.
4563. Rawangkan A, Kengkla K, Kanchanasurakit S, Duangjai A, Saokaew S. Anti-influenza with green tea catechins: a systematic review and meta-analysis. *Molecules*. 2021;26(13):4014.
4564. Furushima D, Nishimura T, Takuma N, et al. Prevention of acute upper respiratory infections by consumption of catechins in healthcare workers: a randomized, placebo-controlled trial. *Nutrients*. 2019;12(1):E4.
4565. Song JM, Lee KH, Seong BL. Antiviral effect of catechins in green tea on influenza virus. *Antiviral Res*. 2005;68:66–74.

4566. Furushima D, Otake Y, Koike N, et al. Investigation of the oral retention of tea catechins in humans: an exploratory interventional study. *Nutrients*. 2021;13(9):3024.
4567. Satomura K, Kitamura T, Kawamura T, et al. Prevention of upper respiratory tract infections by gargling: a randomized trial. *Am J Prev Med*. 2005;29(4):302–7.
4568. Rawangkan A, Kengkla K, Kanchanasurakit S, Duangjai A, Saokaew S. Anti-influenza with green tea catechins: a systematic review and meta-analysis. *Molecules*. 2021;26(13):4014.
4569. Ide K, Yamada H, Kawasaki Y. Effect of gargling with tea and ingredients of tea on the prevention of influenza infection: a meta-analysis. *BMC Public Health*. 2016;16:396.
4570. Goodall EC, Granados AC, Luinstra K, et al. Vitamin D_3 and gargling for the prevention of upper respiratory tract infections: a randomized controlled trial. *BMC Infect Dis*. 2014;14:273.
4571. Chow EP, Howden BP, Walker S, et al. Antiseptic mouthwash against pharyngeal *Neisseria gonorrhoeae*: a randomised controlled trial and an in vitro study. *Sex Transm Infect*. 2017;93(2):88–93.
4572. Maddaford K, Fairley CK, Trumpour S, Chung M, Chow EPF. Sites in the oropharynx reached by different methods of using mouthwash: clinical implication for oropharyngeal gonorrhoea prevention. *Sex Transm Infect*. 2020;96(5):358–60.
4573. Phillips TR, Fairley C, Maddaford K, et al. Duration of gargling and rinsing among frequent mouthwash users: a cross-sectional study. *BMJ Open*. 2020;10(9):e040754.
4574. Kumari M, Kozyrskyj AL. Gut microbial metabolism defines host metabolism: an emerging perspective in obesity and allergic inflammation. *Obes Rev*. 2017;18(1):18–31.
4575. Brown AJ, Goldsworthy SM, Barnes AA, et al. The orphan G protein–coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *J Biol Chem*. 2003;278(13):11312–9.
4576. Ang Z, Ding JL. GPR41 and GPR43 in obesity and inflammation—protective or causative? *Front Immunol*. 2016;7:28.

4577. Jiao J, Xu JY, Zhang W, Han S, Qin LQ. Effect of dietary fiber on circulating C-reactive protein in overweight and obese adults: a meta-analysis of randomized controlled trials. *Int J Food Sci Nutr*. 2015;66(1):114–9.
4578. Halnes I, Baines KJ, Berthon BS, MacDonald-Wicks LK, Gibson PG, Wood LG. Soluble fibre meal challenge reduces airway inflammation and expression of GPR43 and GPR41 in asthma. *Nutrients*. 2017;9(1):57.
4579. Van Landingham CB, Keast DR, Longnecker MP. Serum concentration of antibodies to mumps, but not measles, rubella, or varicella, is associated with intake of dietary fiber in the NHANES, 1999–2004. *Nutrients*. 2021;13(3):813.
4580. Hagan T, Cortese M, Rouphael N, et al. Antibiotics-driven gut microbiome perturbation alters immunity to vaccines in humans. *Cell*. 2019;178(6):1313–28.e13.
4581. Yeh TL, Shih PC, Liu SJ, et al. The influence of prebiotic or probiotic supplementation on antibody titers after influenza vaccination: a systematic review and meta-analysis of randomized controlled trials. *Drug Des Devel Ther*. 2018;12:217–30.
4582. Haak BW, Littmann ER, Chaubard JL, et al. Impact of gut colonization with butyrate-producing microbiota on respiratory viral infection following allo-HCT. *Blood*. 2018;131(26):2978–86.
4583. Williams LM, Stoodley IL, Berthon BS, Wood LG. The effects of prebiotics, synbiotics, and short-chain fatty acids on respiratory tract infections and immune function: a systematic review and meta-analysis. *Adv Nutr*. 2022;13(1):167–92.
4584. Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database Syst Rev*. 2015; (2):CD006895.
4585. Guillemard E, Tondu F, Lacoin F, Schrezenmeir J. Consumption of a fermented dairy product containing the probiotic *Lactobacillus casei* DN-114001 reduces the duration of respiratory infections in the elderly in a randomised controlled trial. *Br J Nutr*. 2010;103(1):58–68.
4586. Fujita R, Iimuro S, Shinozaki T, et al. Decreased duration of acute upper respiratory tract infections with daily intake of fermented milk:

a multicenter, double-blinded, randomized comparative study in users of day care facilities for the elderly population. *Am J Infect Control*. 2013;41(12):1231–5.

4587. Turchet P, Laurenzano M, Auboiron S, Antoine JM. Effect of fermented milk containing the probiotic *Lactobacillus casei* DN-114001 on winter infections in free-living elderly subjects: a randomised, controlled pilot study. *J Nutr Health Aging*. 2003;7(2):75–7.

4588. Xu W, Wong G, Hwang YY, Larbi A. The untwining of immunosenescence and aging. *Semin Immunopathol*. 2020;42(5):559–72.

4589. Malter M, Schriever G, Eilber U. Natural killer cells, vitamins, and other blood components of vegetarian and omnivorous men. *Nutr Cancer*. 1989;12(3):271–8.

4590. Franco EL. The sexually transmitted disease model for cervical cancer: incoherent epidemiologic findings and the role of misclassification of human papillomavirus infection. *Epidemiology*. 1991;2(2):98–106.

4591. Skrabanek P. Cervical cancer in nuns and prostitutes: a plea for scientific continence. *J Clin Epidemiol*. 1988;41(6):577–82.

4592. Snijders PJF, Steenbergen RDM, Heideman DAM, Meijer CJLM. HPV-mediated cervical carcinogenesis: concepts and clinical implications. *J Pathol*. 2006;208(2):152–64.

4593. Goldstein MA, Goodman A, del Carmen MG, Wilbur DC. Case 10–2009: a 23-year-old woman with an abnormal Papanicolaou smear. Cabot RC, Harris NL, Shepard JAO, et al., eds. *N Engl J Med*. 2009;360(13):1337–44.

4594. Srivastava S, Gupta S, Roy JK. High prevalence of oncogenic HPV-16 in cervical smears of asymptomatic women of eastern Uttar Pradesh, India: a population-based study. *J Biosci*. 2012;37(1):63–72.

4595. Sedjo RL, Roe DJ, Abrahamsen M, et al. Vitamin A, carotenoids, and risk of persistent oncogenic human papillomavirus infection. *Cancer Epidemiol Biomarkers Prev*. 2002;11(9):876–84.

4596. Tantamango-Bartley Y, Jaceldo-Siegl K, Fan J, Fraser G. Vegetarian diets and the incidence of cancer in a low-risk population. *Cancer Epidemiol Biomarkers Prev*. 2013;22(2):286–94.

4597. Haddad EH, Berk LS, Kettering JD, Hubbard RW, Peters WR. Dietary intake and biochemical, hematologic, and immune status of vegans compared with nonvegetarians. *Am J Clin Nutr*. 1999;70(3 Suppl):586S-93S.
4598. Merino J, Joshi AD, Nguyen LH, et al. Diet quality and risk and severity of COVID-19: a prospective cohort study. *Gut*. 2021;70(11):2096–104.
4599. Hyun SH, Ahn HY, Kim HJ, et al. Immuno-enhancement effects of Korean Red Ginseng in healthy adults: a randomized, double-blind, placebo-controlled trial. *J Ginseng Res*. 2021;45(1):191–8.
4600. Kim MS. Korean red ginseng tonic extends lifespan in *D. melanogaster*. *Biomol Ther (Seoul)*. 2013;21(3):241–5.
4601. Wang H, Zhang S, Zhai L, et al. Ginsenoside extract from ginseng extends lifespan and health span in *Caenorhabditis elegans*. *Food Funct*. 2021;12(15):6793–808.
4602. Bittles AH, Fulder SJ, Grant EC, Nicholls MR. The effect of ginseng on lifespan and stress responses in mice. *Gerontology*. 1979;25(3):125–31.
4603. Carabin IG, Burdock GA, Chatzidakis C. Safety assessment of *Panax* ginseng. *Int J Toxicol*. 2000;19(4):293–301.
4604. Hyun SH, Ahn HY, Kim HJ, et al. Immuno-enhancement effects of Korean Red Ginseng in healthy adults: a randomized, double-blind, placebo-controlled trial. *J Ginseng Res*. 2021;45(1):191–8.
4605. Scaglione F, Ferrara F, Dugnani S, Falchi M, Santoro G, Fraschini F. Immunomodulatory effects of two extracts of *Panax* ginseng C.A. Meyer. *Drugs Exp Clin Res*. 1990;16(10):537–42.
4606. Antonelli M, Donelli D, Firenzuoli F. Ginseng integrative supplementation for seasonal acute upper respiratory infections: a systematic review and meta-analysis. *Complement Ther Med*. 2020;52:102457.
4607. Siegel RK. Ginseng abuse syndrome. Problems with the panacea. *JAMA*. 1979;241(15):1614–5.
4608. Norelli LJ, Xu C. Manic psychosis associated with ginseng: a report of two cases and discussion of the literature. *J Diet Suppl*. 2015;12(2):119–25.

4609. Kakisaka Y, Ohara T, Tozawa H, et al. Panax ginseng: a newly identified cause of gynecomastia. *Tohoku J Exp Med*. 2012;228(2):143–5.
4610. Viviano A, Steele D, Edsell M, Jahangiri M. Over-the-counter natural products in cardiac surgery: a case of ginseng-related massive perioperative bleeding. *BMJ Case Rep*. 2017;2017:bcr-2016–218068.
4611. Antonelli M, Donelli D, Firenzuoli F. Ginseng integrative supplementation for seasonal acute upper respiratory infections: a systematic review and meta-analysis. *Complement Ther Med*. 2020;52:102457.
4612. Alam I, Almajwal AM, Alam W, et al. The immune–nutrition interplay in aging—facts and controversies. *Nutr Healthy Aging*. 2019;5(2):73–95.
4613. Lesourd B. Nutritional factors and immunological ageing. *Proc Nutr Soc*. 2006;65(3):319–25.
4614. Chandra RK. Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects. *Lancet*. 1992;340(8828):1124–7.
4615. Lesourd B. Nutritional factors and immunological ageing. *Proc Nutr Soc*. 2006;65(3):319–25.
4616. Editors of The Lancet. Retraction—effect of vitamin and trace-element supplementation on immune responses and infection in elderly subject. *Lancet*. 2016;387(10017):417.
4617. Retraction and closure – Nutr Res 2002;22: 5–11 and Nutr Res 2002;22: 85–87. *Nutr Res*. 2016;36(7):756.
4618. Roberts S, Sternberg S. Do nutritional supplements improve cognitive function in the elderly? *Nutrition*. 2003;19(11–12):976–8.
4619. Pryse-Phillips W. Inquiry into Dr. RK Chandra's submitted paper to the BMJ #00/5797. Published October 23, 2009. Accessed Aug 10, 2021.
4620. Vlieg-Boerstra B, de Jong N, Meyer R, et al. Nutrient supplementation for prevention of viral respiratory tract infections in healthy subjects: a systematic review and meta-analysis. *Allergy*. 2022;77(5):1373–88.
4621. Graat JM, Schouten EG, Kok FJ. Effect of daily vitamin E and multivitamin–mineral supplementation on acute respiratory tract

infections in elderly persons: a randomized controlled trial. *JAMA*. 2002;288(6):715–21.

4622. Liu BA, McGeer A, McArthur MA, et al. Effect of multivitamin and mineral supplementation on episodes of infection in nursing home residents: a randomized, placebo-controlled study. *J Am Geriatr Soc*. 2007;55(1):35–42.

4623. Girodon F, Galan P, Monget AL, et al. Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients: a randomized controlled trial. *Arch Intern Med*. 1999;159(7):748–54.

4624. Carpenter KJ. The discovery of vitamin C. *Ann Nutr Metab*. 2012;61(3):259–64.

4625. Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. *Cochrane Database Syst Rev*. 2013;(1):CD000980.

4626. Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. *Cochrane Database Syst Rev*. 2013;(1):CD000980.

4627. Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. *J Am Soc Nephrol*. 2004;15(12):3225–32.

4628. Thomas LDK, Elinder CG, Tiselius HG, Wolk A, Åkesson A. Ascorbic acid supplements and kidney stone incidence among men: a prospective study. *JAMA Intern Med*. 2013;173(5):386.

4629. Thomas LDK, Elinder CG, Tiselius HG, Wolk A, Åkesson A. Ascorbic acid supplements and kidney stone incidence among men: a prospective study. *JAMA Intern Med*. 2013;173(5):386.

4630. Goncalves-Mendes N, Talvas J, Dualé C, et al. Impact of vitamin D supplementation on influenza vaccine response and immune functions in deficient elderly persons: a randomized placebo-controlled trial. *Front Immunol*. 2019;10:65.

4631. Jolliffe DA, Camargo CA, Sluyter JD, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. *Lancet Diabetes Endocrinol*. 2021;9(5):276–92.

4632. Meydani SN, Meydani M, Blumberg JB, et al. Vitamin E supplementation and in vivo immune response in healthy elderly subjects. A randomized controlled trial. *JAMA*. 1997;277(17):1380–6.

4633. Graat JM, Schouten EG, Kok FJ. Effect of daily vitamin E and multivitamin–mineral supplementation on acute respiratory tract infections in elderly persons: a randomized controlled trial. *JAMA*. 2002;288(6):715–21.
4634. Klein EA, Thompson IM, Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*. 2011;306(14):1549–56.
4635. Curtis AJ, Bullen M, Piccenna L, McNeil JJ. Vitamin E supplementation and mortality in healthy people: a meta-analysis of randomised controlled trials. *Cardiovasc Drugs Ther*. 2014;28(6):563–73.
4636. Kasprak A. Did a noted pathologist write this viral coronavirus advice letter? Snopes. https://www.snopes.com/fact-check/zinc-lozenges-coronavirus/. Published March 2, 2020. Updated March 13, 2020. Accessed May 22, 2022.
4637. Monto AS. Medical reviews. Coronaviruses. *Yale J Biol Med*. 1974;47(4):234–51.
4638. Hemilä H. Zinc lozenges and the common cold: a meta-analysis comparing zinc acetate and zinc gluconate, and the role of zinc dosage. *JRSM Open*. 2017;8(5):2054270417694291.
4639. Hemilä H, Petrus EJ, Fitzgerald JT, Prasad A. Zinc acetate lozenges for treating the common cold: an individual patient data meta-analysis. *Br J Clin Pharmacol*. 2016;82(5):1393–8.
4640. Hemilä H, Chalker E. The effectiveness of high dose zinc acetate lozenges on various common cold symptoms: a meta-analysis. *BMC Fam Pract*. 2015;16:24.
4641. Hemilä H. Zinc lozenges and the common cold: a meta-analysis comparing zinc acetate and zinc gluconate, and the role of zinc dosage. *JRSM Open*. 2017;8(5):2054270417694291.
4642. Singh M, Das RR. Zinc for the common cold. *Cochrane Database Syst Rev*. 2013;(6):CD001364.
4643. Sempértegui F, Estrella B, Rodríguez O, et al. Zinc as an adjunct to the treatment of severe pneumonia in Ecuadorian children: a randomized controlled trial. *Am J Clin Nutr*. 2014;99(3):497–505.
4644. Prasad AS. Impact of the discovery of human zinc deficiency on health. *J Am Coll Nutr*. 2009;28(3):257–65.

4645. Ervin RB, Kennedy-Stephenson J. Mineral intakes of elderly adult supplement and non-supplement users in the third National Health and Nutrition Examination Survey. *J Nutr*. 2002;132(11):3422–7.
4646. King JC. Yet again, serum zinc concentrations are unrelated to zinc intakes. *J Nutr*. 2018;148(9):1399–401.
4647. Agricultural Research Service, United States Department of Agriculture. Mollusks, oysters, eastern, canned. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html?query=oysters&utf8=%E2%9C%93&affiliate=usda&commit=Search#/food-details/171981/nutrients. Published April 1, 2019. Accessed May 20, 2022.
4648. Agricultural Research Service, United States Department of Agriculture. Beans, baked, canned, plain or vegetarian. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html?query=baked+beans&utf8=%E2%9C%93&affiliate=usda&commit=Search#/food-details/175182/nutrients. Published April 1, 2019. Accessed May 20, 2022.
4649. Abioye AI, Bromage S, Fawzi W. Effect of micronutrient supplements on influenza and other respiratory tract infections among adults: a systematic review and meta-analysis. *BMJ Glob Health*. 2021;6(1):e003176.
4650. Bogden JD, Oleske JM, Lavenhar MA, et al. Effects of one year of supplementation with zinc and other micronutrients on cellular immunity in the elderly. *J Am Coll Nutr*. 1990;9(3):214–25.
4651. Duchateau J, Delepesse G, Vrijens R, Collet H. Beneficial effects of oral zinc supplementation on the immune response of old people. *Am J Med*. 1981;70(5):1001–4.
4652. Provinciali M, Montenovo A, Di Stefano G, et al. Effect of zinc or zinc plus arginine supplementation on antibody titre and lymphocyte subsets after influenza vaccination in elderly subjects: a randomized controlled trial. *Age Ageing*. 1998;27(6):715–22.
4653. Singh M, Das RR. Zinc for the common cold. *Cochrane Database Syst Rev*. 2013;(6):CD001364.
4654. Davidson TM, Smith WM. The Bradford Hill criteria and zinc-induced anosmia: a causality analysis. *Arch Otolaryngol Head Neck Surg*. 2010;136(7):673–6.

4655. Eby GA. Treatment of acute lymphocytic leukemia using zinc adjuvant with chemotherapy and radiation—a case history and hypothesis. *Med Hypotheses*. 2005;64(6):1124–6.
4656. Centers for Disease Control and Prevention. Ten great public health achievements—United States, 1900–1999. *MMWR Morb Mortal Wkly Rep*. 1999;48(12):241–3.
4657. Vetter V, Denizer G, Friedland LR, Krishnan J, Shapiro M. Understanding modern-day vaccines: what you need to know. *Ann Med*. 2018;50(2):110–20.
4658. Delany I, Rappuoli R, De Gregorio E. Vaccines for the 21st century. *EMBO Mol Med*. 2014;6(6):708–20.
4659. Slifka AM, Park B, Gao L, Slifka MK. Incidence of tetanus and diphtheria in relation to adult vaccination schedules. *Clin Infect Dis*. 2021;72(2):285–92.
4660. National Center for Immunization and Respiratory Diseases. Adult immunization schedule by vaccine and age group: recommendations for ages 19 years or older, United States, 2022. Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html. Updated February 17, 2022. Accessed May 18, 2022.
4661. Gidengil C, Goetz MB, Newberry S, et al. Safety of vaccines used for routine immunization in the United States: an updated systematic review and meta-analysis. *Vaccine*. 2021;39(28):3696–716.
4662. Dudley MZ, Halsey NA, Omer SB, et al. The state of vaccine safety science: systematic reviews of the evidence. *Lancet Infect Dis*. 2020;20(5):e80–9.
4663. Rolfes MA, Foppa IM, Garg S, et al. Annual estimates of the burden of seasonal influenza in the United States: a tool for strengthening influenza surveillance and preparedness. *Influenza Other Respir Viruses*. 2018;12(1):132–7.
4664. Hunter P, Fryhofer SA, Szilagyi PG. Vaccination of adults in general medical practice. *Mayo Clin Proc*. 2020;95(1):169–83.
4665. Resnick B, Gravenstein S, Schaffner W, Sobczyk E, Douglas RG. Beyond prevention of influenza: the value of flu vaccines. *J Gerontol A Biol Sci Med Sci*. 2018;73(12):1635–7.

4666. Grohskopf LA, Alyanak E, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2019–20 influenza season. *MMWR Recomm Rep*. 2019;68(3):1–21.
4667. Hunter P, Fryhofer SA, Szilagyi PG. Vaccination of adults in general medical practice. *Mayo Clin Proc*. 2020;95(1):169–83.
4668. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. *Vaccine*. 2006;24(8):1159–69.
4669. Effectiveness of seasonal flu vaccines from the 2005—2021 flu seasons. Centers for Disease Control and Prevention. https://www.cdc.gov/flu/images/vaccines-work/Vaccine-Effectiveness-Graphs-2021.pptx. Updated March 11, 2022. Accessed May 23, 2022.
4670. Demicheli V, Rivetti D, Deeks JJ, Jefferson TO. Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev*. 2004;(3):CD001269.
4671. Demicheli V, Jefferson T, Di Pietrantonj C, et al. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev*. 2018;2:CD004876.4
4672. Coll PP, Costello VW, Kuchel GA, Bartley J, McElhaney JE. The prevention of infections in older adults: vaccination. *J Am Geriatr Soc*. 2020;68(1):207–14.
4673. Influenza vaccine for 2019–2020. *Med Lett Drugs Ther*. 2019;61(1583):161–6.
4674. Coll PP, Costello VW, Kuchel GA, Bartley J, McElhaney JE. The prevention of infections in older adults: vaccination. *J Am Geriatr Soc*. 2020;68(1):207–14.
4675. Dudley MZ, Halsey NA, Omer SB, et al. The state of vaccine safety science: systematic reviews of the evidence. *Lancet Infect Dis*. 2020;20(5):e80–9.
4676. Influenza vaccine for 2019–2020. *Med Lett Drugs Ther*. 2019;61(1583):161–6.
4677. Demicheli V, Jefferson T, Di Pietrantonj C, et al. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev*.

2018;2:CD004876.4
4678. Kwong JC, Schwartz KL, Campitelli MA, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med*. 2018;378(4):345–53.
4679. Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary syndromes. *Lancet Infect Dis*. 2010;10(2):83–92.
4680. Cheng Y, Cao X, Cao Z, et al. Effects of influenza vaccination on the risk of cardiovascular and respiratory diseases and all-cause mortality. *Ageing Res Rev*. 2020;62:101124.
4681. Okoli GN, Lam OLT, Racovitan F, et al. Seasonal influenza vaccination in older people: a systematic review and meta-analysis of the determining factors. *PLoS One*. 2020;15(6):e0234702.
4682. Yedlapati SH, Khan SU, Talluri S, et al. Effects of influenza vaccine on mortality and cardiovascular outcomes in patients with cardiovascular disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2021;10(6):e019636.
4683. Clar C, Oseni Z, Flowers N, Keshtkar-Jahromi M, Rees K. Influenza vaccines for preventing cardiovascular disease. *Cochrane Database Syst Rev*. 2015;(5):CD005050.
4684. Nyhan B, Reifler J. Does correcting myths about the flu vaccine work? An experimental evaluation of the effects of corrective information. *Vaccine*. 2015;33(3):459–64.
4685. Nyhan B, Reifler J, Richey S, Freed GL. Effective messages in vaccine promotion: a randomized trial. *Pediatrics*. 2014;133(4):e835–42.
4686. Meszaros JR, Asch DA, Baron J, Hershey JC, Kunreuther H, Schwartz-Buzaglo J. Cognitive processes and the decisions of some parents to forego pertussis vaccination for their children. *J Clin Epidemiol*. 1996;49(6):697–703.
4687. Nyhan B, Reifler J. Does correcting myths about the flu vaccine work? An experimental evaluation of the effects of corrective information. *Vaccine*. 2015;33(3):459–64.
4688. "Father of modern medicine": the Johns Hopkins School of Medicine, 1889–1905. William Osler-Profiles in Science. NIH National Library of Medicine.

https://profiles.nlm.nih.gov/spotlight/gf/feature/father-of-modern-medicine-the-johns-hopkins-school-of-medicine-1889-1905. Accessed May 20, 2022.

4689. Brancati FL, Chow JW, Wagener MM, Vacarello SJ, Yu VL. Is pneumonia really the old man's friend? Two-year prognosis after community-acquired pneumonia. *Lancet*. 1993;342(8862):30–3.

4690. The top 10 causes of death. World Health Organization. https://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death. Published December 9, 2022. Accessed May 20, 2022.

4691. Heron M. Deaths: leading causes for 2019. *Natl Vital Stat Rep*. 2021;70(9):1–114.

4692. van Werkhoven CH, Huijts SM. Vaccines to prevent pneumococcal community-acquired pneumonia. *Clin Chest Med*. 2018;39(4):733–52.

4693. van Werkhoven CH, Huijts SM. Vaccines to prevent pneumococcal community-acquired pneumonia. *Clin Chest Med*. 2018;39(4):733–52.

4694. US Department of Health and Human Services. Antibiotics resistance threats in the United States: 2019. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf. Centers for Disease Control and Prevention, US Dept of Health and Human Services. Updated December 2019. Accessed May 20, 2022.

4695. Crooke SN, Ovsyannikova IG, Poland GA, Kennedy RB. Immunosenescence and human vaccine immune responses. *Immun Ageing*. 2019;16:25.

4696. Thomas RE. Pneumococcal pneumonia and invasive pneumococcal disease in those 65 and older: rates of detection, risk factors, vaccine effectiveness, hospitalisation and mortality. *Geriatrics (Basel)*. 2021;6(1):13.

4697. Jaiswal V, Ang SP, Lnu K, et al. Effect of pneumococcal vaccine on mortality and cardiovascular outcomes: a systematic review and meta-analysis. *J Clin Med*. 2022;11(13):3799.

4698. Ecarnot F, Bernabei R, Gabutti G, et al. Adult vaccination as the cornerstone of successful ageing: the case of herpes zoster

vaccination. A European Interdisciplinary Council on Ageing (EICA) expert focus group. *Aging Clin Exp Res*. 2019;31(3):301–7.
4699. McElhaney JE, Verschoor C, Pawelec G. Zoster vaccination in older adults: efficacy and public health implications. *J Gerontol A Biol Sci Med Sci.* 2019;74(8):1239–43.
4700. Gagliardi AMZ, Andriolo BNG, Torloni MR, et al. Vaccines for preventing herpes zoster in older adults. *Cochrane Database Syst Rev*. 2019;2019(11):CD008858.
4701. Schmader K. Herpes zoster. *Ann Intern Med*. 2018;169(3):ITC17.
4702. Schmader K. Herpes zoster. *Ann Intern Med*. 2018;169(3):ITC17.
4703. Zuin M, Rigatelli G, Adami A. Cerebrovascular events after herpes zoster infection: a risk that should be not underestimated. *J Neurovirol*. 2019;25(4):439–47.
4704. Johnson RW, Levin MJ. Herpes zoster and its prevention by vaccination. *Interdiscip Top Gerontol Geriatr*. 2020;43:131–45.
4705. Coll PP, Costello VW, Kuchel GA, Bartley J, McElhaney JE. The prevention of infections in older adults: vaccination. *J Am Geriatr Soc*. 2020;68(1):207–14.
4706. Shafran SD. Prevention of shingles: better protection and better value with recombinant vaccine. *Ann Intern Med*. 2019;170(6):416–7.
4707. Schmader K. Herpes zoster. *Ann Intern Med*. 2018;169(3):ITC17.
4708. Shafran SD. Prevention of shingles: better protection and better value with recombinant vaccine. *Ann Intern Med*. 2019;170(6):416–7.
4709. Johnson RW, Levin MJ. Herpes zoster and its prevention by vaccination. *Interdiscip Top Gerontol Geriatr*. 2020;43:131–45.
4710. Le P. Which shingles vaccine for older adults? *BMJ*. 2018;363:k4203.
4711. Thijssen E, van Caam A, van der Kraan PM. Obesity and osteoarthritis, more than just wear and tear: pivotal roles for inflamed adipose tissue and dyslipidaemia in obesity-induced osteoarthritis. *Rheumatology (Oxford)*. 2015;54(4):588–600.
4712. Kulkarni K, Karssiens T, Kumar V, Pandit H. Obesity and osteoarthritis. *Maturitas*. 2016;89:22–8.
4713. Charlesworth J, Fitzpatrick J, Perera NKP, Orchard J. Osteoarthritis—a systematic review of long-term safety implications for osteoarthritis of the knee. *BMC Musculoskelet Disord*. 2019;20(1):151.

4714. Berenbaum F, Walker C. Osteoarthritis and inflammation: a serious disease with overlapping phenotypic patterns. *Postgrad Med*. 2020;132(4):377–84.
4715. Gress K, Charipova K, An D, et al. Treatment recommendations for chronic knee osteoarthritis. *Best Pract Res Clin Anaesthesiol*. 2020;34(3):369–82.
4716. Leopoldino AO, Machado GC, Ferreira PH, et al. Paracetamol versus placebo for knee and hip osteoarthritis. *Cochrane Database Syst Rev*. 2019;2019(2):CD013273.
4717. Negrini F, Negrini S. Is paracetamol better than placebo for knee and hip osteoarthritis? A Cochrane review summary with commentary. *Int J Rheum Dis*. 2020;23(4):595–6.
4718. Leopoldino AO, Machado GC, Ferreira PH, et al. Paracetamol versus placebo for knee and hip osteoarthritis. *Cochrane Database Syst Rev*. 2019;2019(2):CD013273.
4719. Negrini F, Negrini S. Is paracetamol better than placebo for knee and hip osteoarthritis? A Cochrane review summary with commentary. *Int J Rheum Dis*. 2020;23(4):595–6.
4720. Bunchorntavakul C, Reddy KR. Acetaminophen (APAP or N-acetyl-p-aminophenol) and acute liver failure. *Clin Liver Dis*. 2018;22(2):325–46.
4721. Conaghan PG, Arden N, Avouac B, Migliore A, Rizzoli R. Safety of paracetamol in osteoarthritis: what does the literature say? *Drugs Aging*. 2019;36(Suppl 1):7–14.
4722. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *BMJ*. 2015;350:h1225.
4723. Berenbaum F, Walker C. Osteoarthritis and inflammation: a serious disease with overlapping phenotypic patterns. *Postgrad Med*. 2020;132(4):377–84.
4724. Chow YY, Chin KY. The role of inflammation in the pathogenesis of osteoarthritis. *Mediators Inflamm*. 2020;2020:8293921.
4725. Cooper C, Chapurlat R, Al-Daghri N, et al. Safety of oral non-selective non-steroidal anti-inflammatory drugs in osteoarthritis: what does the literature say? *Drugs Aging*. 2019;36(Suppl 1):15–24.

4726. Ho KY, Cardosa MS, Chaiamnuay S, et al. Practice advisory on the appropriate use of NSAIDs in primary care. *J Pain Res*. 2020;13:1925–39.
4727. Cooper C, Chapurlat R, Al-Daghri N, et al. Safety of oral non-selective non-steroidal anti-inflammatory drugs in osteoarthritis: what does the literature say? *Drugs Aging*. 2019;36(Suppl 1):15–24.
4728. Ong CKS, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. *Clin Med Res*. 2007;5(1):19–34.
4729. Bally M, Dendukuri N, Rich B, et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *BMJ*. 2017;357:j1909.
4730. Cooper C, Chapurlat R, Al-Daghri N, et al. Safety of oral non-selective non-steroidal anti-inflammatory drugs in osteoarthritis: what does the literature say? *Drugs Aging*. 2019;36(Suppl 1):15–24.
4731. Zhang X, Donnan PT, Bell S, Guthrie B. Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: systematic review and meta-analysis. *BMC Nephrol*. 2017;18(1):256.
4732. American Geriatrics Society recommends opioids as second-line therapy for chronic pain, instead of NSAIDs. *Topics in Pain Management*. 2009;25(1):9–10.
4733. Cooper C, Chapurlat R, Al-Daghri N, et al. Safety of oral non-selective non-steroidal anti-inflammatory drugs in osteoarthritis: what does the literature say? *Drugs Aging*. 2019;36(Suppl 1):15–24.
4734. Nissen SE. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med*. 2017;376(14):1390.
4735. Ho KY, Cardosa MS, Chaiamnuay S, et al. Practice advisory on the appropriate use of NSAIDs in primary care. *J Pain Res*. 2020;13:1925–39.
4736. Reginster JY, Bruyère O, Conaghan PG, McAlindon T, Cooper C. Importance of safety in the management of osteoarthritis and the need for updated meta-analyses and recommendations for reporting of harms. *Drugs Aging*. 2019;36(Suppl 1):3–6.
4737. FDA approves three drugs for nonprescription use through Rx-to-OTC switch process. U.S. Food & Drug Administration.

https://www.fda.gov/news-events/press-announcements/fda-approves-three-drugs-nonprescription-use-through-rx-otc-switch-process. Published February 14, 2020. Accessed June 1, 2022.
4738. Derry S, Conaghan P, Da Silva JAP, Wiffen PJ, Moore RA. Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev*. 2016;4:CD007400.
4739. Reginster JY, Bruyère O, Conaghan PG, McAlindon T, Cooper C. Importance of safety in the management of osteoarthritis and the need for updated meta-analyses and recommendations for reporting of harms. *Drugs Aging*. 2019;36(Suppl 1):3–6.
4740. Honvo G, Leclercq V, Geerinck A, et al. Safety of topical non-steroidal anti-inflammatory drugs in osteoarthritis: outcomes of a systematic review and meta-analysis. *Drugs Aging*. 2019;36(Suppl 1):45–64.
4741. Lim CC, Ang ATW, Kadir HBA, et al. Short-course systemic and topical non-steroidal anti-inflammatory drugs: impact on adverse renal events in older adults with co-morbid disease. *Drugs Aging*. 2021;38(2):147–56.
4742. Lin T, Solomon DH, Tedeschi SK, Yoshida K, Kao Yang Y. Comparative risk of cardiovascular outcomes between topical and oral nonselective NSAIDs in Taiwanese patients with rheumatoid arthritis. *JAHA*. 2017;6(11):e006874.
4743. Koenig KM, Ong KL, Lau EC, et al. The use of hyaluronic acid and corticosteroid injections among Medicare patients with knee osteoarthritis. *J Arthroplasty*. 2016;31(2):351–5.
4744. Latourte A, Lellouche H. Update on corticosteroid, hyaluronic acid and platelet-rich plasma injections in the management of osteoarthritis. *Joint Bone Spine*. 2021;88(6):105204.
4745. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis. *JAMA*. 2017;317(19):1967–75.
4746. Orchard JW. Is there a place for intra-articular corticosteroid injections in the treatment of knee osteoarthritis? *BMJ*. 2020;368:l6923.
4747. Kompel AJ, Roemer FW, Murakami AM, Diaz LE, Crema MD, Guermazi A. Intra-articular corticosteroid injections in the hip and

knee: perhaps not as safe as we thought? *Radiology*. 2019;293(3):656–63.
4748. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis. *JAMA*. 2017;317(19):1967–75.
4749. Bliddal H, Henriksen M. Osteoarthritis: time to put steroid injections behind us? *Nat Rev Rheumatol*. 2017;13(9):519–20.
4750. Jevsevar DS. Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. *J Am Acad Orthop Surg*. 2013;21(9):571–6.
4751. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med*. 2002;347(2):81–8.
4752. Maffulli N. We are operating too much. *J Orthop Traumatol*. 2017;18(4):289–92.
4753. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med*. 2002;347(2):81–8.
4754. McCormack RG, Hutchinson MR. Rocking the shoulder surgeon's world. *Br J Sports Med*. 2017;51(24):1727.
4755. Horton R. Surgical research or comic opera: questions, but few answers. *Lancet*. 1996;347(9007):984–5.
4756. Lim HC, Adie S, Naylor JM, Harris IA. Randomised trial support for orthopaedic surgical procedures. *PLoS One*. 2014;9(6):e96745.
4757. Wartolowska K, Judge A, Hopewell S, et al. Use of placebo controls in the evaluation of surgery: systematic review. *BMJ*. 2014;348:g3253.
4758. Thorlund JB, Juhl CB, Roos EM, Lohmander LS. Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms. *BMJ*. 2015;350:h2747.
4759. Rongen JJ, Rovers MM, van Tienen TG, Buma P, Hannink G. Increased risk for knee replacement surgery after arthroscopic surgery for degenerative meniscal tears: a multi-center longitudinal observational study using data from the osteoarthritis initiative. *Osteoarthritis Cartilage*. 2017;25(1):23–9.
4760. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med*.

2002;347(2):81–8.
4761. Thorlund JB. Deconstructing a popular myth: why knee arthroscopy is no better than placebo surgery for degenerative meniscal tears. *Br J Sports Med*. 2017;51(22):1630–1.
4762. Zhang W. The powerful placebo effect in osteoarthritis. *Clin Exp Rheumatol*. 2019;37 Suppl 120(5):118–23.
4763. Radiation dose. RadiologyInfo.org. https://www.radiologyinfo.org/en/info/safety-xray#81426d679d504b8f9a595b2b5d7d1eff. Published February 1, 2021. Accessed May 31, 2022.
4764. Mahler EAM, Minten MJM, Leseman-Hoogenboom MM, et al. Effectiveness of low-dose radiation therapy on symptoms in patients with knee osteoarthritis: a randomised, double-blinded, sham-controlled trial. *Ann Rheum Dis*. 2019;78(1):83–90.
4765. Blackwell B, Bloomfield SS, Buncher CR. Demonstration to medical students of placebo responses and non-drug factors. *Lancet*. 1972;1(7763):1279–82.
4766. de Craen AJM, Roos PJ, de Vries AL, Kleijnen J. Effect of colour of drugs: systematic review of perceived effect of drugs and of their effectiveness. *BMJ*. 1996;313(7072):1624–6.
4767. Branthwaite A, Cooper P. Analgesic effects of branding in treatment of headaches. *BMJ*. 1981;282(6276):1576–8.
4768. Waber RL, Shiv B, Carmon Z, Ariely D. Commercial features of placebo and therapeutic efficacy. *JAMA*. 2008;299(9):1016–7.
4769. Zhang W, Zou K, Doherty M. Placebos for knee osteoarthritis: reaffirmation of "needle is better than pill." *Ann Intern Med*. 2015;163(5):392–3.
4770. Previtali D, Merli G, Di Laura Frattura G, Candrian C, Zaffagnini S, Filardo G. The long-lasting effects of "placebo injections" in knee osteoarthritis: a meta-analysis. *Cartilage*. 2021;13(1_suppl):185S-96S.
4771. Zhang W. The powerful placebo effect in osteoarthritis. *Clin Exp Rheumatol*. 2019;37 Suppl 120(5):118–23.
4772. Kaptchuk TJ, Stason WB, Davis RB, et al. Sham device *v* inert pill: randomised controlled trial of two placebo treatments. *BMJ*. 2006;332(7538):391–7.

4773. Jevsevar DS. Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. *J Am Acad Orthop Surg*. 2013;21(9):571–6.
4774. Starfield B. Is US health really the best in the world? *JAMA*. 2000;284(4):483–5.
4775. Fässler M, Meissner K, Schneider A, Linde K. Frequency and circumstances of placebo use in clinical practice—a systematic review of empirical studies. *BMC Med*. 2010;8:15.
4776. Zhang W. The powerful placebo effect in osteoarthritis. *Clin Exp Rheumatol*. 2019;37 Suppl 120(5):118–23.
4777. Plato. *The Republic*. The Project Gutenberg. https://www.gutenberg.org/files/1497/1497-h/1497-h.htm. Published October 1998. Updated September 11, 2021. Accessed June 5, 2022.
4778. Doherty M, Dieppe P. The "placebo" response in osteoarthritis and its implications for clinical practice. *Osteoarthritis Cartilage*. 2009;17(10):1255–62.
4779. The humble humbug. *Lancet*. 1954;264(6833):321.
4780. de Campos GC. Placebo effect in osteoarthritis: why not use it to our advantage? *World J Orthop*. 2015;6(5):416–20.
4781. Leslie A. Ethics and practice of placebo therapy. *Am J Med*. 1954;16(6):854–62.
4782. Bortoluzzi A, Furini F, Scirè CA. Osteoarthritis and its management – Epidemiology, nutritional aspects and environmental factors. *Autoimmun Rev*. 2018;17(11):1097–104.
4783. Kulkarni K, Karssiens T, Kumar V, Pandit H. Obesity and osteoarthritis. *Maturitas*. 2016;89:22–8.
4784. Berenbaum F, Wallace IJ, Lieberman DE, Felson DT. Modern-day environmental factors in the pathogenesis of osteoarthritis. *Nat Rev Rheumatol*. 2018;14(11):674–81.
4785. Bortoluzzi A, Furini F, Scirè CA. Osteoarthritis and its management – Epidemiology, nutritional aspects and environmental factors. *Autoimmun Rev*. 2018;17(11):1097–104.
4786. Issa RI, Griffin TM. Pathobiology of obesity and osteoarthritis: integrating biomechanics and inflammation. *Pathobiol Aging Age Relat Dis*. 2012;2(2012):17470.
4787. Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women.

Framingham Study. Ann Intern Med. 1992;116(7):535–9.
4788. Gersing AS, Schwaiger BJ, Nevitt MC, et al. Is weight loss associated with less progression of changes in knee articular cartilage among obese and overweight patients as assessed with MR imaging over 48 months? Data from the Osteoarthritis Initiative. *Radiology*. 2017;284(2):508–20.
4789. Christensen R, Astrup A, Bliddal H. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. *Osteoarthr Cartil*. 2005;13(1):20–7.
4790. Bernstein J. Not the last word: safety alert: one in 200 knee replacement patients die within 90 days of surgery. *Clin Orthop Relat Res*. 2017;475(2):318–23.
4791. Albanes D, Jones DY, Micozzi MS, Mattson ME. Associations between smoking and body weight in the US population: analysis of NHANES II. *Am J Public Health*. 1987;77(4):439–44.
4792. Hui M, Doherty M, Zhang W. Does smoking protect against osteoarthritis? Meta-analysis of observational studies. *Ann Rheum Dis*. 2011;70(7):1231–7.
4793. Amin S, Niu J, Guermazi A, et al. Cigarette smoking and the risk for cartilage loss and knee pain in men with knee osteoarthritis. *Ann Rheum Dis*. 2007;66(1):18–22.
4794. Järvholm B, Lewold S, Malchau H, Vingård E. Age, bodyweight, smoking habits and the risk of severe osteoarthritis in the hip and knee in men. *Eur J Epidemiol*. 2005;20(6):537–42.
4795. Palmieri-Smith RM, Cameron KL, DiStefano LJ, et al. The role of athletic trainers in preventing and managing posttraumatic osteoarthritis in physically active populations: a consensus statement of the Athletic Trainers' Osteoarthritis Consortium. *J Athl Train*. 2017;52(6):610–23.
4796. Blackwell B, Bloomfield SS, Buncher CR. Demonstration to medical students of placebo responses and non-drug factors. *Lancet*. 1972;1(7763):1279–82.
4797. Racunica TL, Teichtahl AJ, Wang Y, et al. Effect of physical activity on articular knee joint structures in community-based adults. *Arthritis Rheum*. 2007;57(7):1261–8.

4798. Berenbaum F, Wallace IJ, Lieberman DE, Felson DT. Modern-day environmental factors in the pathogenesis of osteoarthritis. *Nat Rev Rheumatol*. 2018;14(11):674–81.
4799. Juhl C, Christensen R, Roos EM, Zhang W, Lund H. Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-regression analysis of randomized controlled trials. *Arthritis Rheumatol*. 2014;66(3):622–36.
4800. Verhagen AP, Ferreira M, Reijneveld-van de Vendel EAE, et al. Do we need another trial on exercise in patients with knee osteoarthritis?: No new trials on exercise in knee OA. *Osteoarthritis Cartilage*. 2019;27(9):1266–9.
4801. Juhl C, Christensen R, Roos EM, Zhang W, Lund H. Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-regression analysis of randomized controlled trials. *Arthritis Rheumatol*. 2014;66(3):622–36.
4802. Verhagen AP, Ferreira M, Reijneveld-van de Vendel EAE, et al. Do we need another trial on exercise in patients with knee osteoarthritis?: No new trials on exercise in knee OA. *Osteoarthritis Cartilage*. 2019;27(9):1266–9.
4803. Charlesworth J, Fitzpatrick J, Perera NKP, Orchard J. Osteoarthritis – a systematic review of long-term safety implications for osteoarthritis of the knee. *BMC Musculoskelet Disord*. 2019;20(1):151.
4804. Dean E, Gormsen Hansen R. Prescribing optimal nutrition and physical activity as "first-line" interventions for best practice management of chronic low-grade inflammation associated with osteoarthritis: evidence synthesis. *Arthritis*. 2012;2012:1–28.
4805. Campbell TC. History of the term 'whole food, plant based.' T. Colin Campbell Center for Nutrition Studies. https://nutritionstudies.org/history-of-the-term-whole-food-plant-based/. Published November 29, 2016. Updated January 4, 2019. Accessed June 5, 2022.
4806. Wang Y, Teichtahl AJ, Abram F, et al. Knee pain as a predictor of structural progression over 4 years: data from the Osteoarthritis Initiative, a prospective cohort study. *Arthritis Res Ther*. 2018;20(1):250.

4807. Lu B, Driban JB, Xu C, Lapane KL, McAlindon TE, Eaton CB. Dietary fat intake and radiographic progression of knee osteoarthritis: data from the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)*. 2017;69(3):368–75.
4808. Sekar S, Shafie SR, Prasadam I, et al. Saturated fatty acids induce development of both metabolic syndrome and osteoarthritis in rats. *Sci Rep*. 2017;7:46457.
4809. Shen P, Zhu Y, Zhu L, Weng F, Li X, Xu Y. Oxidized low density lipoprotein facilitates tumor necrosis factor-α mediated chondrocyte death via autophagy pathway. *Mol Med Rep*. 2017;16(6):9449–56.
4810. Wu CL, Jain D, McNeill JN, et al. Dietary fatty acid content regulates wound repair and the pathogenesis of osteoarthritis following joint injury. *Ann Rheum Dis*. 2015;74(11):2076–83.
4811. Beier F. Cholesterol and cartilage do not mix well. *Nat Rev Rheumatol*. 2019;15(5):253–4.
4812. Sekar S, Shafie SR, Prasadam I, et al. Saturated fatty acids induce development of both metabolic syndrome and osteoarthritis in rats. *Sci Rep*. 2017;7:46457.
4813. Ertürk C, Altay MA, Bilge A, Çelik H. Is there a relationship between serum ox-LDL, oxidative stress, and PON1 in knee osteoarthritis? *Clin Rheumatol*. 2017;36(12):2775–80.
4814. Shen P, Zhu Y, Zhu L, Weng F, Li X, Xu Y. Oxidized low density lipoprotein facilitates tumor necrosis factor-α mediated chondrocyte death via autophagy pathway. *Mol Med Rep*. 2017;16(6):9449–56.
4815. Cillero-Pastor B, Eijkel G, Kiss A, Blanco FJ, Heeren RMA. Time-of-flight secondary ion mass spectrometry-based molecular distribution distinguishing healthy and osteoarthritic human cartilage. *Anal Chem*. 2012;84(21):8909–16.
4816. Shen P, Zhu Y, Zhu L, Weng F, Li X, Xu Y. Oxidized low density lipoprotein facilitates tumor necrosis factor-α mediated chondrocyte death via autophagy pathway. *Mol Med Rep*. 2017;16(6):9449–56.
4817. Ertürk C, Altay MA, Bilge A, Çelik H. Is there a relationship between serum ox-LDL, oxidative stress, and PON1 in knee osteoarthritis? *Clin Rheumatol*. 2017;36(12):2775–80.
4818. Wang J, Dong J, Yang J, Wang Y, Liu J. Association between statin use and incidence or progression of osteoarthritis: meta-analysis of

observational studies. *Osteoarthritis Cartilage*. 2020;28(9):1170–9.
4819. Haj-Mirzaian A, Mohajer B, Guermazi A, et al. Statin use and knee osteoarthritis outcome measures according to the presence of Heberden nodes: results from the Osteoarthritis Initiative. *Radiology*. 2019;293(2):396–404.
4820. Clockaerts S, Van Osch GJVM, Bastiaansen-Jenniskens YM, et al. Statin use is associated with reduced incidence and progression of knee osteoarthritis in the Rotterdam study. *Ann Rheum Dis*. 2012;71(5):642–7.
4821. Peeters G, Tett SE, Conaghan PG, Mishra GD, Dobson AJ. Is statin use associated with new joint-related symptoms, physical function, and quality of life? Results from two population-based cohorts of women. *Arthritis Care Res (Hoboken)*. 2015;67(1):13–20.
4822. Veronese N, Koyanagi A, Stubbs B, et al. Statin use and knee osteoarthritis outcomes: a longitudinal cohort study. *Arthritis Care Res (Hoboken)*. 2019;71(8):1052–8.
4823. Eymard F, Parsons C, Edwards MH, et al. Statin use and knee osteoarthritis progression: results from a post-hoc analysis of the SEKOIA trial. *Joint Bone Spine*. 2018;85(5):609–14.
4824. Beattie MS, Lane NE, Hung YY, Nevitt MC. Association of statin use and development and progression of hip osteoarthritis in elderly women. *J Rheumatol*. 2005;32(1):106–10.
4825. Wang J, Dong J, Yang J, Wang Y, Liu J. Association between statin use and incidence or progression of osteoarthritis: meta-analysis of observational studies. *Osteoarthritis Cartilage*. 2020;28(9):1170–9.
4826. Kendall CWC, Jenkins DJA. A dietary portfolio: maximal reduction of low-density lipoprotein cholesterol with diet. *Curr Atheroscler Rep*. 2004;6(6):492–8.
4827. Clinton CM, O'Brien S, Law J, Renier CM, Wendt MR. Whole-foods, plant-based diet alleviates the symptoms of osteoarthritis. *Arthritis*. 2015;2015:708152.
4828. Clinton CM, O'Brien S, Law J, Renier CM, Wendt MR. Whole-foods, plant-based diet alleviates the symptoms of osteoarthritis. *Arthritis*. 2015;2015:708152.
4829. Clinton CM, O'Brien S, Law J, Renier CM, Wendt MR. Whole-foods, plant-based diet alleviates the symptoms of osteoarthritis.

Arthritis. 2015;2015:708152.

4830. National Cancer Institute. Identification of Top Food Sources of Various Dietary Components. Epidemiology and Genomics Research Program. https://epi.grants.cancer.gov/diet/foodsources/top-food-sources-report-02212020.pdf. Updated November 30, 2019. Accessed June 2, 2022.

4831. Vane JR. The mode of action of aspirin and similar compounds. *J Allergy Clin Immunol*. 1976;58(6):691–712.

4832. Clinton CM, O'Brien S, Law J, Renier CM, Wendt MR. Whole-foods, plant-based diet alleviates the symptoms of osteoarthritis. *Arthritis*. 2015;2015:708152.

4833. Haug A, Olesen I, Christophersen OA. Individual variation and intraclass correlation in arachidonic acid and eicosapentaenoic acid in chicken muscle. *Lipids Health Dis*. 2010;9:37.

4834. Dean E, Gormsen Hansen R. Prescribing optimal nutrition and physical activity as "first-line" interventions for best practice management of chronic low-grade inflammation associated with osteoarthritis: evidence synthesis. *Arthritis*. 2012;2012:1–28.

4835. Toopchizadeh V, Dolatkhah N, Aghamohammadi D, Rasouli M, Hashemian M. Dietary inflammatory index is associated with pain intensity and some components of quality of life in patients with knee osteoarthritis. *BMC Res Notes*. 2020;13(1):448.

4836. Liu Q, Hebert JR, Shivappa N, et al. Inflammatory potential of diet and risk of incident knee osteoarthritis: a prospective cohort study. *Arthritis Res Ther*. 2020;22(1):209.

4837. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr.* 2014;17(8):1689–96.

4838. Nilsson AC, Östman EM, Knudsen KEB, Holst JJ, Björck IME. A cereal-based evening meal rich in indigestible carbohydrates increases plasma butyrate the next morning. *J Nutr*. 2010;140(11):1932–6.

4839. Meijer K, de Vos P, Priebe MG. Butyrate and other short-chain fatty acids as modulators of immunity: what relevance for health? *Curr Opin Clin Nutr Metab Care*. 2010;13(6):715–21.

4840. Wang B, Zhou J, Wang K. Sodium butyrate abolishes the degradation of type II collagen in human chondrocytes. *Biomed Pharmacother*. 2018;102:1099–104.
4841. Dai Z, Lu N, Niu J, Felson DT, Zhang Y. Dietary fiber intake in relation to knee pain trajectory. *Arthritis Care Res (Hoboken)*. 2017;69(9):1331–9.
4842. Dai Z, Niu J, Zhang Y, Jacques P, Felson DT. Dietary intake of fibre and risk of knee osteoarthritis in two US prospective cohorts [published correction appears in *Ann Rheum Dis*. 2017;76(12):2103]. *Ann Rheum Dis*. 2017;76(8):1411–9.
4843. Schott EM, Farnsworth CW, Grier A, et al. Targeting the gut microbiome to treat the osteoarthritis of obesity. *JCI Insight*. 2018;3(8):95997.
4844. Berenbaum F, Wallace IJ, Lieberman DE, Felson DT. Modern-day environmental factors in the pathogenesis of osteoarthritis. *Nat Rev Rheumatol*. 2018;14(11):674–81.
4845. Berenbaum F, Wallace IJ, Lieberman DE, Felson DT. Modern-day environmental factors in the pathogenesis of osteoarthritis. *Nat Rev Rheumatol*. 2018;14(11):674–81.
4846. Guan VX, Mobasheri A, Probst YC. A systematic review of osteoarthritis prevention and management with dietary phytochemicals from foods. *Maturitas*. 2019;122:35–43.
4847. Canter PH, Wider B, Ernst E. The antioxidant vitamins A, C, E and selenium in the treatment of arthritis: a systematic review of randomized clinical trials. *Rheumatology (Oxford)*. 2007;46(8):1223–33.
4848. Kraus VB, Huebner JL, Stabler T, et al. Ascorbic acid increases the severity of spontaneous knee osteoarthritis in a guinea pig model. *Arthritis Rheum*. 2004;50(6):1822–31.
4849. Haqqi TM, Anthony DD, Gupta S, et al. Prevention of collagen-induced arthritis in mice by a polyphenolic fraction from green tea. *Proc Natl Acad Sci U S A*. 1999;96(8):4524–9.
4850. Leong DJ, Choudhury M, Hanstein R, et al. Green tea polyphenol treatment is chondroprotective, anti-inflammatory and palliative in a mouse posttraumatic osteoarthritis model. *Arthritis Res Ther*. 2014;16(6):508.

4851. Bae JY, Han DW, Wakitani S, Nawata M, Hyon SH. Biological and biomechanical evaluations of osteochondral allografts preserved in cold storage solution containing epigallocatechin gallate. *Cell Transplant*. 2010;19(6):681–9.
4852. Hu J, Webster D, Cao J, Shao A. The safety of green tea and green tea extract consumption in adults—results of a systematic review. *Regul Toxicol Pharmacol*. 2018;95:412–33.
4853. Hashempur MH, Sadrneshin S, Mosavat SH, Ashraf A. Green tea (*Camellia sinensis*) for patients with knee osteoarthritis: a randomized open-label active-controlled clinical trial. *Clin Nutr*. 2018;37(1):85–90.
4854. Connelly AE, Tucker AJ, Tulk H, et al. High-rosmarinic acid spearmint tea in the management of knee osteoarthritis symptoms. *J Med Food*. 2014;17(12):1361–7.
4855. Lu B, Ahmad O, Zhang FF, et al. Soft drink intake and progression of radiographic knee osteoarthritis: data from the Osteoarthritis Initiative. *BMJ Open*. 2013;3(7):e002993.
4856. Lu B, Driban JB, Duryea J, McAlindon T, Lapane KL, Eaton CB. Milk consumption and progression of medial tibiofemoral knee osteoarthritis: data from the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)*. 2014;66(6):802–9.
4857. Denissen KFM, Boonen A, Nielen JTH, et al. Consumption of dairy products in relation to the presence of clinical knee osteoarthritis: The Maastricht Study. *Eur J Nutr*. 2019;58(7):2693–704.
4858. Arjmandi BH, Khalil DA, Lucas EA, et al. Soy protein may alleviate osteoarthritis symptoms. *Phytomedicine*. 2004;11(7–8):567–75.
4859. Minaie M, Rostamian, A, Abbassian A, Ghayoumi A, Mashayekhi A. An investigation of the effect of dairy products on chronic knee osteoarthritis pain in patients referred to Tehran Rheumatology Clinic of Imam Khomeini Hospital. *Int J Biol Pharm Allied Sci*. 2017;6(2):218–26.
4860. Basu A, Kurien BT, Tran H, et al. Strawberries decrease circulating levels of tumor necrosis factor and lipid peroxides in knee osteoarthritis in obese adults. *Food Funct*. 2018;9(12):6218–26.
4861. Schumacher HR, Pullman-Mooar S, Gupta SR, Dinnella JE, Kim R, McHugh MP. Randomized double-blind crossover study of the

efficacy of a tart cherry juice blend in treatment of osteoarthritis (OA) of the knee. *Osteoarthritis Cartilage*. 2013;21(8):1035–41.

4862. Collins MW, Saag KG, Singh JA. Is there a role for cherries in the management of gout? *Ther Adv Musculoskelet Dis*. 2019;11:1759720X19847018.

4863. Ghavipour M, Sotoudeh G, Tavakoli E, Mowla K, Hasanzadeh J, Mazloom Z. Pomegranate extract alleviates disease activity and some blood biomarkers of inflammation and oxidative stress in Rheumatoid Arthritis patients. *Eur J Clin Nutr*. 2017;71(1):92–6.

4864. Rasheed Z. Intake of pomegranate prevents the onset of osteoarthritis: molecular evidences. *Int J Health Sci (Qassim)*. 2016;10(2):V-VIII.

4865. Ahmed S, Wang N, Hafeez BB, Cheruvu VK, Haqqi TM. *Punica granatum* L. extract inhibits IL-1β-induced expression of matrix metalloproteinases by inhibiting the activation of MAP kinases and NF-κB in human chondrocytes in vitro. *J Nutr*. 2005;135(9):2096–102.

4866. Lahart I, Darcy P, Gidlow C, Calogiuri G. The effects of green exercise on physical and mental wellbeing: a systematic review. *Int J Environ Res Public Health*. 2019;16(8):1352.

4867. Moazen S, Amani R, Homayouni Rad A, Shahbazian H, Ahmadi K, Taha Jalali M. Effects of freeze-dried strawberry supplementation on metabolic biomarkers of atherosclerosis in subjects with type 2 diabetes: a randomized double-blind controlled trial. *Ann Nutr Metab*. 2013;63(3):256–64.

4868. Chen T, Yan F, Qian J, et al. Randomized phase II trial of lyophilized strawberries in patients with dysplastic precancerous lesions of the esophagus. *Cancer Prev Res (Phila)*. 2012;5(1):41–50.

4869. Edirisinghe I, Banaszewski K, Cappozzo J, et al. Strawberry anthocyanin and its association with postprandial inflammation and insulin. *Br J Nutr*. 2011;106(6):913–22.

4870. Schell J, Scofield RH, Barrett JR, et al. Strawberries improve pain and inflammation in obese adults with radiographic evidence of knee osteoarthritis. *Nutrients*. 2017;9(9):949.

4871. Basu A, Kurien BT, Tran H, et al. Strawberries decrease circulating levels of tumor necrosis factor and lipid peroxides in knee

osteoarthritis in obese adults. *Food Funct*. 2018;9(12):6218–26.
4872. Rutledge GA, Fisher DR, Miller MG, Kelly ME, Bielinski DF, Shukitt-Hale B. The effects of blueberry and strawberry serum metabolites on age-related oxidative and inflammatory signaling *in vitro*. *Food Funct*. 2019;10(12):7707–13.
4873. Du C, Smith A, Avalos M, et al. Blueberries improve pain, gait performance, and inflammation in individuals with symptomatic knee osteoarthritis. *Nutrients*. 2019;11(2):E290.
4874. Christensen R, Bartels EM, Altman RD, Astrup A, Bliddal H. Does the hip powder of *Rosa canina* (rosehip) reduce pain in osteoarthritis patients?—a meta-analysis of randomized controlled trials. *Osteoarthritis Cartilage*. 2008;16(9):965–72.
4875. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med*. 2015;162(1):46–54.
4876. Christensen R, Bartels EM, Altman RD, Astrup A, Bliddal H. Does the hip powder of *Rosa canina* (rosehip) reduce pain in osteoarthritis patients?—a meta-analysis of randomized controlled trials. *Osteoarthritis Cartilage*. 2008;16(9):965–72.
4877. Davidson RK, Jupp O, de Ferrars R, et al. Sulforaphane represses matrix-degrading proteases and protects cartilage from destruction in vitro and in vivo. *Arthritis Rheum*. 2013;65(12):3130–40.
4878. Davidson R, Gardner S, Jupp O, et al. Isothiocyanates are detected in human synovial fluid following broccoli consumption and can affect the tissues of the knee joint. *Sci Rep*. 2017;7(1):3398.
4879. Davidson RK, Jupp O, de Ferrars R, et al. Sulforaphane represses matrix-degrading proteases and protects cartilage from destruction in vitro and in vivo. *Arthritis Rheum*. 2013;65(12):3130–40.
4880. Broccoli in Osteoarthritis (BRIO). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03878368. Published March 18, 2019. Updated May 17, 2022. Accessed June 5, 2022.
4881. Riso P, Vendrame S, Del Bo' C, et al. Effect of 10-day broccoli consumption on inflammatory status of young healthy smokers. *Int J Food Sci Nutr*. 2014;65(1):106–11.

4882. Araya-Quintanilla F, Gutiérrez-Espinoza H, Muñoz-Yanez MJ, Sanchez-Montoya U, Lopez-Jeldes J. Effectiveness of ginger on pain and function in knee osteoarthritis: a PRISMA systematic review and meta-analysis. *Pain Physician*. 2020;23(2):E151–61.
4883. Haghighi M, Khalvat A, Toliat T, Jallaei S. Comparing the effects of ginger (*Zingiber officinale*) extract and ibuprofen on patients with osteoarthritis. *Arch Iran Med*. 2005; 8(4):267–71.
4884. Drozdov VN, Kim VA, Tkachenko EV, Varvanina GG. Influence of a specific ginger combination on gastropathy conditions in patients with osteoarthritis of the knee or hip. *J Altern Complement Med*. 2012;18(6):583–8.
4885. Caunedo-Alvarez A, Gómez-Rodríguez BJ, Romero-Vázquez J, et al. Macroscopic small bowel mucosal injury caused by chronic nonsteroidal anti-inflammatory drugs (NSAID) use as assessed by capsule endoscopy. *Rev Esp Enferm Dig*. 2010;102(2):80–5.
4886. Therkleson T. Ginger compress therapy for adults with osteoarthritis. *J Adv Nurs*. 2010;66(10):2225–33.
4887. Ding M, Leach MJ, Bradley H. A systematic review of the evidence for topical use of ginger. *Explore (NY)*. 2013;9(6):361–4.
4888. Percival SS, Vanden Heuvel JP, Nieves CJ, Montero C, Migliaccio AJ, Meadors J. Bioavailability of herbs and spices in humans as determined by *ex vivo* inflammatory suppression and DNA strand breaks. *J Am Coll Nutr*. 2012;31(4):288–94.
4889. Wang Z, Singh A, Jones G, et al. Efficacy and safety of turmeric extracts for the treatment of knee osteoarthritis: a systematic review and meta-analysis of randomised controlled trials. *Curr Rheumatol Rep*. 2021;23(2):11.
4890. Jamali N, Adib-Hajbaghery M, Soleimani A. The effect of *curcumin* ointment on knee pain in older adults with osteoarthritis: a randomized placebo trial. *BMC Complement Med Ther*. 2020;20(1):305.
4891. Miyawaki T, Aono H, Toyoda-Ono Y, Maeda H, Kiso Y, Moriyama K. Antihypertensive effects of sesamin in humans. *J Nutr Sci Vitaminol (Tokyo)*. 2009;55(1):87–91.
4892. Wu WH, Kang YP, Wang NH, Jou HJ, Wang TA. Sesame ingestion affects sex hormones, antioxidant status, and blood lipids in

postmenopausal women. *J Nutr*. 2006;136(5):1270–5.
4893. Askari A, Ravansalar SA, Naghizadeh MM, et al. The efficacy of topical sesame oil in patients with knee osteoarthritis: a randomized double-blinded active-controlled non-inferiority clinical trial. *Complement Ther Med*. 2019;47:102183.
4894. Savaş BB, Alparslan GB, Korkmaz C. Effect of flaxseed poultice compress application on pain and hand functions of patients with hand osteoarthritis. *Clin Rheumatol*. 2019;38(7):1961–9.
4895. Hashempur MH, Homayouni K, Ashraf A, Salehi A, Taghizadeh M, Heydari M. Effect of *Linum usitatissimum* L. (linseed) oil on mild and moderate carpal tunnel syndrome: a randomized, double-blind, placebo-controlled clinical trial. *Daru*. 2014;22:43.
4896. Mosavat SH, Masoudi N, Hajimehdipoor H, et al. Efficacy of topical *Linum usitatissimum* L. (flaxseed) oil in knee osteoarthritis: a double-blind, randomized, placebo-controlled clinical trial. *Complement Ther Clin Pract*. 2018;31:302–7.
4897. Nasser M, Tibi A, Savage-Smith E. Ibn Sina's *Canon of Medicine*: 11th century rules for assessing the effects of drugs. *J R Soc Med*. 2009;102(2):78–80.
4898. Hashmi MA, Khan A, Hanif M, Farooq U, Perveen S. Traditional uses, phytochemistry, and pharmacology of *Olea europaea* (olive). *Evid Based Complement Alternat Med*. 2015;2015:541591.
4899. Fernandes J, Fialho M, Santos R, et al. Is olive oil good for you? A systematic review and meta-analysis on anti-inflammatory benefits from regular dietary intake. *Nutrition*. 2020;69:110559.
4900. Khaw KT, Sharp SJ, Finikarides L, et al. Randomised trial of coconut oil, olive oil or butter on blood lipids and other cardiovascular risk factors in healthy men and women. *BMJ Open*. 2018;8(3):e020167.
4901. Bohlooli S, Jastan M, Nakhostin-Roohi B, Mohammadi S, Baghaei Z. A pilot double-blinded, randomized, clinical trial of topical virgin olive oil versus piroxicam gel in osteoarthritis of the knee. *J Clin Rheumatol*. 2012;18(2):99–101.
4902. Hekmatpou D, Mortaji S, Rezaei M, Shaikhi M. The effectiveness of olive oil in controlling morning inflammatory pain of phalanges and knees among women with rheumatoid arthritis: a randomized clinical trial. *Rehabil Nurs*. 2020;45(2):106–13.

4903. Balagué F, Mannion AF, Pellisé F, Cedraschi C. Non-specific low back pain. *Lancet*. 2012;379(9814):482–91.
4904. Zhang TT, Liu Z, Liu YL, Zhao JJ, Liu DW, Tian QB. Obesity as a risk factor for low back pain: a meta-analysis. *Clin Spine Surg*. 2018;31(1):22–7.
4905. Shiri R, Lallukka T, Karppinen J, Viikari-Juntura E. Obesity as a risk factor for sciatica: a meta-analysis. *Am J Epidemiol*. 2014;179(8):929–37.
4906. Xu X, Li X, Wu W. Association between overweight or obesity and lumbar disk diseases. *J Spinal Disord Tech*. 2015;28(10):370–6.
4907. Shiri R, Lallukka T, Karppinen J, Viikari-Juntura E. Obesity as a risk factor for sciatica: a meta-analysis. *Am J Epidemiol*. 2014;179(8):929–37.
4908. Xu X, Li X, Wu W. Association between overweight or obesity and lumbar disk diseases. *J Spinal Disord Tech*. 2015;28(10):370–6.
4909. Kauppila LI. Atherosclerosis and disc degeneration/low-back pain—a systematic review. *Eur J Vasc Endovasc Surg*. 2009;37(6):661–70.
4910. Kauppila LI, Mikkonen R, Mankinen P, Pelto-Vasenius K, Mäenpää I. MR aortography and serum cholesterol levels in patients with long-term nonspecific lower back pain. *Spine (Phila Pa 1976)*. 2004;29(19):2147–52.
4911. Ventegodt S, Merrick J. Dean Ornish should receive the Nobel prize in medicine. *Int J Adolesc Med Health*. 2012;24(2):97–8.
4912. Blankenhorn DH, Hodis HN. George Lyman Duff memorial lecture. Arterial imaging and atherosclerosis reversal. *Arterioscler Thromb.* 1994;14(2):177–92.
4913. Ostfeld RJ, Allen KE, Aspry K, et al. Vasculogenic erectile dysfunction: the impact of diet and lifestyle. *Am J Med*. 2021;134(3):310–6.
4914. Renegar KB, Floyd RA, Krueger JM. Effects of short-term sleep deprivation on murine immunity to influenza virus in young adult and senescent mice. *Sleep*. 1998;21(3):241–8.
4915. Vacaflor BE, Beauchet O, Jarvis GE, Schavietto A, Rej S. Mental health and cognition in older cannabis users: a review. *Can Geriatr J*. 2020;23(3):242–9.

4916. Campeny E, López-Pelayo H, Nutt D, et al. The blind men and the elephant: systematic review of systematic reviews of cannabis use related health harms. *Eur Neuropsychopharmacol*. 2020;33:1–35.
4917. Wang A, Lo A, Ubhi K, Cameron T. Small and transient effect of cannabis oil for osteoarthritis-related joint pain: a case report. *Can J Hosp Pharm*. 2021;74(2):156–8.
4918. Vela J, Dreyer L, Petersen KK, Arendt-Nielsen L, Duch KS, Kristensen S. Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind, placebo-controlled trial. *Pain*. 2022;163(6):1206–14.
4919. Senftleber NK, Nielsen SM, Andersen JR, et al. Marine oil supplements for arthritis pain: a systematic review and meta-analysis of randomized trials. *Nutrients*. 2017;9(1):E42.
4920. Gregory PJ, Sperry M, Wilson AF. Dietary supplements for osteoarthritis. *Am Fam Physician*. 2008;77(2):177–84.
4921. McCarty MF, O'Keefe JH, DiNicolantonio JJ. Glucosamine for the treatment of osteoarthritis: the time has come for higher-dose trials. *J Diet Suppl*. 2019;16(2):179–92.
4922. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2020;72(2):149–62.
4923. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol*. 2020;72(2):220–33.
4924. Reichenbach S, Sterchi R, Scherer M, et al. Meta-analysis: chondroitin for osteoarthritis of the knee or hip. *Ann Intern Med*. 2007;146(8):580–90.
4925. Roman-Blas JA, Castañeda S, Sánchez-Pernaute O, et al. Combined treatment with chondroitin sulfate and glucosamine sulfate shows no superiority over placebo for reduction of joint pain and functional impairment in patients with knee osteoarthritis: a six-month multicenter, randomized, double-blind, placebo-controlled clinical trial. *Arthritis Rheumatol*. 2017;69(1):77–85.

4926. Moskowitz RW. Role of collagen hydrolysate in bone and joint disease. *Semin Arthritis Rheum*. 2000;30(2):87–99.
4927. Moskowitz RW. Role of collagen hydrolysate in bone and joint disease. *Semin Arthritis Rheum*. 2000;30(2):87–99.
4928. Alahakoon AU, Oey I, Silcock P, Bremer P. Understanding the effect of pulsed electric fields on thermostability of connective tissue isolated from beef pectoralis muscle using a model system. *Food Res Int*. 2017;100(Pt 2):261–7.
4929. García-Coronado JM, Martínez-Olvera L, Elizondo-Omaña RE, et al. Effect of collagen supplementation on osteoarthritis symptoms: a meta-analysis of randomized placebo-controlled trials. *Int Orthop*. 2019;43(3):531–8.
4930. von Hippel PT. Do collagen supplements reduce symptoms of osteoarthritis? Meta-analytic results do not support strong conclusions. *Int Orthop*. 2021;45(12):3283–4.
4931. Jabbari M, Barati M, Khodaei M, et al. Is collagen supplementation friend or foe in rheumatoid arthritis and osteoarthritis? A comprehensive systematic review. *Int J Rheum Dis*. 2022;25(9):973–81.
4932. Sambeth A, Riedel WJ, Tillie DE, Blokland A, Postma A, Schmitt JAJ. Memory impairments in humans after acute tryptophan depletion using a novel gelatin-based protein drink. *J Psychopharmacol*. 2009;23(1):56–64.
4933. Jabbari M, Barati M, Khodaei M, et al. Is collagen supplementation friend or foe in rheumatoid arthritis and osteoarthritis? A comprehensive systematic review. *Int J Rheum Dis*. 2022;25(9):973–81.
4934. Bongers CCWG, Ten Haaf DSM, Catoire M, et al. Effectiveness of collagen supplementation on pain scores in healthy individuals with self-reported knee pain: a randomized controlled trial. *Appl Physiol Nutr Metab*. 2020;45(7):793–800.
4935. Delgado-Saborit JM, Guercio V, Gowers AM, Shaddick G, Fox NC, Love S. A critical review of the epidemiological evidence of effects of air pollution on dementia, cognitive function and cognitive decline in adult population. *Sci Total Environ*. 2021;757:143734.

4936. Gu YH, Bai JB, Chen XL, Wu WW, Liu XX, Tan XD. Healthy aging: a bibliometric analysis of the literature. *Exp Gerontol*. 2019;116:93–105.
4937. Ritchie K, Kildea D. Is senile dementia "age-related" or "ageing-related"?—evidence from meta-analysis of dementia prevalence in the oldest old. *Lancet*. 1995;346(8980):931–4.
4938. Wickelgren I. Is hippocampal cell death a myth? *Science*. 1996;271(5253):1229–30.
4939. Sherzai D, Sherzai A. Preventing Alzheimer's: our most urgent health care priority. *Am J Lifestyle Med*. 2019;13(5):451–61.
4940. 2022 Alzheimer's disease facts and figures. Special report. More than normal aging: understanding mild cognitive impairment. Alzheimer's Association. https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. 2022. Accessed January 8, 2023.
4941. Sherzai D, Sherzai A. Preventing Alzheimer's: our most urgent health care priority. *Am J Lifestyle Med*. 2019;13(5):451–61.
4942. de la Torre JC. A turning point for Alzheimer's disease? *Biofactors*. 2012;38(2):78–83.
4943. Lopez OL, Kuller LH. Epidemiology of aging and associated cognitive disorders: prevalence and incidence of Alzheimer's disease and other dementias. *Handb Clin Neurol*. 2019;167:139–48.
4944. Sengoku R. Aging and Alzheimer's disease pathology. *Neuropathol*. 2020;40(1):22–9.
4945. Kawas CH, Kim RC, Sonnen JA, Bullain SS, Trieu T, Corrada MM. Multiple pathologies are common and related to dementia in the oldest-old. *Neurology*. 2015;85(6):535–42.
4946. Viña J, Sanz-Ros J. Alzheimer's disease: only prevention makes sense. *Eur J Clin Invest*. 2018;48(10):e13005.
4947. Román GC. Facts, myths, and controversies in vascular dementia. *J Neurol Sci*. 2004;226(1–2):49–52.
4948. Grau-olivares M, Arboix A. Mild cognitive impairment in stroke patients with ischemic cerebral small-vessel disease: a forerunner of vascular dementia? *Expert Rev Neurother*. 2009;9(8):1201–17.
4949. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*. 2007;69(24):2197–204.

4950. Murphy SL, Kochanek KD, Xu J, Arias E. Mortality in the United States, 2020. *NCHS Data Brief*. 2021;(427):1–8.
4951. Heron M. Deaths: leading causes for 2019. *Natl Vital Stat Rep*. 2021;70(9):1–114.
4952. Haaksma ML, Eriksdotter M, Rizzuto D, et al. Survival time tool to guide care planning in people with dementia. *Neurology*. 2020;94(5):e538–48.
4953. Lopez OL, Kuller LH. Epidemiology of aging and associated cognitive disorders: prevalence and incidence of Alzheimer's disease and other dementias. *Handb Clin Neurol*. 2019;167:139–48.
4954. Cahill S, Pierce M, Werner P, Darley A, Bobersky A. A systematic review of the public's knowledge and understanding of Alzheimer's disease and dementia. *Alzheimer Dis Assoc Disord*. 2015;29(3):255–75.
4955. Goodwin JS. Geriatric ideology: the myth of the myth of senility. *J Am Geriatr Soc*. 1991;39(6):627–31.
4956. Takao M, Hirose N, Arai Y, Mihara B, Mimura M. Neuropathology of supercentenarians – four autopsy case studies. *Acta Neuropathol Commun*. 2016;4(1):97.
4957. den Dunnen WFA, Brouwer WH, Bijlard E, et al. No disease in the brain of a 115-year-old woman. *Neurobiol Aging*. 2008;29(8):1127–32.
4958. Williams RW, Herrup K. The control of neuron number. *Annu Rev Neurosci*. 1988;11:423–53.
4959. von Bartheld CS. Myths and truths about the cellular composition of the human brain: a review of influential concepts. *J Chem Neuroanat*. 2018;93:2–15.
4960. Sherzai D, Sherzai A. Preventing Alzheimer's: our most urgent health care priority. *Am J Lifestyle Med*. 2019;13(5):451–61.
4961. Cahill S, Pierce M, Werner P, Darley A, Bobersky A. A systematic review of the public's knowledge and understanding of Alzheimer's disease and dementia. *Alzheimer Dis Assoc Disord*. 2015;29(3):255–75.
4962. Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst Rev*. 2018;2018(6):CD001190.

4963. McShane R, Westby MJ, Roberts E, et al. Memantine for dementia. *Cochrane Database Syst Rev*. 2019;3:CD003154.
4964. Schmitt HP. On the paradox of ion channel blockade and its benefits in the treatment of Alzheimer disease. *Med Hypotheses*. 2005;65(2):259–65.
4965. Blanco-Silvente L, Castells X, Garre-Olmo J, et al. Study of the strength of the evidence and the redundancy of the research on pharmacological treatment for Alzheimer's disease: a cumulative meta-analysis and trial sequential analysis. *Eur J Clin Pharmacol*. 2019;75(12):1659–67.
4966. Fink HA, Linskens EJ, MacDonald R, et al. Benefits and harms of prescription drugs and supplements for treatment of clinical Alzheimer-type dementia. *Ann Intern Med*. 2020;172(10):656–68.
4967. Blanco-Silvente L, Castells X, Garre-Olmo J, et al. Study of the strength of the evidence and the redundancy of the research on pharmacological treatment for Alzheimer's disease: a cumulative meta-analysis and trial sequential analysis. *Eur J Clin Pharmacol*. 2019;75(12):1659–67.
4968. Rabinovici GD. Controversy and progress in Alzheimer's disease – FDA approval of aducanumab. *N Engl J Med*. 2021;385(9):771–4.
4969. Robinson JC. Why is aducanumab priced at $56,000 per patient? Lessons for drug-pricing reform. *N Engl J Med*. 2021;385(22):2017–9.
4970. Moghavem N, Henderson VW, Greicius MD. Medicare should not cover aducanumab as a treatment for Alzheimer's disease. *Ann Neurol*. 2021;90(3):331–3.
4971. Rubin R. Recently approved Alzheimer drug raises questions that might never be answered. *JAMA*. 2021;326(6):469–72.
4972. Crosson FJ, Covinsky K, Redberg RF. Medicare and the shocking US Food and Drug Administration approval of aducanumab: crisis or opportunity? *JAMA Intern Med*. 2021;181(10):1278–80.
4973. Crosson FJ, Covinsky K, Redberg RF. Medicare and the shocking US Food and Drug Administration approval of aducanumab: crisis or opportunity? *JAMA Intern Med*. 2021;181(10):1278–80.
4974. Rubin R. Recently approved Alzheimer drug raises questions that might never be answered. *JAMA*. 2021;326(6):469–72.

4975. Lundebjerg NE. My head just exploded, now what? Aducanumab. *J Am Geriatr Soc*. 2021;69(9):2689–91.
4976. Reardon S. FDA approves Alzheimer's drug lecanemab amid safety concerns. *Nature*. 2023;613(7943):227–8.
4977. Walsh S, Merrick R, Richard E, Nurock S, Brayne C. Lecanemab for Alzheimer's disease. *BMJ*. 2022;379.
4978. Reitz C. Alzheimer's disease and the amyloid cascade hypothesis: a critical review. *Int J Alzheimers Dis*. 2012;2012:369808.
4979. Price JL. What does it take to stay healthy past 100? *Neurobiol Aging*. 2008;29(8):1140–2.
4980. Barber RC. The genetics of Alzheimer's disease. *Scientifica (Cairo)*. 2012;2012:246210.
4981. Castello MA, Soriano S. On the origin of Alzheimer's disease. Trials and tribulations of the amyloid hypothesis. *Ageing Res Rev*. 2014;13:10–2.
4982. Ayton S, Bush AI. β-amyloid: the known unknowns. *Ageing Res Rev*. 2021;65:101212.
4983. SantaCruz KS, Sonnen JA, Pezhouh MK, Desrosiers MF, Nelson PT, Tyas SL. Alzheimer disease pathology in subjects without dementia in 2 studies of aging: the Nun Study and the Adult Changes in Thought Study. *J Neuropathol Exp Neurol*. 2011;70(10):832–40.
4984. Ayton S, Bush AI. β-amyloid: the known unknowns. *Ageing Res Rev*. 2021;65:101212.
4985. Alzheimer A, Förstl H, Levy R. On certain peculiar diseases of old age. *Hist Psychiatry*. 1991;2(5):71–3.
4986. Piller C. Blots on a field? *Science*. 2022;377(6604):358–63.
4987. Ayton S, Bush AI. β-amyloid: the known unknowns. *Ageing Res Rev*. 2021;65:101212.
4988. Reitz C. Alzheimer's disease and the amyloid cascade hypothesis: a critical review. *Int J Alzheimers Dis*. 2012;2012:369808.
4989. Amtul Z. Why therapies for Alzheimer's disease do not work: do we have consensus over the path to follow? *Ageing Res Rev*. 2016;25:70–84.
4990. Ayton S, Bush AI. β-amyloid: the known unknowns. *Ageing Res Rev*. 2021;65:101212.

4991. Joseph J, Shukitt-Hale B, Denisova NA, Martin A, Perry G, Smith MA. Copernicus revisited: amyloid beta in Alzheimer's disease. *Neurobiol Aging*. 2001;22(1):131–46.
4992. Ayton S, Bush AI. β-amyloid: the known unknowns. *Ageing Res Rev*. 2021;65:101212.
4993. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging*. 1997;18(4):351–7.
4994. Grodstein F. How early can cognitive decline be detected? *BMJ*. 2011;344:d7652.
4995. Torres-Acosta N, O'Keefe JH, O'Keefe EL, Isaacson R, Small G. Therapeutic potential of TNF-α inhibition for Alzheimer's disease prevention. *J Alzheimers Dis*. 2020;78(2):619–26.
4996. Viña J, Sanz-Ros J. Alzheimer's disease: only prevention makes sense. *Eur J Clin Invest*. 2018;48(10):e13005.
4997. de la Torre JC. Alzheimer's disease is incurable but preventable. *J Alzheimers Dis*. 2010;20(3):861–70.
4998. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol*. 2011;10(9):819–28.
4999. Singh-Manoux A, Kivimaki M, Glymour MM, et al. Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. *BMJ*. 2012;344:d7622.
5000. Roher AE, Tyas SL, Maarouf CL, et al. Intracranial atherosclerosis as a contributing factor to Alzheimer's disease dementia. *Alzheimers Dement*. 2011;7(4):436–44.
5001. Alzheimer A, Stelzmann RA, Schnitzlein HN, Murtagh FR. An English translation of Alzheimer's 1907 paper, "Uber eine eigenartige Erkankung der Hirnrinde." *Clin Anat*. 1995;8(6):429–31.
5002. Sharma M. Preventing Alzheimer's disease: some light in the darkness. *J Am Coll Cardiol*. 2019;74(15):1924–5.
5003. Grande G, Qiu C, Fratiglioni L. Prevention of dementia in an ageing world: evidence and biological rationale. *Ageing Res Rev*. 2020;64:101045.
5004. Roher AE, Tyas SL, Maarouf CL, et al. Intracranial atherosclerosis as a contributing factor to Alzheimer's disease dementia. *Alzheimers Dement*. 2011;7(4):436–44.

5005. Yarchoan M, Xie SX, Kling MA, et al. Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias. *Brain*. 2012;135(Pt 12):3749–56.
5006. Honig LS, Kukull W, Mayeux R. Atherosclerosis and AD: analysis of data from the US National Alzheimer's Coordinating Center. *Neurology*. 2005;64(3):494–500.
5007. Roher AE, Tyas SL, Maarouf CL, et al. Intracranial atherosclerosis as a contributing factor to Alzheimer's disease dementia. *Alzheimers Dement*. 2011;7(4):436–44.
5008. de la Torre JC. Vascular basis of Alzheimer's pathogenesis. *Ann N Y Acad Sci*. 2002;977:196–215.
5009. Cahill S, Pierce M, Werner P, Darley A, Bobersky A. A systematic review of the public's knowledge and understanding of Alzheimer's disease and dementia. *Alzheimer Dis Assoc Disord*. 2015;29(3):255–75.
5010. Corsinovi L, Biasi F, Poli G, Leonarduzzi G, Isaia G. Dietary lipids and their oxidized products in Alzheimer's disease. *Mol Nutr Food Res*. 2011;55 Suppl 2:S161–72.
5011. Mizuno T, Nakata M, Naiki H, et al. Cholesterol-dependent generation of a seeding amyloid beta-protein in cell culture. *J Biol Chem*. 1999;274(21):15110–4.
5012. Harris JR, Milton NGN. Cholesterol in Alzheimer's disease and other amyloidogenic disorders. *Subcell Biochem*. 2010;51:47–75.
5013. US Food and Drug Administration. Important safety label changes to cholesterol-lowering statin drugs. http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm. Published July 7, 2012. Accessed June 30, 2022.
5014. Rojas-Fernandez CH, Cameron JC. Is statin-associated cognitive impairment clinically relevant? A narrative review and clinical recommendations. *Ann Pharmacother*. 2012;46(4):549–57.
5015. Sabbagh MN, Perez A, Holland TM, et al. Primary prevention recommendations to reduce the risk of cognitive decline. *Alzheimers Dement*. Published online January 13, 2022.
5016. Barnard ND, Bush AI, Ceccarelli A, et al. Dietary and lifestyle guidelines for the prevention of Alzheimer's disease. *Neurobiol Aging*. 2014;35 Suppl 2:S74–8.

5017. Wood WG, Li L, Müller WE, Eckert GP. Cholesterol as a causative factor in Alzheimer disease: a debatable hypothesis. *J Neurochem*. 2014;129(4):559–72.
5018. Testa G, Staurenghi E, Zerbinati C, et al. Changes in brain oxysterols at different stages of Alzheimer's disease: their involvement in neuroinflammation. *Redox Biol*. 2016;10:24–33.
5019. Marwarha G, Ghribi O. Does the oxysterol 27-hydroxycholesterol underlie Alzheimer's disease—Parkinson's disease overlap? *Exp Gerontol*. 2015;68:13–8.
5020. Wang HL, Wang YY, Liu XG, et al. Cholesterol, 24-hydroxycholesterol, and 27-hydroxycholesterol as surrogate biomarkers in cerebrospinal fluid in mild cognitive impairment and Alzheimer's disease: a meta-analysis. *J Alzheimers Dis*. 2016;51(1):45–55.
5021. Gamba P, Testa G, Gargiulo S, Staurenghi E, Poli G, Leonarduzzi G. Oxidized cholesterol as the driving force behind the development of Alzheimer's disease. *Front Aging Neurosci*. 2015;7:119.
5022. Deschaintre Y, Richard F, Leys D, Pasquier F. Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. *Neurology*. 2009;73(9):674–80.
5023. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373(22):2103–16.
5024. Williamson JD, Pajewski NM, Auchus AP, et al. Effect of intensive vs standard blood pressure control on probable dementia. *JAMA*. 2019;321(6):553–61.
5025. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373(22):2103–16.
5026. Roher AE, Tyas SL, Maarouf CL, et al. Intracranial atherosclerosis as a contributing factor to Alzheimer's disease dementia. *Alzheimers Dement*. 2011;7(4):436–44.
5027. Pase MP, Herbert A, Grima NA, Pipingas A, O'Rourke MF. Arterial stiffness as a cause of cognitive decline and dementia: a systematic review and meta-analysis. *Intern Med J*. 2012;42(7):808–15.

5028. Henskens LHG, van Oostenbrugge RJ, Kroon AA, de Leeuw PW, Lodder J. Brain microbleeds are associated with ambulatory blood pressure levels in a hypertensive population. *Hypertension*. 2008;51(1):62–8.
5029. Kovacic JC, Fuster V. Atherosclerotic risk factors, vascular cognitive impairment, and Alzheimer disease. *Mt Sinai J Med*. 2012;79(6):664–73.
5030. Longstreth WT, Bernick C, Manolio TA, Bryan N, Jungreis CA, Price TR. Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. *Arch Neurol*. 1998;55(9):1217–25.
5031. Vermeer SE, Longstreth WT, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol*. 2007;6(7):611–9.
5032. Beauchet O, Celle S, Roche F, et al. Blood pressure levels and brain volume reduction: a systematic review and meta-analysis [published correction appears in *J Hypertens.* 2013;31(10):2106]. *J Hypertens*. 2013;31(8):1502–16.
5033. Peila R, White LR, Petrovich H, et al. Joint effect of the APOE gene and midlife systolic blood pressure on late-life cognitive impairment: the Honolulu-Asia Aging Study. *Stroke*. 2001;32(12):2882–9.
5034. Singer J, Trollor JN, Baune BT, Sachdev PS, Smith E. Arterial stiffness, the brain and cognition: a systematic review. *Ageing Res Rev*. 2014;15:16–27.
5035. Salvi P, Giannattasio C, Parati G. High sodium intake and arterial stiffness. *J Hypertens*. 2018;36(4):754–8.
5036. D'Elia L, Galletti F, La Fata E, Sabino P, Strazzullo P. Effect of dietary sodium restriction on arterial stiffness: systematic review and meta-analysis of the randomized controlled trials. *J Hypertens*. 2018;36(4):734–43.
5037. Filippini T, Malavolti M, Whelton PK, Naska A, Orsini N, Vinceti M. Blood pressure effects of sodium reduction: dose-response meta-analysis of experimental studies. *Circulation*. 2021;143(16):1542–67.
5038. Siriopol D, Covic A, Iliescu R, et al. Arterial stiffness mediates the effect of salt intake on systolic blood pressure. *J Clin Hypertens (Greenwich)*. 2018;20(11):1587–94.

5039. Santisteban MM, Iadecola C. Hypertension, dietary salt and cognitive impairment. *J Cereb Blood Flow Metab*. 2018;38(12):2112–28.
5040. Faraco G, Hochrainer K, Segarra SG, et al. Dietary salt promotes cognitive impairment through tau phosphorylation. *Nature*. 2019;574(7780):686–90.
5041. Fyfe I. High-salt diet promotes Alzheimer disease–like changes. *Nat Rev Neurol*. 2020;16(1):2–3.
5042. Cahill S, Pierce M, Werner P, Darley A, Bobersky A. A systematic review of the public's knowledge and understanding of Alzheimer's disease and dementia. *Alzheimer Dis Assoc Disord*. 2015;29(3):255–75.
5043. Hudson JM, Pollux PMJ, Mistry B, Hobson S. Beliefs about Alzheimer's disease in Britain. *Aging Ment Health*. 2012;16(7):828–35.
5044. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol*. 2006;5(9):735–41.
5045. Chandra V, Ganguli M, Pandav R, et al. Prevalence of Alzheimer's disease and other dementias in rural India: the Indo-US study. *Neurology*. 1998;51(4):1000–8.
5046. Shetty PS. Nutrition transition in India. *Public Health Nutr*. 2002;5(1A):175–82.
5047. Tsai JH, Huang CF, Lin MN, Chang CE, Chang CC, Lin CL. Taiwanese vegetarians are associated with lower dementia risk: a prospective cohort study. *Nutrients*. 2022;14(3):588.
5048. Giem P, Beeson WL, Fraser GE. The incidence of dementia and intake of animal products: preliminary findings from the Adventist Health Study. *Neuroepidemiology*. 1993;12(1):28–36.
5049. Kivipelto M, Helkala EL, Laakso MP, et al. Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. *Ann Intern Med*. 2002;137(3):149–55.
5050. Deelen J, Evans DS, Arking DE, et al. A meta-analysis of genome-wide association studies identifies multiple longevity genes. *Nat Commun*. 2019;10(1):3669.

5051. Rea IM, Dellet M, Mills KI, The ACUME2 Project. Living long and ageing well: is epigenomics the missing link between nature and nurture? *Biogerontology*. 2016;17(1):33–54.
5052. Caruso C, Aiello A, Accardi G, Ciaglia E, Cattaneo M, Puca A. Genetic signatures of centenarians: implications for achieving successful aging. *Curr Pharm Des*. 2019;25(39):4133–8.
5053. Abdullah MMH, Vazquez-Vidal I, Baer DJ, House JD, Jones PJH, Desmarchelier C. Common genetic variations involved in the inter-individual variability of circulating cholesterol concentrations in response to diets: a narrative review of recent evidence. *Nutrients*. 2021;13(2):695.
5054. Sepehrnia B, Kamboh MI, Adams-Campbell LL, et al. Genetic studies of human apolipoproteins. X. The effect of the apolipoprotein E polymorphism on quantitative levels of lipoproteins in Nigerian blacks. *Am J Hum Genet*. 1989;45(4):586–91.
5055. Laufs U, Dent R, Kostenuik PJ, Toth PP, Catapano AL, Chapman MJ. Why is hypercholesterolaemia so prevalent? A view from evolutionary medicine. *Eur Heart J*. 2019;40(33):2825–30.
5056. World Health Organization. The top 10 causes of death. December 9, 2020. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Accessed December 24, 2022.
5057. Chiarini A, Armato U, Hu P, Dal Prà I. Danger-sensing/patten recognition receptors and neuroinflammation in Alzheimer's disease. *Int J Mol Sci*. 2020;21(23):E9036.
5058. Schmidt R, Schmidt H, Curb JD, Masaki K, White LR, Launer LJ. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. *Ann Neurol*. 2002;52(2):168–74.
5059. Jost BC, Grossberg GT. The natural history of Alzheimer's disease: a brain bank study. *J Am Geriatr Soc*. 1995;43(11):1248–55.
5060. Del Tredici K, Braak H. Neurofibrillary changes of the Alzheimer type in very elderly individuals: neither inevitable nor benign: Commentary on 'No disease in the brain of a 115-year-old woman.' *Neurobiol Aging*. 2008;29(8):1133–6.
5061. Galasko DR, Peskind E, Clark CM, et al. Antioxidants for Alzheimer disease: a randomized clinical trial with cerebrospinal fluid biomarker measures. *Arch Neurol*. 2012;69(7):836–41.

5062. Jensen MK, Cassidy A. Can dietary flavonoids play a role in Alzheimer's disease risk prevention? Tantalizing population-based data out of Framingham. *Am J Clin Nutr*. 2020;112(2):241–2.
5063. Shishtar E, Rogers GT, Blumberg JB, Au R, Jacques PF. Long-term dietary flavonoid intake and change in cognitive function in the Framingham Offspring cohort. *Public Health Nutr*. 2020;23(9):1576–88.
5064. Tarozzi A, Morroni F, Merlicco A, et al. Neuroprotective effects of cyanidin 3-O-glucopyranoside on amyloid beta (25–35) oligomer-induced toxicity. *Neurosci Lett*. 2010;473(2):72–6.
5065. Hattori M, Sugino E, Minoura K, et al. Different inhibitory response of cyanidin and methylene blue for filament formation of tau microtubule-binding domain. *Biochem Biophys Res Commun*. 2008;374(1):158–63.
5066. Mandel SA, Weinreb O, Amit T, Youdim MB. Molecular mechanisms of the neuroprotective/neurorescue action of multi-target green tea polyphenols. *Front Biosci (Schol Ed)*. 2012;4:581–98.
5067. Ward RJ, Zucca FA, Duyn JH, Crichton RR, Zecca L. The role of iron in brain ageing and neurodegenerative disorders. *Lancet Neurol*. 2014;13(10):1045–60.
5068. Crapper DR, Krishnan SS, Dalton AJ. Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration. *Science*. 1973;180(4085):511–3.
5069. Alfrey AC, LeGendre GR, Kaehny WD. The dialysis encephalopathy syndrome: possible aluminum intoxication. *N Engl J Med*. 1976;294(4):184–8.
5070. Tomljenovic L. Aluminum and Alzheimer's disease: after a century of controversy, is there a plausible link? *J Alzheimers Dis*. 2011;23(4):567–98.
5071. Lidsky TI. Is the aluminum hypothesis dead? *J Occup Environ Med*. 2014;56(5 Suppl):S73–9.
5072. Perl DP, Moalem S. Aluminum and Alzheimer's disease, a personal perspective after 25 years. *J Alzheimers Dis*. 2006;9(3 Suppl):291–300.
5073. Lidsky TI. Is the aluminum hypothesis dead? *J Occup Environ Med*. 2014;56(5 Suppl):S73–9.

5074. Virk SA, Eslick GD. Brief report: meta-analysis of antacid use and Alzheimer's disease: implications for the aluminum hypothesis. *Epidemiology*. 2015;26(5):769–73.
5075. Reinke CM, Breitkreutz J, Leuenberger H. Aluminium in over-the-counter drugs: risks outweigh benefits? *Drug Saf*. 2003;26(14):1011–25.
5076. Celik H, Celik N, Kocyigit A, Dikilitas M. The relationship between plasma aluminum content, lymphocyte DNA damage, and oxidative status in persons using aluminum containers and utensils daily. *Clin Biochem*. 2012;45(18):1629–33.
5077. CRF - code of federal regulations Title 21. U.S Food & Drug Administration. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=350&showFR=1. Updated March 29, 2022. Accessed July 4, 2022.
5078. Council of the European Communities. Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products. EUR-Lex. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A31976L0768. Published July 27, 1976. Accessed February 24, 2023.
5079. Darbre PD, Mannello F, Exley C. Aluminium and breast cancer: Sources of exposure, tissue measurements and mechanisms of toxicological actions on breast biology. *J Inorg Biochem*. 2013;128:257–61.
5080. Darbre PD. Metalloestrogens: an emerging class of inorganic xenoestrogens with potential to add to the oestrogenic burden of the human breast. *J Appl Toxicol*. 2006;26(3):191–7.
5081. McGrath KG. An earlier age of breast cancer diagnosis related to more frequent use of antiperspirants/deodorants and underarm shaving. *Eur J Cancer Prev*. 2003;12(6):479–85.
5082. Yokel RA, Hicks CL, Florence RL. Aluminum bioavailability from basic sodium aluminum phosphate, an approved food additive emulsifying agent, incorporated in cheese. *Food Chem Toxicol*. 2008;46(6):2261–6.
5083. Al-Ashmawy MAM. Prevalence and public health significance of aluminum residues in milk and some dairy products. *J Food Sci*.

2011;76(3):T73–6.
5084. Gleason A, Bush AI. Iron and ferroptosis as therapeutic targets in Alzheimer's disease. *Neurotherapeutics*. 2021;18(1):252–64.
5085. Nikseresht S, Bush AI, Ayton S. Treating Alzheimer's disease by targeting iron. *Br J Pharmacol*. 2019;176(18):3622–35.
5086. Gleason A, Bush AI. Iron and ferroptosis as therapeutic targets in Alzheimer's disease. *Neurotherapeutics*. 2021;18(1):252–64.
5087. Ayton S, James SA, Bush AI. Nanoscale imaging reveals big role for iron in Alzheimer's disease. *Cell Chem Biol*. 2017;24(10):1192–4.
5088. Ayton S, Diouf I, Bush AI, Alzheimer's disease Neuroimaging Initiative. Evidence that iron accelerates Alzheimer's pathology: a CSF biomarker study. *J Neurol Neurosurg Psychiatry*. 2018;89(5):456–60.
5089. Miller LM, Wang Q, Telivala TP, Smith RJ, Lanzirotti A, Miklossy J. Synchrotron-based infrared and X-ray imaging shows focalized accumulation of Cu and Zn co-localized with beta-amyloid deposits in Alzheimer's disease. *J Struct Biol*. 2006;155(1):30–7.
5090. Morris MC, Evans DA, Tangney CC, et al. Dietary copper and high saturated and trans fat intakes associated with cognitive decline. *Arch Neurol*. 2006;63(8):1085–8.
5091. Loef M, Walach H. Copper and iron in Alzheimer's disease: a systematic review and its dietary implications. *Br J Nutr*. 2012;107(1):7–19.
5092. Liyanage SI, Vilekar P, Weaver DF. Nutrients in Alzheimer's disease: the interaction of diet, drugs and disease. *Can J Neurol Sci*. 2019;46(1):23–34.
5093. Oleson S, Gonzales MM, Tarumi T, et al. Nutrient intake and cerebral metabolism in healthy middle-aged adults: implications for cognitive aging. *Nutr Neurosci*. 2017;20(8):489–96.
5094. Okereke OI, Rosner BA, Kim DH, et al. Dietary fat types and 4-year cognitive change in community-dwelling older women. *Ann Neurol*. 2012;72(1):124–34.
5095. Cao GY, Li M, Han L, et al. Dietary fat intake and cognitive function among older populations: a systematic review and meta-analysis. *J Prev Alzheimers Dis*. 2019;6(3):204–11.

5096. Barbaresko J, Lellmann AW, Schmidt A, et al. Dietary factors and neurodegenerative disorders: an umbrella review of meta-analyses of prospective studies. *Adv Nutr*. 2020;11(5):1161–73.
5097. Liyanage SI, Vilekar P, Weaver DF. Nutrients in Alzheimer's disease: the interaction of diet, drugs and disease. *Can J Neurol Sci*. 2019;46(1):23–34.
5098. Kahle L, Krebs-Smith SM, Reedy J, Rodgers AB, Signes C. *Identification of Top Food Sources of Various Dietary Components*. National Cancer Institute. https://epi.grants.cancer.gov/diet/foodsources. Updated June 8, 2022. Accessed June 30, 2022.
5099. Wahl D, Solon-Biet SM, Cogger VC, et al. Aging, lifestyle and dementia. *Neurobiol Dis*. 2019;130:104481.
5100. Verheggen ICM, de Jong JJA, van Boxtel MPJ, et al. Increase in blood-brain barrier leakage in healthy, older adults. *Geroscience*. 2020;42(4):1183–93.
5101. Farrall AJ, Wardlaw JM. Blood-brain barrier: ageing and microvascular disease—systematic review and meta-analysis. *Neurobiol Aging*. 2009;30(3):337–52.
5102. Nation DA, Sweeney MD, Montagne A, et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. *Nat Med*. 2019;25(2):270–6.
5103. Verheggen ICM, de Jong JJA, van Boxtel MPJ, et al. Increase in blood-brain barrier leakage in healthy, older adults. *Geroscience*. 2020;42(4):1183–93.
5104. Farrall AJ, Wardlaw JM. Blood-brain barrier: ageing and microvascular disease—systematic review and meta-analysis. *Neurobiol Aging*. 2009;30(3):337–52.
5105. Verheggen ICM, de Jong JJA, van Boxtel MPJ, et al. Increase in blood-brain barrier leakage in healthy, older adults. *Geroscience*. 2020;42(4):1183–93.
5106. Gustafson DR, Karlsson C, Skoog I, Rosengren L, Lissner L, Blennow K. Mid-life adiposity factors relate to blood-brain barrier integrity in late life. *J Intern Med*. 2007;262(6):643–50.
5107. Freeman LR, Granholm ACE. Vascular changes in rat hippocampus following a high saturated fat and cholesterol diet. *J Cereb Blood*

Flow Metab. 2012;32(4):643–53.
5108. Ghribi O, Golovko MY, Larsen B, Schrag M, Murphy EJ. Deposition of iron and β-amyloid plaques is associated with cortical cellular damage in rabbits fed with long-term cholesterol-enriched diets. *J Neurochem*. 2006;99(2):438–49.
5109. Takechi R, Galloway S, Pallebage-Gamarallage MM, Lam V, Dhaliwal SS, Mamo JC. Probucol prevents blood–brain barrier dysfunction in wild-type mice induced by saturated fat or cholesterol feeding. *Clin Exp Pharmacol Physiol*. 2013;40(1):45–52.
5110. Galloway S, Takechi R, Nesbit M, Pallebage-Gamarallage MM, Lam V, Mamo JCL. The differential effects of fatty acids on enterocytic abundance of amyloid-beta. *Lipids Health Dis*. 2019;18(1):209.
5111. Boyt AA, Taddei K, Hallmayer J, et al. Relationship between lipid metabolism and plasma concentration of amyloid precursor protein and apolipoprotein E. *Alzheimer's Rep*. 1999;2(6):339–46.
5112. Takechi R, Galloway S, Pallebage-Gamarallage MMS, Lam V, Mamo JCL. Dietary fats, cerebrovasculature integrity and Alzheimer's disease risk. *Prog Lipid Res*. 2010;49(2):159–70.
5113. Kauwe G, Tracy TE. Amyloid beta emerges from below the neck to disable the brain. *PLoS Biol*. 2021;19(9):e3001388.
5114. Edwards LM, Murray AJ, Holloway CJ, et al. Short-term consumption of a high-fat diet impairs whole-body efficiency and cognitive function in sedentary men. *FASEB J*. 2011;25(3):1088–96.
5115. Attuquayefio T, Stevenson RJ, Oaten MJ, Francis HM. A four-day Western-style dietary intervention causes reductions in hippocampal-dependent learning and memory and interoceptive sensitivity. *PLoS ONE*. 2017;12(2):e0172645.
5116. Madison AA, Belury MA, Andridge R, et al. Afternoon distraction: a high-saturated-fat meal and endotoxemia impact postmeal attention in a randomized crossover trial. *Am J Clin Nutr*. 2020;111(6):1150–8.
5117. Valdearcos M, Robblee MM, Benjamin DI, Nomura DK, Xu AW, Koliwad SK. Microglia dictate the impact of saturated fat consumption on hypothalamic inflammation and neuronal function. *Cell Rep*. 2014;9(6):2124–38.
5118. Laposata M. Fatty acids: biochemistry to clinical significance. *Am J Clin Pathol*. 1995;104(2):172–9.

5119. Sergi D, Kahn DE, Morris AC, Williams LM. Palmitic acid induces inflammation in hypothalamic neurons via ceramide synthesis. *Proc Nutr Soc*. 2016;75(OCE2):E46.
5120. Berkseth KE, Guyenet SJ, Melhorn SJ, et al. Hypothalamic gliosis associated with high-fat diet feeding is reversible in mice: a combined immunohistochemical and magnetic resonance imaging study. *Endocrinology*. 2014;155(8):2858–67.
5121. Ioannidis JP. Extrapolating from animals to humans. *Sci Transl Med*. 2012;4(151):151ps15.
5122. Borg ML, Omran SF, Weir J, Meikle PJ, Watt MJ. Consumption of a high-fat diet, but not regular endurance exercise training, regulates hypothalamic lipid accumulation in mice. *J Physiol (Lond)*. 2012;590(17):4377–89.
5123. Agricultural Research Service, United States Department of Agriculture. Pork, cured, bacon, cooked, baked. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html#/food-details/167914/nutrients. Published April 1, 2019. Accessed June 30, 2022.
5124. Kien CL, Bunn JY, Tompkins CL, et al. Substituting dietary monounsaturated fat for saturated fat is associated with increased daily physical activity and resting energy expenditure and with changes in mood. *Am J Clin Nutr*. 2013;97(4):689–97.
5125. Dumas JA, Bunn JY, Nickerson J, et al. Dietary saturated fat and monounsaturated fat have reversible effects on brain function and the secretion of pro-inflammatory cytokines in young women. *Metab Clin Exp*. 2016;65(10):1582–8.
5126. Kien CL, Bunn JY, Tompkins CL, et al. Substituting dietary monounsaturated fat for saturated fat is associated with increased daily physical activity and resting energy expenditure and with changes in mood. *Am J Clin Nutr*. 2013;97(4):689–97.
5127. Sherzai D, Sherzai A. Preventing Alzheimer's: our most urgent health care priority. *Am J Lifestyle Med*. 2019;13(5):451–61.
5128. West RK, Moshier E, Lubitz I, et al. Dietary advanced glycation end products are associated with decline in memory in young elderly. *Mech Ageing Dev*. 2014;140:10–2.
5129. Srikanth V, Westcott B, Forbes J, et al. Methylglyoxal, cognitive function and cerebral atrophy in older people. *J Gerontol A Biol Sci*

Med Sci. 2013;68(1):68–73.
5130. Igase M, Ohara M, Igase K, et al. Skin autofluorescence examination as a diagnostic tool for mild cognitive impairment in healthy people. *J Alzheimers Dis*. 2017;55(4):1481–7.
5131. Ko S, Ko H, Chu K, et al. The possible mechanism of advanced glycation end products (AGEs) for Alzheimer's disease. *PLoS One*. 2015;10(11):e0143345.
5132. Chou P, Wu M, Yang C, Shen C, Yang Y. Effect of advanced glycation end products on the progression of Alzheimer's disease. *J Alzheimers Dis*. 2019;72(1):191–7.
5133. Kim K-S, Lee Y-M, Lee H-W, Jacobs DR, Lee D-H. Associations between organochlorine pesticides and cognition in U.S. elders: National Health and Nutrition Examination Survey 1999–2002. *Environ Int*. 2015;75:87–92.
5134. Bernard A. Elevated serum DDE and risk for Alzheimer disease. *JAMA Neurol*. 2014;71(8):1055–6.
5135. Schecter A, Cramer P, Boggess K, Stanley J, Olson JR. Levels of dioxins, dibenzofurans, PCB and DDE congeners in pooled food samples collected in 1995 at supermarkets across the United States. *Chemosphere*. 1997;34(5–7):1437–47.
5136. André P, Laugerette F, Féart C. Metabolic endotoxemia: a potential underlying mechanism of the relationship between dietary fat intake and risk for cognitive impairments in humans? *Nutrients*. 2019;11(8):1887.
5137. Ghanim H, Batra M, Abuaysheh S, et al. Antiinflammatory and ROS suppressive effects of the addition of fiber to a high-fat high-calorie meal. *J Clin Endocrinol Metab*. 2017;102(3):858–69.
5138. Risk Reduction of Cognitive Decline and Dementia: WHO Guidelines. World Health Organization; 2019.
5139. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission. *Lancet*. 2020;396(10248):413–46.
5140. Theadom A, Mahon S, Hume P, et al. Incidence of sports-related traumatic brain injury of all severities: a systematic review. *Neuroepidemiology*. 2020;54(2):192–9.

5141. Mackay DF, Russell ER, Stewart K, MacLean JA, Pell JP, Stewart W. Neurodegenerative disease mortality in former professional soccer players. *N Engl J Med*. 2019;381(19):1801–8.
5142. Asken BM, Rabinovici GD. Professional soccer and dementia risk—the ugly side of the beautiful game. *JAMA Neurol*. 2021;78(9):1049–51.
5143. Walton SR, Brett BL, Chandran A, et al. Mild cognitive impairment and dementia reported by former professional football players over 50 yr of age: an NFL-LONG study. *Med Sci Sports Exerc*. 2022;54(3):424–31.
5144. Castellani RJ, Perry G. Dementia pugilistica revisited. *J Alzheimers Dis*. 60(4):1209–21.
5145. GBD 2019 Dementia Collaborators. The burden of dementia due to Down syndrome, Parkinson's disease, stroke, and traumatic brain injury: a systematic analysis for the Global Burden of Disease Study 2019. *Neuroepidemiology*. 2021;55(4):286–96.
5146. Høye A. Bicycle helmets—to wear or not to wear? A meta-analyses of the effects of bicycle helmets on injuries. *Accid Anal Prev*. 2018;117:85–97.
5147. Enniss TM, Basiouny K, Brewer B, et al. Primary prevention of contact sports–related concussions in amateur athletes: a systematic review from the Eastern Association for the Surgery of Trauma. *Trauma Surg Acute Care Open*. 2018;3(1):e000153.
5148. Emery CA, Black AM, Kolstad A, et al. What strategies can be used to effectively reduce the risk of concussion in sport? A systematic review. *Br J Sports Med*. 2017;51(12):978–84.
5149. Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. *Nat Rev Neurol*. 2018;14(11):653–66.
5150. Wahl D, Solon-Biet SM, Cogger VC, et al. Aging, lifestyle and dementia. *Neurobiol Dis*. 2019;130:104481.
5151. Zhong G, Wang Y, Zhang Y, Guo JJ, Zhao Y. Smoking is associated with an increased risk of dementia: a meta-analysis of prospective cohort studies with investigation of potential effect modifiers. *PLoS One*. 2015;10(3):e0118333.

5152. Almeida OP, Garrido GJ, Alfonso H, et al. 24-month effect of smoking cessation on cognitive function and brain structure in later life. *Neuroimage*. 2011;55(4):1480–9.
5153. Serrano-Pozo A, Growdon JH. Is Alzheimer's disease risk modifiable? *J Alzheimers Dis*. 2019;67(3):795–819.
5154. Delgado-Saborit JM, Guercio V, Gowers AM, Shaddick G, Fox NC, Love S. A critical review of the epidemiological evidence of effects of air pollution on dementia, cognitive function and cognitive decline in adult population. *Sci Total Environ*. 2021;757:143734.
5155. Calderón-Garcidueñas L, Azzarelli B, Acuna H, et al. Air pollution and brain damage. *Toxicol Pathol*. 2002;30(3):373–89.
5156. Maher BA, Ahmed IAM, Karloukovski V, et al. Magnetite pollution nanoparticles in the human brain. *Proc Natl Acad Sci U S A*. 2016;113(39):10797–801.
5157. Delgado-Saborit JM, Guercio V, Gowers AM, Shaddick G, Fox NC, Love S. A critical review of the epidemiological evidence of effects of air pollution on dementia, cognitive function and cognitive decline in adult population. *Sci Total Environ*. 2021;757:143734.
5158. Gupta S, Warner J. Alcohol-related dementia: a 21st-century silent epidemic? *Br J Psychiatry*. 2008;193(5):351–3.
5159. Wahl D, Solon-Biet SM, Cogger VC, et al. Aging, lifestyle and dementia. *Neurobiol Dis*. 2019;130:104481.
5160. Brennan SE, McDonald S, Page MJ, et al. Long-term effects of alcohol consumption on cognitive function: a systematic review and dose-response analysis of evidence published between 2007 and 2018. *Syst Rev*. 2020;9(1):33.
5161. Andrews SJ, Goate A, Anstey KJ. Association between alcohol consumption and Alzheimer's disease: a Mendelian randomization study. *Alzheimers Dement*. 2020;16(2):345–53.
5162. van Eijk J, Demirakca T, Frischknecht U, Hermann D, Mann K, Ende G. Rapid partial regeneration of brain volume during the first 14 days of abstinence from alcohol. *Alcohol Clin Exp Res*. 2013;37(1):67–74.
5163. Luna S, Cameron DJ, Ethell DW. Amyloid-β and APP deficiencies cause severe cerebrovascular defects: important work for an old villain. *PLoS One*. 2013;8(9):e75052.

5164. Soscia SJ, Kirby JE, Washicosky KJ, et al. The Alzheimer's disease–associated amyloid beta-protein is an antimicrobial peptide. *PLoS One*. 2010;5(3):e9505.
5165. Eimer WA, Vijaya Kumar DK, Navalpur Shanmugam NK, et al. Alzheimer's disease–associated β-amyloid is rapidly seeded by *Herpesviridae* to protect against brain infection. *Neuron*. 2018;99(1):56–63.e3.
5166. Itzhaki RF, Lathe R, Balin BJ, et al. Microbes and Alzheimer's disease. *J Alzheimers Dis*. 2016;51(4):979–84.
5167. Tzeng NS, Chung CH, Lin FH, et al. Anti-herpetic medications and reduced risk of dementia in patients with herpes simplex virus infections—a nationwide, population-based cohort study in Taiwan. *Neurotherapeutics*. 2018;15(2):417–29.
5168. Ogilvie RP, Patel SR. The epidemiology of sleep and obesity. *Sleep Health*. 2017;3(5):383–8.
5169. Everson CA, Bergmann BM, Rechtschaffen A. Sleep deprivation in the rat: III. Total sleep deprivation. *Sleep*. 1989;12(1):13–21.
5170. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science*. 2013;342(6156):373–7.
5171. Absinta M, Ha SK, Nair G, et al. Human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by MRI. *Elife*. 2017;6:e29738.
5172. Shokri-Kojori E, Wang G, Wiers C, et al. β-Amyloid accumulation in the human brain after one night of sleep deprivation. *PNAS*. 2018;115(17):4483–8.
5173. Kress BT, Iliff JJ, Xia M, et al. Impairment of paravascular clearance pathways in the aging brain. *Ann Neurol*. 2014;76(6):845–61.
5174. Simka M, Czaja J, Kowalczyk D. Collapsibility of the internal jugular veins in the lateral decubitus body position: a potential protective role of the cerebral venous outflow against neurodegeneration. *Med Hypotheses*. 2019;133:109397.
5175. Romanella SM, Roe D, Tatti E, et al. The sleep side of aging and Alzheimer's disease. *Sleep Med*. 2021;77:209–25.
5176. Brusco LI, Márquez M, Cardinali DP. Monozygotic twins with Alzheimer's disease treated with melatonin: case report. *J Pineal Res*. 1998;25(4):260–3.

5177. Vincent B. Protective roles of melatonin against the amyloid-dependent development of Alzheimer's disease: a critical review. *Pharmacol Res*. 2018;134:223–37.
5178. Wang YY, Zheng W, Ng CH, Ungvari GS, Wei W, Xiang YT. Meta-analysis of randomized, double-blind, placebo-controlled trials of melatonin in Alzheimer's disease. *Int J Geriatr Psychiatry*. 2017;32(1):50–7.
5179. Loef M, Walach H. Midlife obesity and dementia: meta-analysis and adjusted forecast of dementia prevalence in the United States and China. *Obesity (Silver Spring)*. 2013;21(1):E51–5.
5180. Yang Y, Shields GS, Guo C, Liu Y. Executive function performance in obesity and overweight individuals: a meta-analysis and review. *Neurosci Biobehav Rev*. 2018;84:225–44.
5181. Walther K, Birdsill AC, Glisky EL, Ryan L. Structural brain differences and cognitive functioning related to body mass index in older females. *Hum Brain Mapp*. 2010;31(7):1052–64.
5182. Willette AA, Kapogiannis D. Does the brain shrink as the waist expands? Ageing Res Rev. 2015;20:86–97.
5183. Veronese N, Facchini S, Stubbs B, et al. Weight loss is associated with improvements in cognitive function among overweight and obese people: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2017;72:87–94.
5184. Veronese N, Facchini S, Stubbs B, et al. Weight loss is associated with improvements in cognitive function among overweight and obese people: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2017;72:87–94.
5185. Napoli N, Shah K, Waters DL, Sinacore DR, Qualls C, Villareal DT. Effect of weight loss, exercise, or both on cognition and quality of life in obese older adults. *Am J Clin Nutr*. 2014;100(1):189–98.
5186. Erickson KI, Hillman C, Stillman CM, et al. Physical activity, cognition, and brain outcomes: a review of the 2018 physical activity guidelines. *Med Sci Sports Exerc*. 2019;51(6):1242–51.
5187. Lee J. Effects of aerobic and resistance exercise interventions on cognitive and physiologic adaptations for older adults with mild cognitive impairment: a systematic review and meta-analysis of

randomized control trials. *Int J Environ Res Public Health*. 2020;17(24):E9216.
5188. Gomes-Osman J, Cabral DF, Morris TP, et al. Exercise for cognitive brain health in aging: a systematic review for an evaluation of dose. *Neurol Clin Pract*. 2018;8(3):257–65.
5189. Sanders LMJ, Hortobágyi T, la Bastide-van Gemert S, van der Zee EA, van Heuvelen MJG. Dose-response relationship between exercise and cognitive function in older adults with and without cognitive impairment: a systematic review and meta-analysis. *PLoS One*. 2019;14(1):e0210036.
5190. Gomes-Osman J, Cabral DF, Morris TP, et al. Exercise for cognitive brain health in aging: a systematic review for an evaluation of dose. *Neurol Clin Pract*. 2018;8(3):257–65.
5191. Lamb SE, Sheehan B, Atherton N, et al. Dementia And Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial. *BMJ*. 2018;361:k1675.
5192. Ng TKS, Ho CSH, Tam WWS, Kua EH, Ho RCM. Decreased serum brain-derived neurotrophic factor (BDNF) levels in patients with Alzheimer's disease (AD): a systematic review and meta-analysis. *Int J Mol Sci*. 2019;20(2):E257.
5193. Qin XY, Cao C, Cawley NX, et al. Decreased peripheral brain-derived neurotrophic factor levels in Alzheimer's disease: a meta-analysis study (*N*=7277). *Mol Psychiatry*. 2017;22(2):312–20.
5194. Hsu TM, Kanoski SE. Blood-brain barrier disruption: mechanistic links between Western diet consumption and dementia. *Front Aging Neurosci*. 2014;6:88.
5195. Du Y, Wu HT, Qin XY, et al. Postmortem brain, cerebrospinal fluid, and blood neurotrophic factor levels in Alzheimer's disease: a systematic review and meta-analysis. *J Mol Neurosci*. 2018;65(3):289–300.
5196. Qin XY, Cao C, Cawley NX, et al. Decreased peripheral brain-derived neurotrophic factor levels in Alzheimer's disease: a meta-analysis study (*N*=7277). *Mol Psychiatry*. 2017;22(2):312–20.
5197. Ng TKS, Ho CSH, Tam WWS, Kua EH, Ho RCM. Decreased serum brain-derived neurotrophic factor (BDNF) levels in patients with

Alzheimer's disease (AD): a systematic review and meta-analysis. *Int J Mol Sci*. 2019;20(2):E257.

5198. Qin XY, Cao C, Cawley NX, et al. Decreased peripheral brain-derived neurotrophic factor levels in Alzheimer's disease: a meta-analysis study (*N*=7277). *Mol Psychiatry*. 2017;22(2):312–20.

5199. Lima Giacobbo B, Doorduin J, Klein HC, Dierckx RAJO, Bromberg E, de Vries EFJ. Brain-derived neurotrophic factor in brain disorders: focus on neuroinflammation. *Mol Neurobiol*. 2019;56(5):3295–312.

5200. Weinstein G, Beiser AS, Choi SH, et al. Serum brain-derived neurotrophic factor and the risk for dementia: the Framingham Heart Study. *JAMA Neurol*. 2014;71(1):55–61.

5201. Laske C, Stellos K, Hoffmann N, et al. Higher BDNF serum levels predict slower cognitive decline in Alzheimer's disease patients. *Int J Neuropsychopharmacol*. 2011;14(3):399–404.

5202. McPhee GM, Downey LA, Stough C. Neurotrophins as a reliable biomarker for brain function, structure and cognition: a systematic review and meta-analysis. *Neurobiol Learn Mem*. 2020;175:107298.

5203. Lima Giacobbo B, Doorduin J, Klein HC, Dierckx RAJO, Bromberg E, de Vries EFJ. Brain-derived neurotrophic factor in brain disorders: focus on neuroinflammation. *Mol Neurobiol*. 2019;56(5):3295–312.

5204. Szuhany KL, Bugatti M, Otto MW. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. *J Psychiatr Res*. 2015;60:56–64.

5205. Marquez CMS, Vanaudenaerde B, Troosters T, Wenderoth N. High-intensity interval training evokes larger serum BDNF levels compared with intense continuous exercise. *J Appl Physiol (1985)*. 2015;119(12):1363–73.

5206. Ferris LT, Williams JS, Shen CL. The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. *Med Sci Sports Exerc*. 2007;39(4):728–34.

5207. Coelho FM, Pereira DS, Lustosa LP, et al. Physical therapy intervention (PTI) increases plasma brain-derived neurotrophic factor (BDNF) levels in non-frail and pre-frail elderly women. *Arch Gerontol Geriatr*. 2012;54(3):415–20.

5208. Loprinzi PD. Does brain-derived neurotrophic factor mediate the effects of exercise on memory? *Phys Sportsmed*. 2019;47(4):395–

405.
5209. Guelpa G. Starvation and purgation in the relief of disease. *Br Med J.* 1910;2(2597):1050–1.
5210. Watkins E, Serpell L. The psychological effects of short-term fasting in healthy women. *Front Nutr*. 2016;3:27.
5211. Fond G, Macgregor A, Leboyer M, Michalsen A. Fasting in mood disorders: neurobiology and effectiveness. A review of the literature. *Psychiatry Res*. 2013;209(3):253–8.
5212. Araya AV, Orellana X, Espinoza J. Evaluation of the effect of caloric restriction on serum BDNF in overweight and obese subjects: preliminary evidences. *Endocrine*. 2008;33(3):300–4.
5213. Witte AV, Fobker M, Gellner R, Knecht S, Flöel A. Caloric restriction improves memory in elderly humans. *Proc Natl Acad Sci U S A*. 2009;106(4):1255–60.
5214. Araya AV, Orellana X, Espinoza J. Evaluation of the effect of caloric restriction on serum BDNF in overweight and obese subjects: preliminary evidences. *Endocrine*. 2008;33(3):300–4.
5215. Guimarães LR, Jacka FN, Gama CS, et al. Serum levels of brain-derived neurotrophic factor in schizophrenia on a hypocaloric diet. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(6):1595–8.
5216. Karczewska-Kupczewska M, Kowalska I, Nikołajuk A, et al. Circulating brain-derived neurotrophic factor concentration is downregulated by intralipid/heparin infusion or high-fat meal in young healthy male subjects. *Diabetes Care*. 2012;35(2):358–62.
5217. Park HR, Park M, Choi J, Park KY, Chung HY, Lee J. A high-fat diet impairs neurogenesis: involvement of lipid peroxidation and brain-derived neurotrophic factor. *Neurosci Lett*. 2010;482(3):235–9.
5218. Cott A. Controlled fasting treatment for schizophrenia. *Orthomolecular Psychiatry*. 1974;3(4):301–11.
5219. Beezhold BL, Johnston CS. Restriction of meat, fish, and poultry in omnivores improves mood: a pilot randomized controlled trial. *Nutr J*. 2012;11:9.
5220. Neshatdoust S, Saunders C, Castle SM, et al. High-flavonoid intake induces cognitive improvements linked to changes in serum brain-derived neurotrophic factor: two randomised, controlled trials. *Nutr Healthy Aging*. 4(1):81–93.

5221. Sánchez-Villegas A, Galbete C, Martinez-González MA, et al. The effect of the Mediterranean diet on plasma brain-derived neurotrophic factor (BDNF) levels: the PREDIMED-NAVARRA randomized trial. *Nutr Neurosci*. 2011;14(5):195–201.
5222. Geethanjali A, Lalitha P, Firdhouse JM. Analysis of curcumin content of turmeric samples from various states of India. *Int J Pharma Chem Res*. 2016;2(1):55–62.
5223. Miller KB, Hurst WJ, Payne MJ, et al. Impact of alkalization on the antioxidant and flavanol content of commercial cocoa powders. *J Agric Food Chem*. 2008;56(18):8527–33.
5224. Agricultural Research Service, United States Department of Agriculture. Cocoa, dry powder, unsweetened. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html?query=cocoa&utf8=%E2%9C%93&affiliate=usda&commit=Search#/food-details/169593/nutrients. Published April 1, 2019. Accessed June 30, 2022.
5225. Neshatdoust S, Saunders C, Castle SM, et al. High-flavonoid intake induces cognitive improvements linked to changes in serum brain-derived neurotrophic factor: two randomised, controlled trials. *Nutr Healthy Aging*. 4(1):81–93.
5226. Sandberg JC, Björck IME, Nilsson AC. Increased plasma brain-derived neurotrophic factor 10.5 h after intake of whole grain rye-based products in healthy subjects. *Nutrients*. 2018;10(8):E1097.
5227. Intlekofer KA, Berchtold NC, Malvaez M, et al. Exercise and sodium butyrate transform a subthreshold learning event into long-term memory via a brain-derived neurotrophic factor-dependent mechanism. *Neuropsychopharmacology*. 2013;38(10):2027–34.
5228. Gravesteijn E, Mensink RP, Plat J. Effects of nutritional interventions on BDNF concentrations in humans: a systematic review. *Nutritional Neuroscience*. Published online January 10, 2021:1–12.
5229. Marizzoni M, Cattaneo A, Mirabelli P, et al. Short-chain fatty acids and lipopolysaccharide as mediators between gut dysbiosis and amyloid pathology in Alzheimer's disease. *J Alzheimers Dis*. 2020;78(2):683–97.
5230. Vinarskaya AK, Balaban PM, Roshchin MV, Zuzina AB. Sodium butyrate as a selective cognitive enhancer for weak or impaired

memory. *Neurobiol Learn Mem*. 2021;180:107414.
5231. Fernando WMADB, Martins IJ, Morici M, et al. Sodium butyrate reduces brain amyloid-β levels and improves cognitive memory performance in an Alzheimer's disease transgenic mouse model at an early disease stage. *J Alzheimers Dis*. 2020;74(1):91–9.
5232. Govindarajan N, Agis-Balboa RC, Walter J, Sananbenesi F, Fischer A. Sodium butyrate improves memory function in an Alzheimer's disease mouse model when administered at an advanced stage of disease progression. *J Alzheimers Dis*. 2011;26(1):187–97.
5233. Bourassa MW, Alim I, Bultman SJ, Ratan RR. Butyrate, neuroepigenetics and the gut microbiome: can a high fiber diet improve brain health? *Neurosci Lett*. 2016;625:56–63.
5234. Braniste V, Al-Asmakh M, Kowal C, et al. The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med*. 2014;6(263):263ra158.
5235. Chen T, Kim CY, Kaur A, et al. Dietary fibre-based SCFA mixtures promote both protection and repair of intestinal epithelial barrier function in a Caco-2 cell model. *Food Funct*. 2017;8(3):1166–73.
5236. Braniste V, Al-Asmakh M, Kowal C, et al. The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med*. 2014;6(263):263ra158.
5237. Bercik P, Park AJ, Sinclair D, et al. The anxiolytic effect of *Bifidobacterium longum* NCC3001 involves vagal pathways for gut-brain communication. *Neurogastroenterol Motil*. 2011;23(12):1132–9.
5238. Bravo JA, Forsythe P, Chew MV, et al. Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci U S A*. 2011;108(38):16050–5.
5239. Clark KB, Naritoku DK, Smith DC, Browning RA, Jensen RA. Enhanced recognition memory following vagus nerve stimulation in human subjects. *Nat Neurosci*. 1999;2(1):94–8.
5240. Liyanage SI, Vilekar P, Weaver DF. Nutrients in Alzheimer's disease: the interaction of diet, drugs and disease. *Can J Neurol Sci*. 2019;46(1):23–34.

5241. McGrattan AM, McGuinness B, McKinley MC, et al. Diet and inflammation in cognitive ageing and Alzheimer's disease. *Curr Nutr Rep*. 2019;8(2):53–65.
5242. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;505(7484):559–63.
5243. van Soest APM, Hermes GDA, Berendsen AAM, et al. Associations between pro- and anti-inflammatory gastro-intestinal microbiota, diet, and cognitive functioning in Dutch healthy older adults: the NU-AGE Study. *Nutrients*. 2020;12(11):E3471.
5244. Bruce-Keller AJ, Salbaum JM, Luo M, et al. Obese-type gut microbiota induce neurobehavioral changes in the absence of obesity. *Biol Psychiatry*. 2015;77(7):607–15.
5245. Loeb MB, Molloy DW, Smieja M, et al. A randomized, controlled trial of doxycycline and rifampin for patients with Alzheimer's disease. *J Am Geriatr Soc*. 2004;52(3):381–7.
5246. Molloy DW, Standish TI, Zhou Q, Guyatt G, The DARAD Study Group. A multicenter, blinded, randomized, factorial controlled trial of doxycycline and rifampin for treatment of Alzheimer's disease: the DARAD trial. *Int J Geriatr Psychiatry*. 2013;28(5):463–70.
5247. Marx W, Scholey A, Firth J, et al. Prebiotics, probiotics, fermented foods and cognitive outcomes: a meta-analysis of randomized controlled trials. *Neurosci Biobehav Rev*. 2020;118:472–84.
5248. Benton D, Williams C, Brown A. Impact of consuming a milk drink containing a probiotic on mood and cognition. *Eur J Clin Nutr*. 2007;61(3):355–61.
5249. Den H, Dong X, Chen M, Zou Z. Efficacy of probiotics on cognition, and biomarkers of inflammation and oxidative stress in adults with Alzheimer's disease or mild cognitive impairment—a meta-analysis of randomized controlled trials. *Aging (Albany NY)*. 2020;12(4):4010–39.
5250. Ito K, Romero K. Placebo effect in subjects with cognitive impairment. *Int Rev Neurobiol*. 2020;153:213–30.
5251. Block BR, Albanese SG, Hume AL. Online promotion of "brain health" supplements. *Sr Care Pharm*. 2021;36(10):489–92.

5252. Stoehr GP, Jacobsen E, Jia Y, Snitz BE, Ganguli M. Trends in the use of medications and supplements to treat or prevent dementia: a population-based study. *Alzheimer Dis Assoc Disord*. 2020;34(2):148–55.
5253. Block BR, Albanese SG, Hume AL. Online promotion of "brain health" supplements. *Sr Care Pharm*. 2021;36(10):489–92.
5254. Case 1:17-cv-00124-LLS Document 72. Federal Trade Commission and People of the State of New York v Quincy Bioscience Holding Company, Inc. https://www.ftc.gov/system/files/documents/cases/quincy_bioscience_opinion_and_order.pdf. Published July 14, 2019. Accessed July 10, 2022.
5255. Fair L. Prevagen complaint suggests mindfulness about memory claims. Federal Trade Commission. https://www.ftc.gov/business-guidance/blog/2017/01/prevagen-complaint-suggests-mindfulness-about-memory-claims. Published January 9, 2017. Accessed June 21, 2022.
5256. Gabriel BA. AARP asks court to declare Prevagen ads misleading. AARP. https://www.aarp.org/politics-society/advocacy/info-2018/overturn-prevagen-decision-fd.html. Published March 21, 2018. Accessed June 21, 2022.
5257. Scott GN. Does Prevagen® help memory loss? Medscape. https://www.medscape.com/viewarticle/860395. Published March 18, 2016. Accessed June 21, 2022.
5258. Eisner C. Americans took Prevagen for years—as the FDA questioned its safety. Wired. https://www.wired.com/story/prevagen-made-millions-fda-questioned-safety/. Published October 21, 2020. Accessed June 21, 2022.
5259. Crawford C, Deuster PA. Be in the know: dietary supplements for cognitive performance. *J Spec Oper Med*. 2020;20(2):132–5.
5260. Crawford C, Boyd C, Avula B, Wang YH, Khan IA, Deuster PA. A public health issue: dietary supplements promoted for brain health and cognitive performance. *J Altern Complement Med*. 2020;26(4):265–72.
5261. Block BR, Albanese SG, Hume AL. Online promotion of "brain health" supplements. *Sr Care Pharm*. 2021;36(10):489–92.

5262. Franke AG, Heinrich I, Lieb K, Fellgiebel A. The use of *Ginkgo biloba* in healthy elderly. *Age (Dordr)*. 2014;36(1):435–44.
5263. Yuan Q, Wang CW, Shi J, Lin ZX. Effects of *Ginkgo biloba* on dementia: an overview of systematic reviews. *J Ethnopharmacol*. 2017;195:1–9.
5264. Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. *Cochrane Database Syst Rev*. 2009;(1):CD003120.
5265. Wang Y, Yang G, Gong J, et al. Ginseng for Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. *Curr Top Med Chem*. 2015;16(5):529–36.
5266. Shakespeare W. The Tragedy of Hamlet, Prince of Denmark. Act IV, scene 5, line 3053. OpenSourceShakespeare. https://www.opensourceshakespeare.org/views/plays/play_view.php?WorkID=hamlet&Act=4&Scene=5&Scope=scene. Published 1786. Accessed July 1, 2022.
5267. Perry EK, Pickering AT, Wang WW, Houghton PJ, Perry NS. Medicinal plants and Alzheimer's disease: from ethnobotany to phytotherapy. *J Pharm Pharmacol*. 1999;51(5):527–34.
5268. Moss M, Cook J, Wesnes K, Duckett P. Aromas of rosemary and lavender essential oils differentially affect cognition and mood in healthy adults. *Int J Neurosci*. 2003;113(1):15–38.
5269. Moss M, Oliver L. Plasma 1,8-cineole correlates with cognitive performance following exposure to rosemary essential oil aroma. *Ther Adv Psychopharmacol*. 2012;2(3):103–13.
5270. Pengelly A, Snow J, Mills SY, Scholey A, Wesnes K, Butler LR. Short-term study on the effects of rosemary on cognitive function in an elderly population. *J Med Food*. 2012;15(1):10–7.
5271. Shinjyo N, Green J. Are sage, rosemary and lemon balm effective interventions in dementia? A narrative review of the clinical evidence. *Eur J Integr Med*. 2017;15:83–96.
5272. Kennedy DO, Wake G, Savelev S, et al. Modulation of mood and cognitive performance following acute administration of single doses of *Melissa officinalis* (lemon balm) with human CNS nicotinic and muscarinic receptor-binding properties. *Neuropsychopharmacology*. 2003;28(10):1871–81.

5273. Perry NSL, Menzies R, Hodgson F, et al. A randomised double-blind placebo-controlled pilot trial of a combined extract of sage, rosemary and melissa, traditional herbal medicines, on the enhancement of memory in normal healthy subjects, including influence of age. *Phytomedicine*. 2018;39:42–8.
5274. Moss M, Cook J, Wesnes K, Duckett P. Aromas of rosemary and lavender essential oils differentially affect cognition and mood in healthy adults. *Int J Neurosci*. 2003;113(1):15–38.
5275. Jimbo D, Kimura Y, Taniguchi M, Inoue M, Urakami K. Effect of aromatherapy on patients with Alzheimer's disease. *Psychogeriatrics*. 2009;9(4):173–9.
5276. Eriksson PS. Neurogenesis and its implications for regeneration in the adult brain. *J Rehabil Med*. 2003;(41 Suppl):17–9.
5277. Eriksson PS, Perfilieva E, Björk-Eriksson T, et al. Neurogenesis in the adult human hippocampus. *Nat Med*. 1998;4(11):1313–7.
5278. Take comfort in human neurogenesis. *Nat Med*. 1998;4(11):1207.
5279. Jimbo D, Kimura Y, Taniguchi M, Inoue M, Urakami K. Effect of aromatherapy on patients with Alzheimer's disease. *Psychogeriatrics*. 2009;9(4):173–9.
5280. Aydin Yildirim T, Kitiş Y. The effect of aromatherapy application on cognitive functions and daytime sleepiness in older adults living in a nursing home. *Holist Nurs Pract*. 2020;34(2):83–90.
5281. Ayaz M, Sadiq A, Junaid M, Ullah F, Subhan F, Ahmed J. Neuroprotective and anti-aging potentials of essential oils from aromatic and medicinal plants. *Front Aging Neurosci*. 2017;9:168.
5282. Zalomonson S, Freud T, Punchik B, Samson T, Lebedinsky S, Press Y. The results of a crossover placebo-controlled study of the effect of lavender oil on behavioral and psychological symptoms of dementia. *Rejuvenation Res*. 2019;22(3):246–53.
5283. Ball EL, Owen-Booth B, Gray A, Shenkin SD, Hewitt J, McCleery J. Aromatherapy for dementia. *Cochrane Database Syst Rev*. 2020;2020(8):CD003150.
5284. Burns A, Perry E, Holmes C, et al. A double-blind placebo-controlled randomized trial of *Melissa officinalis* oil and donepezil for the treatment of agitation in Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2011;31(2):158–64.

5285. Watson K, Hatcher D, Good A. A randomised controlled trial of lavender (*Lavandula angustifolia*) and lemon balm (*Melissa officinalis*) essential oils for the treatment of agitated behaviour in older people with and without dementia. *Complement Ther Med*. 2019;42:366–73.
5286. Hishikawa N, Takahashi Y, Amakusa Y, et al. Effects of turmeric on Alzheimer's disease with behavioral and psychological symptoms of dementia. *Ayu*. 2012;33(4):499–504.
5287. Zhu LN, Mei X, Zhang ZG, Xie YP, Lang F. Curcumin intervention for cognitive function in different types of people: a systematic review and meta-analysis. *Phytother Res*. 2019;33(3):524–33.
5288. Baum L, Lam CWK, Cheung SKK, et al. Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease. *J Clin Psychopharmacol*. 2008;28(1):110–3.
5289. Ringman JM, Frautschy SA, Teng E, et al. Oral curcumin for Alzheimer's disease: tolerability and efficacy in a 24-week randomized, double blind, placebo-controlled study. *Alzheimers Res Ther*. 2012;4(5):43.
5290. Gupta SC, Sung B, Kim JH, Prasad S, Li S, Aggarwal BB. Multitargeting by turmeric, the golden spice: from kitchen to clinic. *Mol Nutr Food Res*. 2013;57(9):1510–28.
5291. Ahmed T, Gilani AH. Therapeutic potential of turmeric in Alzheimer's disease: curcumin or curcuminoids? *Phytother Res*. 2014;28(4):517–25.
5292. Hishikawa N, Takahashi Y, Amakusa Y, et al. Effects of turmeric on Alzheimer's disease with behavioral and psychological symptoms of dementia. *Ayu*. 2012;33(4):499–504.
5293. Moazen-Zadeh E, Abbasi SH, Safi-Aghdam H, et al. Effects of saffron on cognition, anxiety, and depression in patients undergoing coronary artery bypass grafting: a randomized double-blind placebo-controlled trial. *J Altern Complement Med*. 2018;24(4):361–8.
5294. Farokhnia M, Shafiee Sabet M, Iranpour N, et al. Comparing the efficacy and safety of *Crocus sativus* L. with memantine in patients with moderate to severe Alzheimer's disease: a double-blind randomized clinical trial. *Hum Psychopharmacol*. 2014;29(4):351–9.

5295. Hausenblas HA, Heekin K, Mutchie HL, Anton S. A systematic review of randomized controlled trials examining the effectiveness of saffron (*Crocus sativus* L.) on psychological and behavioral outcomes. *J Integr Med*. 2015;13(4):231–40.
5296. Ayati Z, Yang G, Ayati MH, Emami SA, Chang D. Saffron for mild cognitive impairment and dementia: a systematic review and meta-analysis of randomised clinical trials. *BMC Complement Med Ther*. 2020;20(1):333.
5297. Tóth B, Hegyi P, Lantos T, et al. The efficacy of saffron in the treatment of mild to moderate depression: a meta-analysis. *Planta Med*. 2019;85(1):24–31.
5298. Tabeshpour J, Sobhani F, Sadjadi SA, et al. A double-blind, randomized, placebo-controlled trial of saffron stigma (*Crocus sativus* L.) in mothers suffering from mild-to-moderate postpartum depression. *Phytomedicine*. 2017;36:145–52.
5299. Finley JW, Gao S. A perspective on Crocus sativus L. (saffron) constituent crocin: a potent water-soluble antioxidant and potential therapy for Alzheimer's disease. *J Agric Food Chem*. 2017;65(5):1005–20.
5300. World Health Organization. *WHO Monographs on Selected Medicinal Plants. Vol 3*. World Health Organization; 2001.
5301. Block BR, Albanese SG, Hume AL. Online promotion of "brain health" supplements. *Sr Care Pharm*. 2021;36(10):489–92.
5302. Goodwill AM, Szoeke C. A systematic review and meta-analysis of the effect of low vitamin D on cognition. *J Am Geriatr Soc*. 2017;65(10):2161–8.
5303. Kalra A, Teixeira AL, Diniz BS. Association of vitamin D levels with incident all-cause dementia in longitudinal observational studies: a systematic review and meta-analysis. *J Prev Alzheimers Dis*. 2020;7(1):14–20.
5304. Orces C, Lorenzo C, Guarneros JE. The prevalence and determinants of vitamin D inadequacy among U.S. older adults: National Health and Nutrition Examination Survey 2007–2014. *Cureus*. 2019;11(8):e5300.

5305. Riaz S, Malcangio M, Miller M, Tomlinson DR. A vitamin D_3 derivative (CB1093) induces nerve growth factor and prevents neurotrophic deficits in streptozotocin-diabetic rats. *Diabetologia*. 1999;42(11):1308–13.
5306. Durk MR, Han K, Chow ECY, et al. 1α,25-Dihydroxyvitamin D_3 reduces cerebral amyloid-β accumulation and improves cognition in mouse models of Alzheimer's disease. *J Neurosci*. 2014;34(21):7091–101.
5307. Hu J, Jia J, Zhang Y, Miao R, Huo X, Ma F. Effects of vitamin D_3 supplementation on cognition and blood lipids: a 12-month randomised, double-blind, placebo-controlled trial. *J Neurol Neurosurg Psychiatry*. 2018;89(12):1341–7.
5308. Jia J, Hu J, Huo X, Miao R, Zhang Y, Ma F. Effects of vitamin D supplementation on cognitive function and blood Aβ-related biomarkers in older adults with Alzheimer's disease: a randomised, double-blind, placebo-controlled trial. *J Neurol Neurosurg Psychiatry*. 2019;90(12):1347–52.
5309. Castle M, Fiedler N, Pop LC, et al. Three doses of vitamin D and cognitive outcomes in older women: a double-blind randomized controlled trial. *J Gerontol A Biol Sci Med Sci*. 2020;75(5):835–42.
5310. Schietzel S, Fischer K, Brugger P, et al. Effect of 2000 IU compared with 800 IU vitamin D on cognitive performance among adults age 60 years and older: a randomized controlled trial. *Am J Clin Nutr*. 2019;110(1):246–53.
5311. Pettersen JA. Does high dose vitamin D supplementation enhance cognition?: a randomized trial in healthy adults. *Exp Gerontol*. 2017;90:90–7.
5312. Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA Cooperative Randomized Trial. *JAMA*. 2014;311(1):33–44.
5313. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med.* 1997;336(17):1216–22.
5314. Lloret A, Badía MC, Mora NJ, Pallardó FV, Alonso MD, Viña J. Vitamin E paradox in Alzheimer's disease: it does not prevent loss of

cognition and may even be detrimental. *J Alzheimers Dis*. 2009;17(1):143–9.
5315. Yaffe K, Clemons TE, McBee WL, Lindblad AS. Impact of antioxidants, zinc, and copper on cognition in the elderly: a randomized, controlled trial. *Neurology*. 2004;63(9):1705–7.
5316. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360(9326):23–33.
5317. Grodstein F, O'Brien J, Kang JH, et al. Long-term multivitamin supplementation and cognitive function in men: a randomized trial. *Ann Intern Med*. 2013;159(12):806–14.
5318. Maylor EA, Simpson EEA, Secker DL, et al. Effects of zinc supplementation on cognitive function in healthy middle-aged and older adults: the ZENITH study. *Br J Nutr*. 2006;96(4):752–60.
5319. Yaffe K, Clemons TE, McBee WL, Lindblad AS. Impact of antioxidants, zinc, and copper on cognition in the elderly: a randomized, controlled trial. *Neurology*. 2004;63(9):1705–7.
5320. Kern J, Kern S, Blennow K, et al. Calcium supplementation and risk of dementia in women with cerebrovascular disease. *Neurology*. 2016;87(16):1674–80.
5321. Obeid R, Herrmann W. Mechanisms of homocysteine neurotoxicity in neurodegenerative diseases with special reference to dementia. *FEBS Lett*. 2006;580(13):2994–3005.
5322. Rutjes AWS, Denton DA, Di Nisio M, et al. Vitamin and mineral supplementation for maintaining cognitive function in cognitively healthy people in mid and late life. *Cochrane Database Syst Rev*. 2018;12:CD011906.
5323. Zhang DM, Ye JX, Mu JS, Cui XP. Efficacy of vitamin B supplementation on cognition in elderly patients with cognitive-related diseases. *J Geriatr Psychiatry Neurol*. 2017;30(1):50–9.
5324. Behrens A, Graessel E, Pendergrass A, Donath C. Vitamin B—Can it prevent cognitive decline? A systematic review and meta-analysis. *Syst Rev*. 2020;9(1):111.
5325. de Jager CA, Oulhaj A, Jacoby R, Refsum H, Smith AD. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment

in mild cognitive impairment: a randomized controlled trial. *Int J Geriatr Psychiatry*. 2012;27(6):592–600.

5326. Wyss-Coray T. Ageing, neurodegeneration and brain rejuvenation. *Nature*. 2016;539(7628):180–6.

5327. Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. *PLoS One*. 2010;5(9):e12244.

5328. Douaud G, Refsum H, de Jager CA, et al. Preventing Alzheimer's disease–related gray matter atrophy by B-vitamin treatment. *Proc Natl Acad Sci U S A*. 2013;110(23):9523–8.

5329. Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. *PLoS One*. 2010;5(9):e12244.

5330. McCaddon A, Miller JW. Assessing the association between homocysteine and cognition: reflections on Bradford Hill, meta-analyses, and causality. *Nutr Rev*. 2015;73(10):723–35.

5331. Smith AD, Refsum H, Bottiglieri T, et al. Homocysteine and dementia: an international consensus statement. *J Alzheimers Dis*. 62(2):561–70.

5332. Clarke R, Bennett D, Parish S, et al. Effects of homocysteine lowering with B vitamins on cognitive aging: meta-analysis of 11 trials with cognitive data on 22,000 individuals. *Am J Clin Nutr*. 2014;100(2):657–66.

5333. McCaddon A, Miller JW. Assessing the association between homocysteine and cognition: reflections on Bradford Hill, meta-analyses, and causality. *Nutr Rev*. 2015;73(10):723–35.

5334. Aisen PS, Schneider LS, Sano M, et al. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. *JAMA*. 2008;300(15):1774–83.

5335. Douaud G, Refsum H, de Jager CA, et al. Preventing Alzheimer's disease–related gray matter atrophy by B-vitamin treatment. *Proc Natl Acad Sci U S A*. 2013;110(23):9523–8.

5336. Zhang S, Tomata Y, Sugiyama K, Sugawara Y, Tsuji I. Mushroom consumption and incident dementia in elderly Japanese: the Ohsaki

Cohort 2006 Study. *J Am Geriatr Soc*. 2017;65(7).
5337. Durga J, van Boxtel MPJ, Schouten EG, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. *Lancet*. 2007;369(9557):208–16.
5338. DeRose DJ, Charles-Marcel ZL, Jamison JM, et al. Vegan diet-based lifestyle program rapidly lowers homocysteine levels. *Prev Med*. 2000;30(3):225–33.
5339. Chandrasekhar C, Kiranmayi VS, Pasupuleti SK, Sarma KV, Sarma PV. Assessment of reference range of serum homocysteine from the post-therapy values of cobalamin and folate deficiency patients. *J Assoc Physicians India*. 2020;68(9):36–42.
5340. Houghton LA, Green TJ, Donovan UM, Gibson RS, Stephen AM, O'Connor DL. Association between dietary fiber intake and the folate status of a group of female adolescents. *Am J Clin Nutr*. 1997;66(6):1414–21.
5341. Guttormsen AB, Schneede J, Fiskerstrand T, Ueland PM, Refsum HM. Plasma concentrations of homocysteine and other aminothiol compounds are related to food intake in healthy human subjects. *J Nutr*. 1994;124(10):1934–41.
5342. Obersby D, Chappell DC, Dunnett A, Tsiami AA. Plasma total homocysteine status of vegetarians compared with omnivores: a systematic review and meta-analysis. *Br J Nutr*. 2013;109(5):785–94.
5343. Öztürk Ş, Altieri M, Troisi P. Leonardo Da Vinci and stroke—vegetarian diet as a possible cause. *Front Neurol Neurosci*. 2010;27:1–10.
5344. Crane MG, Register UD, Lukens RH, Gregory R. Cobalamin (CBL) studies on two total vegetarian (vegan) families. *Vegetarian Nutrition (United Kingdom)*. 1998;2(3):87–92.
5345. Verghese J, Lipton RB, Katz MJ, et al. Leisure activities and the risk of dementia in the elderly. *N Engl J Med*. 2003;348(25):2508–16.
5346. Cafferata RMT, Hicks B, von Bastian CC. Effectiveness of cognitive stimulation for dementia: a systematic review and meta-analysis. *Psychol Bull*. 2021;147(5):455–76.
5347. Bian X, Wang Y, Zhao X, Zhang Z, Ding C. Does music therapy affect the global cognitive function of patients with dementia? A

meta-analysis. *NeuroRehabilitation*. 2021;48(4):553–62.
5348. Moreno-Morales C, Calero R, Moreno-Morales P, Pintado C. Music therapy in the treatment of dementia: a systematic review and meta-analysis. *Front Med*. 2020;7:160.
5349. Lam HL, Li WTV, Laher I, Wong RY. Effects of music therapy on patients with dementia—a systematic review. *Geriatrics (Basel)*. 2020;5(4):E62.
5350. Wahl D, Solon-Biet SM, Cogger VC, et al. Aging, lifestyle and dementia. *Neurobiol Dis*. 2019;130:104481.
5351. Liu YH, Gao X, Na M, Kris-Etherton PM, Mitchell DC, Jensen GL. Dietary pattern, diet quality, and dementia: a systematic review and meta-analysis of prospective cohort studies. *J Alzheimers Dis*. 2020;78(1):151–68.
5352. Akbaraly T, Sabia S, Hagger-Johnson G, et al. Does overall diet in midlife predict future aging phenotypes? A cohort study. *Am J Med*. 2013;126(5):411–9.e3.
5353. Risk Reduction of Cognitive Decline and Dementia: WHO Guidelines. World Health Organization; 2019.
5354. Hughes TF, Andel R, Small BJ, et al. Midlife fruit and vegetable consumption and risk of dementia in later life in Swedish twins. *Am J Geriatr Psychiatry*. 2010;18(5):413–20.
5355. Jiang X, Huang J, Song D, Deng R, Wei J, Zhang Z. Increased consumption of fruit and vegetables is related to a reduced risk of cognitive impairment and dementia: meta-analysis. *Front Aging Neurosci*. 2017;9:18.
5356. Sherzai D, Sherzai A. Preventing Alzheimer's: our most urgent health care priority. *Am J Lifestyle Med*. 2019;13(5):451–61.
5357. Millin PM, Rickert GM. Effect of a strawberry and spinach dietary supplement on spatial learning in early and late middle-aged female rats. *Antioxidants (Basel)*. 2018;8(1):E1.
5358. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid Med Cell Longev*. 2009;2(5):270–8.
5359. Cherniack EP. A plant-tastic treatment for cognitive disorders. *Maturitas*. 2012;72(4):265–6.
5360. Khoo HE, Azlan A, Tang ST, Lim SM. Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients,

and the potential health benefits. *Food Nutr Res*. 2017;61(1):1361779.
5361. Shukitt-Hale B, Bielinski DF, Lau FC, Willis LM, Carey AN, Joseph JA. The beneficial effects of berries on cognition, motor behaviour and neuronal function in ageing. *Br J Nutr*. 2015;114(10):1542–9.
5362. Krikorian R, Shidler MD, Nash TA, et al. Blueberry supplementation improves memory in older adults. *J Agric Food Chem*. 2010;58(7):3996–4000.
5363. Miller MG, Hamilton DA, Joseph JA, Shukitt-Hale B. Dietary blueberry improves cognition among older adults in a randomized, double-blind, placebo-controlled trial. *Eur J Nutr*. 2018;57(3):1169–80.
5364. Krikorian R, Kalt W, McDonald JE, Shidler MD, Summer SS, Stein AL. Cognitive performance in relation to urinary anthocyanins and their flavonoid-based products following blueberry supplementation in older adults at risk for dementia. *J Funct Foods*. 2020;64:103667.
5365. Barfoot KL, May G, Lamport DJ, Ricketts J, Riddell PM, Williams CM. The effects of acute wild blueberry supplementation on the cognition of 7–10-year-old schoolchildren. *Eur J Nutr*. 2019;58(7):2911–20.
5366. Whyte AR, Schafer G, Williams CM. Cognitive effects following acute wild blueberry supplementation in 7- to 10-year-old children. *Eur J Nutr*. 2016;55(6):2151–62.
5367. Whyte AR, Schafer G, Williams CM. The effect of cognitive demand on performance of an executive function task following wild blueberry supplementation in 7 to 10 years old children. *Food Funct*. 2017;8(11):4129–38.
5368. Barfoot KL, Istas G, Feliciano RP, et al. Effects of daily consumption of wild blueberry on cognition and urinary metabolites in school-aged children: a pilot study. *Eur J Nutr*. 2021;60(8):4263–78.
5369. Whyte AR, Rahman S, Bell L, et al. Improved metabolic function and cognitive performance in middle-aged adults following a single dose of wild blueberry. *Eur J Nutr*. 2021;60(3):1521–36.
5370. Whyte AR, Williams CM. Effects of a single dose of a flavonoid-rich blueberry drink on memory in 8 to 10 y old children. *Nutrition*. 2015;31(3):531–4.

5371. Lorenz M, Jochmann N, von Krosigk A, et al. Addition of milk prevents vascular protective effects of tea. *Eur Heart J*. 2007;28(2):219–23.
5372. Effect of simultaneous consumption of soymilk and coffee on the urinary excretion of isoflavones, chlorogenic acids and metabolites in healthy adults. *J Funct Foods*. 2015;19:688–99.
5373. Serafini M, Bugianesi R, Maiani G, Valtuena S, De Santis S, Crozier A. Plasma antioxidants from chocolate. *Nature*. 2003;424(6952):1013.
5374. Duarte GS, Farah A. Effect of simultaneous consumption of milk and coffee on chlorogenic acids' bioavailability in humans. *J Agric Food Chem*. 2011;59(14):7925–31.
5375. Serafini M, Testa MF, Villaño D, et al. Antioxidant activity of blueberry fruit is impaired by association with milk. *Free Radic Biol Med*. 2009;46(6):769–74.
5376. Xiao D, Sandhu A, Huang Y, Park E, Edirisinghe I, Burton-Freeman BM. The effect of dietary factors on strawberry anthocyanins oral bioavailability. *Food Funct*. 2017;8(11):3970–9.
5377. Serafini M, Testa MF, Villaño D, et al. Antioxidant activity of blueberry fruit is impaired by association with milk. *Free Radic Biol Med*. 2009;46(6):769–74.
5378. Zhu Y, Sun J, Lu W, et al. Effects of blueberry supplementation on blood pressure: a systematic review and meta-analysis of randomized clinical trials. *J Hum Hypertens*. 2017;31(3):165–71.
5379. Ahles S, Joris PJ, Plat J. Effects of berry anthocyanins on cognitive performance, vascular function and cardiometabolic risk markers: a systematic review of randomized placebo-controlled intervention studies in humans. *Int J Mol Sci*. 2021;22(12):6482.
5380. Barfoot KL, Istas G, Feliciano RP, et al. Effects of daily consumption of wild blueberry on cognition and urinary metabolites in school-aged children: a pilot study. *Eur J Nutr*. 2021;60(8):4263–78.
5381. Ahles S, Joris PJ, Plat J. Effects of berry anthocyanins on cognitive performance, vascular function and cardiometabolic risk markers: a systematic review of randomized placebo-controlled intervention studies in humans. *Int J Mol Sci*. 2021;22(12):6482.

5382. Curtis PJ, Berends L, van der Velpen V, et al. Blueberry anthocyanin intake attenuates the postprandial cardiometabolic effect of an energy-dense food challenge: results from a double blind, randomized controlled trial in metabolic syndrome participants. *Clin Nutr*. 2022;41(1):165–76.
5383. Boespflug EL, Eliassen JC, Dudley JA, et al. Enhanced neural activation with blueberry supplementation in mild cognitive impairment. *Nutr Neurosci*. 2018;21(4):297–305.
5384. McNamara RK, Kalt W, Shidler MD, et al. Cognitive response to fish oil, blueberry, and combined supplementation in older adults with subjective cognitive impairment. *Neurobiol Aging*. 2018;64:147–56.
5385. Newman S, Stygall J, Hirani S, Shaefi S, Maze M. Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. *Anesthesiology*. 2007;106(3):572–90.
5386. Traupe I, Giacalone M, Agrimi J, et al. Postoperative cognitive dysfunction and short-term neuroprotection from blueberries: a pilot study. *Minerva Anestesiol*. 2018;84(12):1352–60.
5387. Brydges CR, Gaeta L. There is no meta-analytic evidence of blueberries improving cognitive performance or mood. *Brain Behav Immun*. 2020;85:192.
5388. Giacalone M, Di Sacco F, Traupe I, Topini R, Forfori F, Giunta F. Antioxidant and neuroprotective properties of blueberry polyphenols: a critical review. *Nutr Neurosci*. 2011;14(3):119–25.
5389. Carey AN, Pintea GI, Van Leuven S, et al. Red raspberry (*Rubus ideaus*) supplementation mitigates the effects of a high-fat diet on brain and behavior in mice. *Nutr Neurosci*. 2021;24(6):406–16.
5390. Thangthaeng N, Poulose SM, Gomes SM, Miller MG, Bielinski DF, Shukitt-Hale B. Tart cherry supplementation improves working memory, hippocampal inflammation, and autophagy in aged rats. *Age (Dordr)*. 2016;38(5–6):393–404.
5391. Kent K, Charlton K, Roodenrys S, et al. Consumption of anthocyanin-rich cherry juice for 12 weeks improves memory and cognition in older adults with mild-to-moderate dementia. *Eur J Nutr*. 2017;56(1):333–41.
5392. Chai SC, Jerusik J, Davis K, Wright RS, Zhang Z. Effect of Montmorency tart cherry juice on cognitive performance in older

adults: a randomized controlled trial. *Food Funct*. 2019;10(7):4423–31.
5393. Crews WD Jr, Harrison DW, Griffin ML, et al. A double-blinded, placebo-controlled, randomized trial of the neuropsychologic efficacy of cranberry juice in a sample of cognitively intact older adults: pilot study findings. *J Altern Complement Med*. 2005;11(2):305–9.
5394. Whyte AR, Cheng N, Butler LT, Lamport DJ, Williams CM. Flavonoid-rich mixed berries maintain and improve cognitive function over a 6 h period in young healthy adults. *Nutrients*. 2019;11(11):2685.
5395. Nilsson A, Salo I, Plaza M, Björck I. Effects of a mixed berry beverage on cognitive functions and cardiometabolic risk markers; a randomized cross-over study in healthy older adults. *PLoS One*. 2017;12(11):e0188173.
5396. Ahles S, Joris PJ, Plat J. Effects of berry anthocyanins on cognitive performance, vascular function and cardiometabolic risk markers: a systematic review of randomized placebo-controlled intervention studies in humans. *Int J Mol Sci*. 2021;22(12):6482.
5397. Jennings A, Steves CJ, Macgregor A, Spector T, Cassidy A. Increased habitual flavonoid intake predicts attenuation of cognitive ageing in twins. *BMC Med*. 2021;19(1):185.
5398. Lee S, Kim EY, Shin C. Changes in brain volume associated with vegetable intake in a general population. *J Am Coll Nutr*. 2019;38(6):506–12.
5399. Kang JH, Ascherio A, Grodstein F. Fruit and vegetable consumption and cognitive decline in aging women. *Ann Neurol*. 2005;57(5):713–20.
5400. Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS. Associations of vegetable and fruit consumption with age-related cognitive change. *Neurology*. 2006;67(8):1370–6.
5401. Li W, Sun L, Yue L, Li G, Xiao S. The association between eating green vegetables every day and mild cognitive impairment: a community-based cross-sectional study in Shanghai. *Neuropsychiatr Dis Treat*. 2019;15:3213–8.
5402. Morris MC, Wang Y, Barnes LL, Bennett DA, Dawson-Hughes B, Booth SL. Nutrients and bioactives in green leafy vegetables and

cognitive decline: prospective study. *Neurology*. 2018;90(3):e214–22.
5403. Kang JH, Ascherio A, Grodstein F. Fruit and vegetable consumption and cognitive decline in aging women. *Ann Neurol*. 2005;57(5):713–20.
5404. Masci A, Mattioli R, Costantino P, et al. Neuroprotective effect of *Brassica oleracea* sprouts crude juice in a cellular model of Alzheimer's disease. *Oxid Med Cell Longev*. 2015;2015:781938.
5405. Klomparens EA, Ding Y. The neuroprotective mechanisms and effects of sulforaphane. *Brain Circ*. 2019;5(2):74–83.
5406. Panjwani AA, Liu H, Fahey JW. Crucifers and related vegetables and supplements for neurologic disorders: what is the evidence? *Curr Opin Clin Nutr Metab Care*. 2018;21(6):451–7.
5407. Song L, Thornalley PJ. Effect of storage, processing and cooking on glucosinolate content of *Brassica* vegetables. *Food Chem Toxicol*. 2007;45(2):216–24.
5408. Nouchi R, Hu Q, Saito T, Kawata NYdS, Nouchi H, Kawashima R. Brain training and sulforaphane intake interventions separately improve cognitive performance in healthy older adults, whereas a combination of these interventions does not have more beneficial effects: evidence from a randomized controlled trial. *Nutrients*. 2021;13(2):352.
5409. Jiraungkoorskul W. Review of neuro-nutrition used as anti-Alzheimer plant, spinach, *Spinacia oleracea*. *Pharmacogn Rev*. 2016;10(20):105–8.
5410. Stanaway L, Rutherfurd-Markwick K, Page R, Ali A. Performance and health benefits of dietary nitrate supplementation in older adults: a systematic review. *Nutrients*. 2017;9(11):E1171.
5411. Petrie M, Rejeski WJ, Basu S, et al. Beet root juice: an ergogenic aid for exercise and the aging brain. *J Gerontol A Biol Sci Med Sci*. 2017;72(9):1284–9.
5412. Hammond BR, Renzi LM. Carotenoids. *Adv Nutr*. 2013;4(4):474–6.
5413. Booth SL. Vitamin K: food composition and dietary intakes. *Food Nutr Res*. 2012;56:5505.
5414. Tanprasertsuk J, Ferland G, Johnson MA, et al. Concentrations of circulating phylloquinone, but not cerebral menaquinone-4, are

positively correlated with a wide range of cognitive measures: exploratory findings in centenarians. *J Nutr*. 2020;150(1):82–90.
5415. Johnson EJ. Role of lutein and zeaxanthin in visual and cognitive function throughout the lifespan. *Nutr Rev*. 2014;72(9):605–12.
5416. Erdman JW, Smith JW, Kuchan MJ, et al. Lutein and brain function. *Foods*. 2015;4(4):547–64.
5417. Johnson EJ. Role of lutein and zeaxanthin in visual and cognitive function throughout the lifespan. *Nutr Rev*. 2014;72(9):605–12.
5418. Kelly D, Coen RF, Akuffo KO, et al. Cognitive function and its relationship with macular pigment optical density and serum concentrations of its constituent carotenoids. *J Alzheimers Dis*. 2015;48(1):261–77.
5419. Vishwanathan R, Schalch W, Johnson EJ. Macular pigment carotenoids in the retina and occipital cortex are related in humans. *Nutr Neurosci*. 2016;19(3):95–101.
5420. Mewborn CM, Terry DP, Renzi-Hammond LM, Hammond BR, Miller LS. Relation of retinal and serum lutein and zeaxanthin to white matter integrity in older adults: a diffusion tensor imaging study. *Arch Clin Neuropsychol*. 2018;33(7):861–74.
5421. Johnson EJ. Role of lutein and zeaxanthin in visual and cognitive function throughout the lifespan. *Nutr Rev*. 2014;72(9):605–12.
5422. Edwards CG, Walk AM, Thompson SV, et al. Effects of 12-week avocado consumption on cognitive function among adults with overweight and obesity. *Int J Psychophysiol*. 2020;148:13–24.
5423. Edwards CG, Walk AM, Thompson SV, et al. Effects of 12-week avocado consumption on cognitive function among adults with overweight and obesity. *Int J Psychophysiol*. 2020;148:13–24.
5424. Hammond BR, Johnson EJ, Russell RM, et al. Dietary modification of human macular pigment density. *Invest Ophthalmol Vis Sci*. 1997;38(9):1795–801.
5425. Bovier ER, Hammond BR. A randomized placebo-controlled study on the effects of lutein and zeaxanthin on visual processing speed in young healthy subjects. *Arch Biochem Biophys*. 2015;572:54–7.
5426. Nouchi R, Suiko T, Kimura E, et al. Effects of lutein and astaxanthin intake on the improvement of cognitive functions among healthy

adults: a systematic review of randomized controlled trials. *Nutrients*. 2020;12(3):E617.

5427. Renzi LM, Dengler MJ, Puente A, Miller LS, Hammond BR. Relationships between macular pigment optical density and cognitive function in unimpaired and mildly cognitively impaired older adults. *Neurobiol Aging*. 2014;35(7):1695–9.

5428. Nolan JM, Loskutova E, Howard A, et al. The impact of supplemental macular carotenoids in Alzheimer's disease: a randomized clinical trial. *J Alzheimers Dis*. 2015;44(4):1157–69.

5429. Saitsu Y, Nishide A, Kikushima K, Shimizu K, Ohnuki K. Improvement of cognitive functions by oral intake of *Hericium erinaceus*. *Biomed Res*. 2019;40(4):125–31.

5430. Mori K, Inatomi S, Ouchi K, Azumi Y, Tuchida T. Improving effects of the mushroom Yamabushitake (*Hericium erinaceus*) on mild cognitive impairment: a double-blind placebo-controlled clinical trial. *Phytother Res*. 2009;23(3):367–72.

5431. Rajaram S, Jones J, Lee GJ. Plant-based dietary patterns, plant foods, and age-related cognitive decline. *Adv Nutr*. 2019;10(Suppl_4):S422–36.

5432. Huang Q, Braffett BH, Simmens SJ, Young HA, Ogden CL. Dietary polyphenol intake in us adults and 10-year trends: 2007–2016. *J Acad Nutr Diet*. 2020;120(11):1821–33.

5433. Pham K, Mulugeta A, Zhou A, O'Brien JT, Llewellyn DJ, Hyppönen E. High coffee consumption, brain volume and risk of dementia and stroke. *Nutr Neurosci*. Published online June 24, 2021:1–12.

5434. Ran LS, Liu WH, Fang YY, et al. Alcohol, coffee and tea intake and the risk of cognitive deficits: a dose-response meta-analysis. *Epidemiol Psychiatr Sci*. 2021;30:e13.

5435. Ran LS, Liu WH, Fang YY, et al. Alcohol, coffee and tea intake and the risk of cognitive deficits: a dose-response meta-analysis. *Epidemiol Psychiatr Sci*. 2021;30:e13.

5436. Einöther SJ, Martens VE. Acute effects of tea consumption on attention and mood. *Am J Clin Nutr*. 2013;98(6 Suppl):1700S-8S.

5437. Liu X, Du X, Han G, Gao W. Association between tea consumption and risk of cognitive disorders: a dose-response meta-analysis of observational studies. *Oncotarget*. 2017;8(26):43306–21.

5438. Li XH, Li CY, Lu JM, Tian RB, Wei J. Allicin ameliorates cognitive deficits ageing-induced learning and memory deficits through enhancing of Nrf2 antioxidant signaling pathways. *Neurosci Lett*. 2012;514(1):46–50.
5439. Luo JF, Dong Y, Chen JY, Lu JH. The effect and underlying mechanisms of garlic extract against cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis of experimental animal studies. *J Ethnopharmacol*. 2021;280:114423.
5440. Tasnim S, Haque PS, Bari MS, et al. *Allium sativum* L. improves visual memory and attention in healthy human volunteers. *Evid Based Complement Alternat Med*. 2015;2015:103416.
5441. Saenghong N, Wattanathorn J, Muchimapura S, et al. *Zingiber officinale* improves cognitive function of the middle-aged healthy women. *Evid Based Complement Alternat Med*. 2012;2012:383062.
5442. Bin Sayeed MS, Shams T, Fahim Hossain S, et al. *Nigella sativa* L. seeds modulate mood, anxiety and cognition in healthy adolescent males. *J Ethnopharmacol*. 2014;152(1):156–62.
5443. Bin Sayeed MS, Asaduzzaman M, Morshed H, Hossain MM, Kadir MF, Rahman MR. The effect of *Nigella sativa* Linn. seed on memory, attention and cognition in healthy human volunteers. *J Ethnopharmacol*. 2013;148(3):780–6.
5444. Mazza E, Fava A, Ferro Y, et al. Impact of legumes and plant proteins consumption on cognitive performances in the elderly. *J Transl Med*. 2017;15(1):109.
5445. An R, Liu G, Khan N, Yan H, Wang Y. Dietary habits and cognitive impairment risk among oldest-old Chinese. *J Gerontol B Psychol Sci Soc Sci*. 2019;74(3):474–83.
5446. Cui C, Birru RL, Snitz BE, et al. Effects of soy isoflavones on cognitive function: a systematic review and meta-analysis of randomized controlled trials. *Nutr Rev*. 2020;78(2):134–44.
5447. File SE, Jarrett N, Fluck E, Duffy R, Casey K, Wiseman H. Eating soya improves human memory. *Psychopharmacology (Berl)*. 2001;157(4):430–6.
5448. Bhagwat S, Haytowitz DB, Holden JM. USDA database for the isoflavone content of selected foods: release 2.0. Agricultural Research Service, United States Department of Agriculture.

https://www.ars.usda.gov/arsuserfiles/80400525/data/isoflav/isoflav_r2.pdf. Published September 2008. Accessed June 28, 2022.
5449. Gleason CE, Fischer BL, Dowling NM, et al. Cognitive effects of soy isoflavones in patients with Alzheimer's disease. *J Alzheimers Dis*. 2015;47(4):1009–19.
5450. Sekikawa A, Higashiyama A, Lopresti BJ, et al. Associations of equol-producing status with white matter lesion and amyloid-β deposition in cognitively normal elderly Japanese. *Alzheimers Dement (N Y)*. 2020;6(1):e12089.
5451. Yuan JP, Wang JH, Liu X. Metabolism of dietary soy isoflavones to equol by human intestinal microflora—implications for health. *Mol Nutr Food Res*. 2007;51(7):765–81.
5452. Yuan JP, Wang JH, Liu X. Metabolism of dietary soy isoflavones to equol by human intestinal microflora—implications for health. *Mol Nutr Food Res*. 2007;51(7):765–81.
5453. Sugiyama Y, Masumori N, Fukuta F, et al. Influence of isoflavone intake and equol-producing intestinal flora on prostate cancer risk. *Asian Pac J Cancer Prev*. 2013;14(1):1–4.
5454. Setchell KDR, Cole SJ. Method of defining equol-producer status and its frequency among vegetarians. *J Nutr*. 2006;136(8):2188–93.
5455. Rowland IR, Wiseman H, Sanders TA, Adlercreutz H, Bowey EA. Interindividual variation in metabolism of soy isoflavones and lignans: influence of habitual diet on equol production by the gut microflora. *Nutr Cancer*. 2000;36(1):27–32.
5456. Setchell KDR, Brown NM, Summer S, et al. Dietary factors influence production of the soy isoflavone metabolite s-(-)equol in healthy adults. *J Nutr*. 2013;143(12):1950–8.
5457. Setchell KDR, Cole SJ. Method of defining equol-producer status and its frequency among vegetarians. *J Nutr*. 2006;136(8):2188–93.
5458. Foscolou A, D'Cunha NM, Naumovski N, et al. The association between whole grain products consumption and successful aging: a combined analysis of MEDIS and ATTICA epidemiological studies. *Nutrients*. 2019;11(6):E1221.
5459. Shimizu C, Wakita Y, Kihara M, Kobayashi N, Tsuchiya Y, Nabeshima T. Association of lifelong intake of barley diet with healthy aging: changes in physical and cognitive functions and

intestinal microbiome in senescence-accelerated mouse-prone 8(SAMP8). *Nutrients*. 2019;11(8):E1770.

5460. Liu X, Guasch-Ferré M, Tobias DK, Li Y. Association of walnut consumption with total and cause-specific mortality and life expectancy in U.S. Adults. *Nutrients*. 2021;13(8):2699.

5461. O'Brien J, Okereke O, Devore E, Rosner B, Breteler M, Grodstein F. Long-term intake of nuts in relation to cognitive function in older women. *J Nutr Health Aging*. 2014;18(5):496–502.

5462. Valls-Pedret C, Sala-Vila A, Serra-Mir M, et al. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. *JAMA Intern Med*. 2015;175(7):1094.

5463. Greenwood CE, Parrott MD. Nutrition as a component of dementia risk reduction strategies. *Healthc Manage Forum*. 2017;30(1):40–5.

5464. Jayedi A, Shab-Bidar S. Fish consumption and the risk of chronic disease: an umbrella review of meta-analyses of prospective cohort studies. *Adv Nutr*. 2020;11(5):1123–33.

5465. Patan MJ, Kennedy DO, Husberg C, et al. Supplementation with oil rich in eicosapentaenoic acid, but not in docosahexaenoic acid, improves global cognitive function in healthy, young adults: results from randomized controlled trials. *Am J Clin Nutr*. 2021;114(3):914–24.

5466. Macaron T, Giudici KV, Bowman GL, et al. Associations of Omega-3 fatty acids with brain morphology and volume in cognitively healthy older adults: a narrative review. *Ageing Res Rev*. 2021;67:101300.

5467. Wennberg M, Tornevi A, Johansson I, Hörnell A, Norberg M, Bergdahl IA. Diet and lifestyle factors associated with fish consumption in men and women: a study of whether gender differences can result in gender-specific confounding. *Nutr J*. 2012;11:101.

5468. Maciel E da S, Sonati JG, Galvão JA, Oetterer M. Fish consumption and lifestyle: a cross-sectional study. *Food Sci Technol*. 2019;39(suppl 1):141–5.

5469. Li ZH, Zhong WF, Liu S, et al. Associations of habitual fish oil supplementation with cardiovascular outcomes and all cause mortality: evidence from a large population based cohort study. *BMJ*. 2020;368:m456.

5470. Burckhardt M, Herke M, Wustmann T, Watzke S, Langer G, Fink A. Omega-3 fatty acids for the treatment of dementia. *Cochrane Database Syst Rev*. 2016;2016(4):CD009002.
5471. Peters R, Breitner J, James S, et al. Dementia risk reduction: why haven't the pharmacological risk reduction trials worked? An in-depth exploration of seven established risk factors. *Alzheimers Dement (N Y)*. 2021;7(1):e12202.
5472. Brainard JS, Jimoh OF, Deane KHO, et al. Omega-3, omega-6, and polyunsaturated fat for cognition: systematic review and meta-analysis of randomized trials. *J Am Med Dir Assoc*. 2020;21(10):1439–50.e21.
5473. Piro A, Tagarelli G, Lagonia P, Tagarelli A, Quattrone A. Casimir Funk: his discovery of the vitamins and their deficiency disorders. *Ann Nutr Metab*. 2010;57(2):85–8.
5474. Casmir F. The Journal of State Medicine. Volume XX: 341–368, 1912. The etiology of the deficiency diseases, Beri-beri, polyneuritis in birds, epidemic dropsy, scurvy, experimental scurvy in animals, infantile scurvy, ship beri-beri, pellagra. *Nutr Rev*. 1975;33(6):176–7.
5475. Semba RD. The discovery of the vitamins. *Int J Vitam Nutr Res*. 2012;82(5):310–5.
5476. Holman RT. The slow discovery of the importance of omega 3 essential fatty acids in human health. *J Nutr*. 1998;128(2 Suppl):427S-33S.
5477. Davis BC, Kris-Etherton PM. Achieving optimal essential fatty acid status in vegetarians: current knowledge and practical implications. *Am J Clin Nutr*. 2003;78(3 Suppl):640S-6S.
5478. Andrieu S, Guyonnet S, Coley N, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol*. 2017;16(5):377–89.
5479. Hooper C, Vellas B. Commentary: Fatty acids and Alzheimer's disease: evidence on cognition and cortical β-amyloid from secondary analyses of the Multidomain Alzheimer Preventive Trial. *J Prev Alzheimers Dis*. 2018;5(3):168–70.

5480. Witte AV, Kerti L, Hermannstädter HM, et al. Long-chain omega-3 fatty acids improve brain function and structure in older adults. *Cereb Cortex*. 2014;24(11):3059–68.
5481. Zhang YP, Miao R, Li Q, Wu T, Ma F. Effects of DHA supplementation on hippocampal volume and cognitive function in older adults with mild cognitive impairment: a 12-month randomized, double-blind, placebo-controlled trial. *J Alzheimers Dis*. 2017;55(2):497–507.
5482. Sun GY, Simonyi A, Fritsche KL, et al. Docosahexaenoic acid (DHA): An essential nutrient and a nutraceutical for brain health and diseases. *Prostaglandins Leukot Essent Fatty Acids*. 2018;136:3–13.
5483. Muskiet FAJ, Fokkema MR, Schaafsma A, Boersma ER, Crawford MA. Is docosahexaenoic acid (DHA) essential? Lessons from DHA status regulation, our ancient diet, epidemiology and randomized controlled trials. *J Nutr*. 2004;134(1):183–6.
5484. Balachandar R, Soundararajan S, Bagepally BS. Docosahexaenoic acid supplementation in age-related cognitive decline: a systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2020;76(5):639–48.
5485. Lane KE, Wilson M, Hellon TG, Davies IG. Bioavailability and conversion of plant based sources of omega-3 fatty acids—a scoping review to update supplementation options for vegetarians and vegans. *Crit Rev Food Sci Nutr*. Published online February 12, 2021:1–16.
5486. Davis BC, Kris-Etherton PM. Achieving optimal essential fatty acid status in vegetarians: current knowledge and practical implications. *Am J Clin Nutr*. 2003;78(3 Suppl):640S-6S.
5487. Brainard JS, Jimoh OF, Deane KHO, et al. Omega-3, omega-6, and polyunsaturated fat for cognition: systematic review and meta-analysis of randomized trials. *J Am Med Dir Assoc*. 2020;21(10):1439–50.e21.
5488. Danthiir V, Hosking D, Burns NR, et al. Cognitive performance in older adults is inversely associated with fish consumption but not erythrocyte membrane n-3 fatty acids. *J Nutr*. 2014;144(3):311–20.
5489. Laurin D, Verreault R, Lindsay J, Dewailly E, Holub BJ. Omega-3 fatty acids and risk of cognitive impairment and dementia. *J Alzheimers Dis*. 2003;5(4):315–22.

5490. Foley MM, Seidel I, Sevier J, Wendt J, Kogan M. One man's swordfish story: the link between Alzheimer's disease and mercury exposure. *Complement Ther Med*. 2020;52:102499.
5491. Xu L, Zhang W, Liu X, Zhang C, Wang P, Zhao X. Circulatory levels of toxic metals (aluminum, cadmium, mercury, lead) in patients with Alzheimer's disease: a quantitative meta-analysis and systematic review. *J Alzheimers Dis*. 2018;62(1):361–72.
5492. Srikumar TS, Johansson GK, Ockerman PA, Gustafsson JA, Akesson B. Trace element status in healthy subjects switching from a mixed to a lactovegetarian diet for 12 mo. *Am J Clin Nutr*. 1992;55(4):885–90.
5493. Sherzai D, Sherzai A. Preventing Alzheimer's: our most urgent health care priority. *Am J Lifestyle Med*. 2019;13(5):451–61.
5494. Morris MC, Brockman J, Schneider JA, et al. Association of seafood consumption, brain mercury level, and *APOE ε4* status with brain neuropathology in older adults. *JAMA*. 2016;315(5):489–97.
5495. Glynn A, Aune M, Darnerud PO, et al. Determinants of serum concentrations of organochlorine compounds in Swedish pregnant women: a cross-sectional study. *Environ Health*. 2007;6:2.
5496. Bourdon JA, Bazinet TM, Arnason TT, Kimpe LE, Blais JM, White PA. Polychlorinated biphenyls (PCBs) contamination and aryl hydrocarbon receptor (AhR) agonist activity of Omega-3 polyunsaturated fatty acid supplements: implications for daily intake of dioxins and PCBs. *Food Chem Toxicol*. 2010;48(11):3093–7.
5497. Arterburn LM, Oken HA, Bailey Hall E, Hamersley J, Kuratko CN, Hoffman JP. Algal-oil capsules and cooked salmon: nutritionally equivalent sources of docosahexaenoic acid. *J Am Diet Assoc*. 2008;108(7):1204–9.
5498. Greene J, Ashburn SM, Razzouk L, Smith DA. Fish oils, coronary heart disease, and the environment. *Am J Public Health*. 2013;103(9):1568–76.
5499. Cox PA, Sacks OW. Cycad neurotoxins, consumption of flying foxes, and ALS-PDC disease in Guam. *Neurology*. 2002;58(6):956–9.
5500. Banack SA, Cox PA. Biomagnification of cycad neurotoxins in flying foxes: implications for ALS-PDC in Guam. *Neurology*. 2003;61(3):387–9.

5501. Pablo J, Banack SA, Cox PA, et al. Cyanobacterial neurotoxin BMAA in ALS and Alzheimer's disease. *Acta Neurol Scand*. 2009;120(4):216–25.
5502. Brand LE, Pablo J, Compton A, Hammerschlag N, Mash DC. Cyanobacterial blooms and the occurrence of the neurotoxin beta-N-methylamino-$_{L}$-alanine (BMAA) in South Florida aquatic food webs. *Harmful Algae*. 2010;9(6):620–35.
5503. Bradley WG, Mash DC. Beyond Guam: the cyanobacteria/BMAA hypothesis of the cause of ALS and other neurodegenerative diseases. *Amyotroph Lateral Scler*. 2009;10 Suppl 2:7–20.
5504. Cox PA, Davis DA, Mash DC, Metcalf JS, Banack SA. Dietary exposure to an environmental toxin triggers neurofibrillary tangles and amyloid deposits in the brain. *Proc R Soc B*. 2016;283(1823):20152397.
5505. Meneely JP, Chevallier OP, Graham S, Greer B, Green BD, Elliott CT. β-methylamino-L-alanine (BMAA) is not found in the brains of patients with confirmed Alzheimer's disease. *Sci Rep*. 2016;6:36363.
5506. Banack SA, Murch SJ. Methods for the chemical analysis of β-*N*-Methylamino-L-alanine: what is known and what remains to be determined. *Neurotox Res*. 2018;33(1):184–91.
5507. Mondo K, Hammerschlag N, Basile M, Pablo J, Banack SA, Mash DC. Cyanobacterial neurotoxin β-*N*-methylamino-L-alanine (BMAA) in shark fins. *Mar Drugs*. 2012;10(2):509–20.
5508. Torbick N, Ziniti B, Stommel E, et al. Assessing cyanobacterial harmful algal blooms as risk factors for amyotrophic lateral sclerosis. *Neurotox Res*. 2018;33(1):199–212.
5509. Holtcamp W. Shark fin consumption may expose people to neurotoxic BMAA. *Environ Health Perspect*. 2012;120(5):a191.
5510. Lance E, Arnich N, Maignien T, Biré R. Occurrence of β-*N*-methylamino-$_{L}$-alanine (BMAA) and isomers in aquatic environments and aquatic food sources for humans. *Toxins (Basel)*. 2018;10(2):E83.
5511. Mondo K, Broc Glover W, Murch SJ, et al. Environmental neurotoxins β-N-methylamino-$_{L}$-alanine (BMAA) and mercury in shark cartilage dietary supplements. *Food Chem Toxicol*. 2014;70:26–32.

5512. Roy-Lachapelle A, Solliec M, Bouchard MF, Sauvé S. Detection of cyanotoxins in algae dietary supplements. *Toxins (Basel)*. 2017;9(3):E76.
5513. Glover WB, Baker TC, Murch SJ, Brown P. Determination of β-*N*-methylamino-L-alanine, *N*-(2-aminoethyl)glycine, and 2,4-diaminobutyric acid in food products containing cyanobacteria by ultra-performance liquid chromatography and tandem mass spectrometry: single-laboratory validation. *J AOAC Int*. 2015;98(6):1559–65.
5514. Lehtisalo J, Levälahti E, Lindström J, et al. Dietary changes and cognition over 2 years within a multidomain intervention trial—The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). *Alzheimers Dement*. 2019;15(3):410–7.
5515. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015;385(9984):2255–63.
5516. Montero-Odasso M, Ismail Z, Livingston G. One third of dementia cases can be prevented within the next 25 years by tackling risk factors. The case "for" and "against." *Alzheimers Res Ther*. 2020;12:81.
5517. Lehtisalo J, Levälahti E, Lindström J, et al. Dietary changes and cognition over 2 years within a multidomain intervention trial—The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). *Alzheimers Dement*. 2019;15(3):410–7.
5518. Knight A, Bryan J, Murphy K. The Mediterranean diet and age-related cognitive functioning: a systematic review of study findings and neuropsychological assessment methodology. *Nutr Neurosci*. 2017;20(8):449–68.
5519. Coelho-Júnior HJ, Trichopoulou A, Panza F. Cross-sectional and longitudinal associations between adherence to Mediterranean diet with physical performance and cognitive function in older adults: a systematic review and meta-analysis. *Ageing Res Rev*. 2021;70:101395.

5520. Radd-Vagenas S, Duffy SL, Naismith SL, Brew BJ, Flood VM, Fiatarone Singh MA. Effect of the Mediterranean diet on cognition and brain morphology and function: a systematic review of randomized controlled trials. *Am J Clin Nutr*. 2018;107(3):389–404.
5521. Marseglia A, Xu W, Fratiglioni L, et al. Effect of the NU-AGE diet on cognitive functioning in older adults: a randomized controlled trial. *Front Physiol*. 2018;9:349.
5522. Roberts RO, Geda YE, Cerhan JR, et al. Vegetables, unsaturated fats, moderate alcohol intake, and mild cognitive impairment. *Dement Geriatr Cogn Disord*. 2010;29(5):413–23.
5523. Titova OE, Ax E, Brooks SJ, et al. Mediterranean diet habits in older individuals: associations with cognitive functioning and brain volumes. *Exp Gerontol*. 2013;48(12):1443–8.
5524. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimers Dement*. 2015;11(9):1007–14.
5525. Marcason W. What are the components to the MIND diet? *J Acad Nutr Diet*. 2015;115(10):1744.
5526. Kheirouri S, Alizadeh M. MIND diet and cognitive performance in older adults: a systematic review. *Crit Rev Food Sci Nutr*. 2022;62(29):8059–77.
5527. Morris MC, Tangney CC, Wang Y, et al. MIND diet slows cognitive decline with aging. *Alzheimers Dement*. 2015;11(9):1015–22.
5528. Corley J. Adherence to the MIND diet is associated with 12-year all-cause mortality in older adults. *Public Health Nutr*. Published online September 3, 2020:1–10.
5529. Arjmand G, Abbas-Zadeh M, Eftekhari MH. Effect of MIND diet intervention on cognitive performance and brain structure in healthy obese women: a randomized controlled trial. *Sci Rep*. 2022;12(1):2871.
5530. Berendsen AM, Kang JH, Feskens EJM, de Groot CPGM, Grodstein F, van de Rest O. Association of long-term adherence to the mind diet with cognitive function and cognitive decline in American women. *J Nutr Health Aging*. 2018;22(2):222–9.
5531. Titova OE, Ax E, Brooks SJ, et al. Mediterranean diet habits in older individuals: associations with cognitive functioning and brain

volumes. *Exp Gerontol*. 2013;48(12):1443–8.
5532. Giem P, Beeson WL, Fraser GE. The incidence of dementia and intake of animal products: preliminary findings from the Adventist Health Study. *Neuroepidemiology*. 1993;12(1):28–36.
5533. Morris MC, Tangney CC. Dietary fat composition and dementia risk. *Neurobiol Aging*. 2014;35 Suppl 2:S59–64.
5534. Takechi R, Galloway S, Pallebage-Gamarallage MM, Lam V, Dhaliwal SS, Mamo JC. Probucol prevents blood–brain barrier dysfunction in wild-type mice induced by saturated fat or cholesterol feeding. *Clin Exp Pharmacol Physiol*. 2013;40(1):45–52.
5535. Ortolá R, Struijk EA, García-Esquinas E, Rodríguez-Artalejo F, Lopez-Garcia E. Changes in dietary intake of animal and vegetable protein and unhealthy aging. *Am J Med*. 2020;133(2):231–9.
5536. Szczechowiak K, Diniz BS, Leszek J. Diet and Alzheimer's dementia —nutritional approach to modulate inflammation. *Pharmacol Biochem Behav*. 2019;184:172743.
5537. Wu J, Song X, Chen GC, et al. Dietary pattern in midlife and cognitive impairment in late life: a prospective study in Chinese adults. *Am J Clin Nutr*. 2019;110(4):912–20.
5538. Kheirouri S, Alizadeh M. MIND diet and cognitive performance in older adults: a systematic review. *Crit Rev Food Sci Nutr*. Published online May 14, 2021:1–19.
5539. Pistollato F, Battino M. Role of plant-based diets in the prevention and regression of metabolic syndrome and neurodegenerative diseases. *Trends Food Sci Technol.* 2014;40(1):62–81.
5540. Sherchan P, Miles F, Orlich M, et al. Effects of lifestyle factors on cognitive resilience: commentary on "What this sunny, religious town in California teaches us about living longer." *Transl Stroke Res.* 2020;11:161–4.
5541. Sherzai D, Sherzai A. Preventing Alzheimer's: our most urgent health care priority. *Am J Lifestyle Med*. 2019;13(5):451–61.
5542. Plassman BL, Williams JW, Burke JR, Holsinger T, Benjamin S. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. *Ann Intern Med*. 2010;153(3):182–93.

5543. Daviglus ML, Plassman BL, Pirzada A, et al. Risk factors and preventive interventions for Alzheimer disease: state of the science. *Arch Neurol*. 2011;68(9):1185–90.
5544. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA.* 1998;279(15):1200–5.
5545. Friedland RP, Nandi S. A modest proposal for a longitudinal study of dementia prevention (with apologies to Jonathan Swift, 1729). *J Alzheimers Dis*. 2013;33(2):313–5.
5546. Friedland RP, Nandi S. A modest proposal for a longitudinal study of dementia prevention (with apologies to Jonathan Swift, 1729). *J Alzheimers Dis*. 2013;33(2):313–5.
5547. Preventive Medicine Research Institute. Lifestyle intervention for early Alzheimer's disease. Identifier: NCT04606420. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04606420. Published October 28, 2020. Accessed June 24, 2022.
5548. CITATION TK 000—Will be ready in September to insert. For now: Dean Ornish, Personal Communication.
5549. Faulkner JA, Larkin LM, Claflin DR, Brooks SV. Age-related changes in the structure and function of skeletal muscles. *Clin Exp Pharmacol Physiol*. 2007;34(11):1091–6.
5550. Garatachea N, Pareja-Galeano H, Sanchis-Gomar F, et al. Exercise attenuates the major hallmarks of aging. *Rejuvenation Res*. 2015;18(1):57–89.
5551. Fougère B, van Kan GA, Vellas B, Cesari M. Redox systems, antioxidants and sarcopenia. *Curr Protein Pept Sci*. 2018;19(7):643–8.
5552. Faulkner JA, Larkin LM, Claflin DR, Brooks SV. Age-related changes in the structure and function of skeletal muscles. *Clin Exp Pharmacol Physiol*. 2007;34(11):1091–6.
5553. Scott D, Blizzard L, Fell J, Jones G. The epidemiology of sarcopenia in community living older adults: what role does lifestyle play? *J Cachexia Sarcopenia Muscle*. 2011;2(3):125–34.
5554. Physical activity: PA-1 Reduce the proportion of adults who engage in no leisure-time physical activity. HealthyPeople.gov.

https://www.healthypeople.gov/2020/data-search/Search-the-Data?nid=5052. Accessed August 12, 2022.

5555. Faulkner JA, Larkin LM, Claflin DR, Brooks SV. Age-related changes in the structure and function of skeletal muscles. *Clin Exp Pharmacol Physiol*. 2007;34(11):1091–6.

5556. Fougère B, van Kan GA, Vellas B, Cesari M. Redox systems, antioxidants and sarcopenia. *Curr Protein Pept Sci*. 2018;19(7):643–8.

5557. Garatachea N, Pareja-Galeano H, Sanchis-Gomar F, et al. Exercise attenuates the major hallmarks of aging. *Rejuvenation Res*. 2015;18(1):57–89.

5558. Xia L, Zhao R, Wan Q, et al. Sarcopenia and adverse health-related outcomes: an umbrella review of meta-analyses of observational studies. *Cancer Med*. 2020;9(21):7964–78.

5559. Li R, Xia J, Zhang X, et al. Associations of muscle mass and strength with all-cause mortality among US older adults. *Med Sci Sports Exerc*. 2018;50(3):458–67.

5560. Newman AB, Kupelian V, Visser M, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *J Gerontol A Biol Sci Med Sci*. 2006;61(1):72–7.

5561. Talar K, Hernández-Belmonte A, Vetrovsky T, Steffl M, Kałamacka E, Courel-Ibáñez J. Benefits of resistance training in early and late stages of frailty and sarcopenia: a systematic review and meta-analysis of randomized controlled studies. *J Clin Med*. 2021;10(8):1630.

5562. Rantanen T, Guralnik JM, Foley D, et al. Midlife hand grip strength as a predictor of old age disability. *JAMA*. 1999;281(6):558–60.

5563. The Lancet. Bringing frailty into all realms of medicine. *Lancet*. 2019;394(10206):1298.

5564. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci.* 2001;56(3):M146–57.

5565. Pansarasa O, Pistono C, Davin A, et al. Altered immune system in frailty: genetics and diet may influence inflammation. *Ageing Res Rev*. 2019;54:100935.

5566. Garatachea N, Pareja-Galeano H, Sanchis-Gomar F, et al. Exercise attenuates the major hallmarks of aging. *Rejuvenation Res*. 2015;18(1):57–89.
5567. Rodríguez-Mañas L. Determinants of frailty and longevity: are they the same ones? *Nestle Nutr Inst Workshop Ser*. 2015;83:29–39.
5568. Scott D, Blizzard L, Fell J, Jones G. The epidemiology of sarcopenia in community living older adults: what role does lifestyle play? *J Cachexia Sarcopenia Muscle*. 2011;2(3):125–34.
5569. Frontera WR, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ, Roubenoff R. Aging of skeletal muscle: a 12-yr longitudinal study. *J Appl Physiol (1985)*. 2000;88(4):1321–6.
5570. Shimokata H, Ando F, Yuki A, Otsuka R. Age-related changes in skeletal muscle mass among community-dwelling Japanese: a 12-year longitudinal study. *Geriatr Gerontol Int*. 2014;14 Suppl 1:85–92.
5571. Moore SA, Hrisos N, Errington L, et al. Exercise as a treatment for sarcopenia: an umbrella review of systematic review evidence. *Physiotherapy*. 2020;107:189–201.
5572. Paproski JJ, Finello GC, Murillo A, Mandel E. The importance of protein intake and strength exercises for older adults. *JAAPA*. 2019;32(11):32–6.
5573. Moore SA, Hrisos N, Errington L, et al. Exercise as a treatment for sarcopenia: an umbrella review of systematic review evidence. *Physiotherapy*. 2020;107:189–201.
5574. Talar K, Hernández-Belmonte A, Vetrovsky T, Steffl M, Kałamacka E, Courel-Ibáñez J. Benefits of resistance training in early and late stages of frailty and sarcopenia: a systematic review and meta-analysis of randomized controlled studies. *J Clin Med*. 2021;10(8):1630.
5575. Leenders M, Verdijk LB, van der Hoeven L, van Kranenburg J, Nilwik R, van Loon LJC. Elderly men and women benefit equally from prolonged resistance-type exercise training. *J Gerontol A Biol Sci Med Sci*. 2013;68(7):769–79.
5576. Buatois S, Miljkovic D, Manckoundia P, et al. Five times sit to stand test is a predictor of recurrent falls in healthy community-living subjects aged 65 and older. *J Am Geriatr Soc*. 2008;56(8):1575–7.

5577. Kidd T, Mold F, Jones C, et al. What are the most effective interventions to improve physical performance in pre-frail and frail adults? A systematic review of randomised control trials. *BMC Geriatr*. 2019;19(1):184.
5578. Tarazona-Santabalbina FJ, Gómez-Cabrera MC, Pérez-Ros P, et al. A multicomponent exercise intervention that reverses frailty and improves cognition, emotion, and social networking in the community-dwelling frail elderly: a randomized clinical trial. *J Am Med Dir Assoc*. 2016;17(5):426–33.
5579. Paddon-Jones D, Leidy H. Dietary protein and muscle in older persons. *Curr Opin Clin Nutr Metab Care*. 2014;17(1):5–11.
5580. Paddon-Jones D, Sheffield-Moore M, Urban RJ, et al. Essential amino acid and carbohydrate supplementation ameliorates muscle protein loss in humans during 28 days bedrest. *J Clin Endocrinol Metab*. 2004;89(9):4351–8.
5581. Hvid LG, Suetta C, Nielsen JH, et al. Aging impairs the recovery in mechanical muscle function following 4 days of disuse. *Exp Gerontol*. 2014;52:1–8.
5582. Lafont C, Gérard S, Voisin T, et al. Reducing "iatrogenic disability" in the hospitalized frail elderly. *J Nutr Health Aging*. 2011;15(8):645–60.
5583. Breen L, Stokes KA, Churchward-Venne TA, et al. Two weeks of reduced activity decreases leg lean mass and induces "anabolic resistance" of myofibrillar protein synthesis in healthy elderly. *J Clin Endocrinol Metab*. 2013;98(6):2604–12.
5584. Breen L, Stokes KA, Churchward-Venne TA, et al. Two weeks of reduced activity decreases leg lean mass and induces "anabolic resistance" of myofibrillar protein synthesis in healthy elderly. *J Clin Endocrinol Metab*. 2013;98(6):2604–12.
5585. Berardi E, Madaro L, Lozanoska-Ochser B, et al. A pound of flesh: what cachexia is and what it is not. *Diagnostics (Basel)*. 2021;11(1):116.
5586. Bano G, Trevisan C, Carraro S, et al. Inflammation and sarcopenia: a systematic review and meta-analysis. *Maturitas*. 2017;96:10–5.
5587. Marcos-Pérez D, Sánchez-Flores M, Proietti S, et al. Association of inflammatory mediators with frailty status in older adults: results

from a systematic review and meta-analysis. *Geroscience*. 2020;42(6):1451–73.

5588. Tuttle CSL, Thang LAN, Maier AB. Markers of inflammation and their association with muscle strength and mass: a systematic review and meta-analysis. *Ageing Res Rev*. 2020;64:101185.

5589. Pansarasa O, Pistono C, Davin A, et al. Altered immune system in frailty: genetics and diet may influence inflammation. *Ageing Res Rev*. 2019;54:100935.

5590. Bagheri A, Soltani S, Hashemi R, Heshmat R, Motlagh AD, Esmaillzadeh A. Inflammatory potential of the diet and risk of sarcopenia and its components. *Nutr J*. 2020;19(1):129.

5591. Geng J, Deng L, Qiu S, et al. Dietary inflammatory potential and risk of sarcopenia: data from National Health and Nutrition Examination Surveys. *Aging (Albany NY)*. 2020;13(2):1913–28.

5592. Laclaustra M, Rodriguez-Artalejo F, Guallar-Castillon P, et al. The inflammatory potential of diet is related to incident frailty and slow walking in older adults. *Clin Nutr*. 2020;39(1):185–91.

5593. Kim D, Park Y. Association between the dietary inflammatory index and risk of frailty in older individuals with poor nutritional status. *Nutrients*. 2018;10(10):E1363.

5594. Laclaustra M, Rodriguez-Artalejo F, Guallar-Castillon P, et al. The inflammatory potential of diet is related to incident frailty and slow walking in older adults. *Clin Nutr*. 2020;39(1):185–91.

5595. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. 2014;17(8):1689–96.

5596. Montiel-Rojas D, Santoro A, Nilsson A, et al. Beneficial role of replacing dietary saturated fatty acids with polyunsaturated fatty acids in the prevention of sarcopenia: findings from the NU-AGE cohort. *Nutrients*. 2020;12(10):E3079.

5597. Stoody EE, Obbagy J, Pannucci TR, et al. Dietary Guidelines for Americans 2020–2025: make every bite count with the dietary guidelines. Dietary Guidelines for Americans. https://www.dietaryguidelines.gov/sites/default/files/2020–12/Dietary_Guidelines_for_Americans_2020–2025.pdf. Published December 2020. Accessed August 4, 2022.

5598. Saturated fat. American Heart Association. https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/fats/saturated-fats. Updated November 1, 2021. Accessed August 12, 2022.
5599. Welch AA, MacGregor AJ, Minihane AM, et al. Dietary fat and fatty acid profile are associated with indices of skeletal muscle mass in women aged 18–79 years. *J Nutr*. 2014;144(3):327–34.
5600. Kephart WC, Pledge CD, Roberson PA, et al. The three-month effects of a ketogenic diet on body composition, blood parameters, and performance metrics in CrossFit trainees: a pilot study. *Sports (Basel)*. 2018;6(1):1.
5601. Hall KD, Chen KY, Guo J, et al. Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men. *Am J Clin Nutr*. 2016;104(2):324–33.
5602. Carpenter KJ. The history of enthusiasm for protein. *J Nutr*. 1986;116(7):1364–70.
5603. McLaren DS. The great protein fiasco. *Lancet.* 1974;2(7872):93–6.
5604. Carpenter KJ. The history of enthusiasm for protein. *J Nutr*. 1986;116(7):1364–70.
5605. McLaren DS. The great protein fiasco revisited. *Nutrition*. 2000;16(6):464–5.
5606. Carpenter KJ. Protein requirements of adults from an evolutionary perspective. *Am J Clin Nutr*. 1992;55(5):913–7.
5607. Speth JD. The Paleoanthropology and Archaeology of Big-Game Hunting: Protein, Fat, or Politics? Springer; 2010.
5608. Davis TA, Nguyen HV, Garcia-Bravo R, et al. Amino acid composition of human milk is not unique. *J Nutr*. 1994;124(7):1126–32.
5609. Ziegler EE. Adverse effects of cow's milk in infants. *Nestle Nutr Workshop Ser Pediatr Program*. 2007;60:185–99.
5610. Pedersen AN, Cederholm T. Health effects of protein intake in healthy elderly populations: a systematic literature review. *Food Nutr Res*. 2014;58:10.3402/fnr.v58.23364.
5611. Berryman CE, Lieberman HR, Fulgoni VL, Pasiakos SM. Protein intake trends and conformity with the dietary reference intakes in the United States: analysis of the National Health and Nutrition

Examination Survey, 2001–2014. *Am J Clin Nutr*. 2018;108(2):405–13.
5612. Institute of Medicine of the National Academies. Dietary Reference Intakes for Energy, Carbohydrates, Fiber, Fat, Protein and Amino Acids (Macronutrients). The National Academies Press; 2002/2005.
5613. Delimaris I. Adverse effects associated with protein intake above the recommended dietary allowance for adults. *ISRN Nutr*. 2013;2013:126929.
5614. Volpi E, Campbell WW, Dwyer JT, et al. Is the optimal level of protein intake for older adults greater than the recommended dietary allowance? *J Gerontol A Biol Sci Med Sci*. 2013;68(6):677–81.
5615. Shad BJ, Thompson JL, Breen L. Does the muscle protein synthetic response to exercise and amino acid–based nutrition diminish with advancing age? A systematic review. *Am J Physiol Endocrinol Metab*. 2016;311(5):E803–17.
5616. Millward DJ. Protein requirements and aging. *Am J Clin Nutr*. 2014;100(4):1210–2.
5617. Millward DJ, Fereday A, Gibson N, Pacy PJ. Aging, protein requirements, and protein turnover. *Am J Clin Nutr*. 1997;66(4):774–86.
5618. Institute of Medicine of the National Academies. Dietary Reference Intakes for Energy, Carbohydrates, Fiber, Fat, Protein and Amino Acids (Macronutrients). The National Academies Press; 2002/2005.
5619. European Food Safety Authority Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific opinion on dietary reference values for protein: dietary reference values for protein. *EFSA J*. 2012;10:2557–623.
5620. Joint Expert Consultation on Protein and Amino Acid Requirements in Human Nutrition, Weltgesundheitsorganisation, FAO, United Nations University, eds. *Protein and Amino Acid Requirements in Human Nutrition: Report of a Joint WHO/FAO/UNU Expert Consultation [Geneva, 9–16 April 2002]*. WHO; 2007.
5621. Tieland M, Franssen R, Dullemeijer C, et al. The impact of dietary protein or amino acid supplementation on muscle mass and strength in elderly people: individual participant data and meta-analysis of RCT's. *J Nutr Health Aging*. 2017;21(9):994–1001.

5622. Reidy PT. Muscle or nothing! Where is the excess protein going in men with high protein intakes engaged in strength training? *J Nutr*. 2020;150(3):421–2.
5623. Fluharty FL, McClure KE. Effects of dietary energy intake and protein concentration on performance and visceral organ mass in lambs. *J Anim Sci*. 1997;75(3):604–10.
5624. Reidy PT. Muscle or nothing! Where is the excess protein going in men with high protein intakes engaged in strength training? *J Nutr*. 2020;150(3):421–2.
5625. Reidy PT, Rasmussen BB. Role of ingested amino acids and protein in the promotion of resistance exercise–induced muscle protein anabolism. *J Nutr*. 2016;146(2):155–83.
5626. Gielen E, Beckwée D, Delaere A, et al. Nutritional interventions to improve muscle mass, muscle strength, and physical performance in older people: an umbrella review of systematic reviews and meta-analyses. *Nutr Rev*. 2021;79(2):121–47.
5627. ten Haaf DSM, Nuijten MAH, Maessen MFH, Horstman AMH, Eijsvogels TMH, Hopman MTE. Effects of protein supplementation on lean body mass, muscle strength, and physical performance in nonfrail community-dwelling older adults: a systematic review and meta-analysis. *Am J Clin Nutr*. 2018;108(5):1043–59.
5628. Wouters OJ. Lobbying expenditures and campaign contributions by the pharmaceutical and health product industry in the United States, 1999–2018. *JAMA Intern Med*. 2020;180(5):688–97.
5629. de Moraes MB, Avgerinou C, Fukushima FB, Vidal EIO. Nutritional interventions for the management of frailty in older adults: systematic review and meta-analysis of randomized clinical trials. *Nutr Rev*. 2021;79(8):889–913.
5630. Tu DY, Kao FM, Tsai ST, Tung TH. Sarcopenia among the elderly population: a systematic review and meta-analysis of randomized controlled trials. *Healthcare (Basel)*. 2021;9(6):650.
5631. Roschel H, Hayashi AP, Fernandes AL, et al. Supplement-based nutritional strategies to tackle frailty: a multifactorial, double-blind, randomized placebo-controlled trial. *Clin Nutr*. 2021;40(8):4849–58.
5632. Granic A, Hurst C, Dismore L, et al. Milk for skeletal muscle health and sarcopenia in older adults: a narrative review. *Clin Interv Aging*.

2020;15:695–714.
5633. Huang LP, Condello G, Kuo CH. Effects of milk protein in resistance training–induced lean mass gains for older adults aged ≥ 60 y: a systematic review and meta-analysis. *Nutrients*. 2021;13(8):2815.
5634. Xu ZR, Tan ZJ, Zhang Q, Gui QF, Yang YM. The effectiveness of leucine on muscle protein synthesis, lean body mass and leg lean mass accretion in older people: a systematic review and meta-analysis. *Br J Nutr*. 2015;113(1):25–34.
5635. Witkamp RF, van Norren K. Let thy food be thy medicine.…when possible. *Eur J Pharmacol*. 2018;836:102–14.
5636. Groen BBL, Horstman AM, Hamer HM, et al. Post-prandial protein handling: you are what you just ate. *PLoS One*. 2015;10(11):e0141582.
5637. Figueiredo VC. Revisiting the roles of protein synthesis during skeletal muscle hypertrophy induced by exercise. *Am J Physiol Regul Integr Comp Physiol*. 2019;317(5):R709–18.
5638. Mitchell CJ, Churchward-Venne TA, Parise G, et al. Acute post-exercise myofibrillar protein synthesis is not correlated with resistance training–induced muscle hypertrophy in young men. *PLoS One*. 2014;9(2):e89431.
5639. Figueiredo VC. Revisiting the roles of protein synthesis during skeletal muscle hypertrophy induced by exercise. *Am J Physiol Regul Integr Comp Physiol*. 2019;317(5):R709–18.
5640. Murphy CH, Oikawa SY, Phillips SM. Dietary protein to maintain muscle mass in aging: a case for per-meal protein recommendations. *J Frailty Aging*. 2016;5(1):49–58.
5641. Bouillanne O, Neveux N, Nicolis I, Curis E, Cynober L, Aussel C. Long-lasting improved amino acid bioavailability associated with protein pulse feeding in hospitalized elderly patients: a randomized controlled trial. *Nutrition.* 2014;30(5):544–50.
5642. Arnal MA, Mosoni L, Boirie Y, et al. Protein feeding pattern does not affect protein retention in young women. *J Nutr.* 2000;130(7):1700–4.
5643. Arnal MA, Mosoni L, Boirie Y, et al. Protein pulse feeding improves protein retention in elderly women. *Am J Clin Nutr.* 1999;69(6):1202–8.

5644. Bouillanne O, Curis E, Hamon-Vilcot B, et al. Impact of protein pulse feeding on lean mass in malnourished and at-risk hospitalized elderly patients: a randomized controlled trial. *Clin Nutr.* 2013;32(2):186–92.
5645. Lim MT, Pan BJ, Toh DWK, Sutanto CN, Kim JE. Animal protein versus plant protein in supporting lean mass and muscle strength: a systematic review and meta-analysis of randomized controlled trials. *Nutrients*. 2021;13(2):661.
5646. Tang JE, Moore DR, Kujbida GW, Tarnopolsky MA, Phillips SM. Ingestion of whey hydrolysate, casein, or soy protein isolate: effects on mixed muscle protein synthesis at rest and following resistance exercise in young men. *J Appl Physiol (1985).* 2009;107(3):987–92.
5647. Haub MD, Wells AM, Tarnopolsky MA, Campbell WW. Effect of protein source on resistive-training-induced changes in body composition and muscle size in older men. *Am J Clin Nutr*. 2002;76(3):511–7.
5648. Haub MD, Wells AM, Campbell WW. Beef and soy-based food supplements differentially affect serum lipoprotein–lipid profiles because of changes in carbohydrate intake and novel nutrient intake ratios in older men who resistive-train. *Metabolism*. 2005;54(6):769–74.
5649. Wright CS, Zhou J, Sayer RD, Kim JE, Campbell WW. Effects of a high-protein diet including whole eggs on muscle composition and indices of cardiometabolic health and systemic inflammation in older adults with overweight or obesity: a randomized controlled trial. *Nutrients*. 2018;10(7):946.
5650. Iglay HB, Apolzan JW, Gerrard DE, Eash JK, Anderson JC, Campbell WW. Moderately increased protein intake predominately from egg sources does not influence whole body, regional, or muscle composition responses to resistance training in older people. *J Nutr Health Aging*. 2009;13(2):108–14.
5651. Bartholomae E, Incollingo A, Vizcaino M, Wharton C, Johnston CS. Mung bean protein supplement improves muscular strength in healthy, underactive vegetarian adults. *Nutrients*. 2019;11(10):E2423.
5652. Vasconcelos QDJS, Bachur TPR, Aragão GF. Whey protein supplementation and its potentially adverse effects on health: a systematic review. *Appl Physiol Nutr Metab*. 2021;46(1):27–33.

5653. Silverberg NB. Whey protein precipitating moderate to severe acne flares in 5 teenaged athletes. *Cutis*. 2012;90(2):70–2.
5654. Simonart T. Acne and whey protein supplementation among bodybuilders. *Dermatology*. 2012;225(3):256–8.
5655. Melnik BC, Zouboulis CC. Potential role of FoxO1 and mTORC1 in the pathogenesis of Western diet–induced acne. *Exp Dermatol*. 2013;22(5):311–5.
5656. Liu KA, Lashinger LM, Rasmussen AJ, Hursting SD. Leucine supplementation differentially enhances pancreatic cancer growth in lean and overweight mice. *Cancer Metab*. 2014;2(1):6.
5657. Cederroth CR, Vinciguerra M, Gjinovci A, et al. Dietary phytoestrogens activate AMP-activated protein kinase with improvement in lipid and glucose metabolism. *Diabetes*. 2008;57(5):1176–85.
5658. Aubertin-Leheudre M, Lord C, Khalil A, Dionne IJ. Six months of isoflavone supplement increases fat-free mass in obese-sarcopenic postmenopausal women: a randomized double-blind controlled trial. *Eur J Clin Nutr*. 2007;61(12):1442–4.
5659. Bhagwat S, Haytowitz DB, Holden JM. *USDA database for the isoflavone content of selected foods: release 2.0*. Agricultural Research Service, United States Department of Agriculture. https://www.ars.usda.gov/arsuserfiles/80400525/data/isoflav/isoflav_r2.pdf. Published September 2008. Accessed April 15, 2022.
5660. Chan H, Ribeiro RV, Haden S, Hirani V. Plant-based dietary patterns, body composition, muscle strength and function in middle and older age: a systematic review. *J Nutr Health Aging*. 2021;25(8):1012–22.
5661. Montiel-Rojas D, Nilsson A, Santoro A, et al. Fighting sarcopenia in ageing European adults: the importance of the amount and source of dietary proteins. *Nutrients*. 2020;12(12):3601.
5662. Hengeveld LM, Wijnhoven HAH, Olthof MR, et al. Prospective associations of diet quality with incident frailty in older adults: the health, aging, and body composition study. *J Am Geriatr Soc*. 2019;67(9):1835–42.
5663. Gazzani D, Zamboni F, Spelta F, et al. Vegetable but not animal protein intake is associated to a better physical performance: a study

on a general population sample of adults. *Food Nutr Res*. 2019;63:3422.
5664. Ortolá R, Struijk EA, García-Esquinas E, Rodríguez-Artalejo F, Lopez-Garcia E. Changes in dietary intake of animal and vegetable protein and unhealthy aging. *Am J Med*. 2020;133(2):231–9.e7.
5665. Foscolou A, Critselis E, Tyrovolas S, et al. The association of animal and plant protein with successful ageing: a combined analysis of MEDIS and ATTICA epidemiological studies. *Public Health Nutr*. 2021;24(8):2215–24.
5666. The nutrition source: protein. Harvard T.H. Chan School of Public Health. https://www.hsph.harvard.edu/nutritionsource/what-should-you-eat/protein/. Accessed August 3, 2022.
5667. Mariotti F, Gardner CD. Dietary protein and amino acids in vegetarian diets—a review. *Nutrients*. 2019;11(11):2661.
5668. Ramarao PB, Norton HW, Johnson BC. The amino acids composition and nutritive value of proteins. v. amino acid requirements as a pattern for protein evaluation. *J Nutr*. 1964;82:88–92.
5669. Mariotti F, Gardner CD. Dietary protein and amino acids in vegetarian diets—a review. *Nutrients*. 2019;11(11):2661.
5670. Osborne TB, Mendel LB. Amino-acids in nutrition and growth. 1914. *J Am Coll Nutr*. 1993;12(5):484–5.
5671. Davis TA, Nguyen HV, Garcia-Bravo R, et al. Amino acid composition of human milk is not unique. *J Nutr*. 1994;124(7):1126–32.
5672. Sengupta P. The laboratory rat: relating its age with human's. *Int J Prev Med*. 2013;4(6):624–30.
5673. Young VR, Pellett PL. Plant proteins in relation to human protein and amino acid nutrition. *Am J Clin Nutr*. 1994;59(5 Suppl):1203S-12S.
5674. Mariotti F, Gardner CD. Dietary protein and amino acids in vegetarian diets—a review. *Nutrients*. 2019;11(11):2661.
5675. Hevia-Larraín V, Gualano B, Longobardi I, et al. High-protein plant-based diet versus a protein-matched omnivorous diet to support resistance training adaptations: a comparison between habitual vegans and omnivores. *Sports Med*. 2021;51(6):1317–30.
5676. Damiano S, Muscariello E, La Rosa G, Di Maro M, Mondola P, Santillo M. Dual role of reactive oxygen species in muscle function:

can antioxidant dietary supplements counteract age-related sarcopenia? *Int J Mol Sci*. 2019;20(15):E3815.

5677. Muller FL, Song W, Liu Y, et al. Absence of CuZn superoxide dismutase leads to elevated oxidative stress and acceleration of age-dependent skeletal muscle atrophy. *Free Radic Biol Med*. 2006;40(11):1993–2004.

5678. Sahni S, Dufour AB, Fielding RA, et al. Total carotenoid intake is associated with reduced loss of grip strength and gait speed over time in adults: The Framingham Offspring Study. *Am J Clin Nutr*. 2021;113(2):437–45.

5679. Carr AC, Bozonet SM, Pullar JM, Simcock JW, Vissers MCM. Human skeletal muscle ascorbate is highly responsive to changes in vitamin C intake and plasma concentrations. *Am J Clin Nutr*. 2013;97(4):800–7.

5680. Carr AC, Bozonet SM, Pullar JM, Simcock JW, Vissers MCM. Human skeletal muscle ascorbate is highly responsive to changes in vitamin C intake and plasma concentrations. *Am J Clin Nutr*. 2013;97(4):800–7.

5681. Lewis LN, Hayhoe RPG, Mulligan AA, Luben RN, Khaw KT, Welch AA. Lower dietary and circulating vitamin C in middle- and older-aged men and women are associated with lower estimated skeletal muscle mass. *J Nutr*. 2020;150(10):2789–98.

5682. Welch AA, Jennings A, Kelaiditi E, Skinner J, Steves CJ. Cross-sectional associations between dietary antioxidant vitamins C, E and carotenoid intakes and sarcopenic indices in women aged 18–79 years. *Calcif Tissue Int*. 2020;106(4):331–42.

5683. Scott D, Blizzard L, Fell J, Giles G, Jones G. Associations between dietary nutrient intake and muscle mass and strength in community-dwelling older adults: the Tasmanian Older Adult Cohort Study. *J Am Geriatr Soc*. 2010;58(11):2129–34.

5684. Saito K, Yokoyama T, Yoshida H, et al. A significant relationship between plasma vitamin C concentration and physical performance among Japanese elderly women. *J Gerontol A Biol Sci Med Sci*. 2012;67(3):295–301.

5685. Takahashi F, Hashimoto Y, Kaji A, et al. Vitamin intake and loss of muscle mass in older people with type 2 diabetes: a prospective study

of the KAMOGAWA-DM cohort. *Nutrients*. 2021;13(7):2335.
5686. Saito K, Yokoyama T, Yoshida H, et al. A significant relationship between plasma vitamin C concentration and physical performance among Japanese elderly women. *J Gerontol A Biol Sci Med Sci.* 2012;67(3):295–301.
5687. Tak YJ, Lee JG, Yi YH, et al. Association of handgrip strength with dietary intake in the Korean population: findings based on the Seventh Korea National Health and Nutrition Examination Survey (KNHANES VII-1), 2016. *Nutrients*. 2018;10(9):1180.
5688. Gedmantaite A, Celis-Morales CA, Ho F, Pell JP, Ratkevicius A, Gray SR. Associations between diet and handgrip strength: a cross-sectional study from UK Biobank. *Mech Ageing Dev*. 2020;189:111269.
5689. Fingeret M, Vollenweider P, Marques-Vidal P. No association between vitamin C and E supplementation and grip strength over 5 years: the Colaus study. *Eur J Nutr*. 2019;58(2):609–17.
5690. Kenjale AA, Ham KL, Stabler T, et al. Dietary nitrate supplementation enhances exercise performance in peripheral arterial disease. *J Appl Physiol (1985)*. 2011;110(6):1582–91.
5691. Sobko T, Marcus C, Govoni M, Kamiya S. Dietary nitrate in Japanese traditional foods lowers diastolic blood pressure in healthy volunteers. *Nitric Oxide*. 2010;22(2):136–40.
5692. *What we eat in America, NHANES 2017–March 2020 prepandemic*. Agricultural Research Service, United States Department of Agriculture. https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/1720/Table_1_NIN_GEN_1720.pdf. Published 2022. Accessed January 13, 2023.
5693. Abete I, Konieczna J, Zulet MA, et al. Association of lifestyle factors and inflammation with sarcopenic obesity: data from the PREDIMED-Plus trial. *J Cachexia Sarcopenia Muscle*. 2019;10(5):974–84.
5694. Chaput JP, Lord C, Cloutier M, et al. Relationship between antioxidant intakes and class I sarcopenia in elderly men and women. *J Nutr Health Aging*. 2007;11(4):363–9.
5695. Verlaan S, Aspray TJ, Bauer JM, et al. Nutritional status, body composition, and quality of life in community-dwelling sarcopenic

and non-sarcopenic older adults: a case-control study. *Clin Nutr*. 2017;36(1):267–74.

5696. ter Borg S, de Groot LCPGM, Mijnarends DM, et al. Differences in nutrient intake and biochemical nutrient status between sarcopenic and nonsarcopenic older adults—results from the Maastricht Sarcopenia Study. J *Am Med Dir Assoc*. 2016;17(5):393–401.

5697. Clifford T, Jeffries O, Stevenson EJ, Davies KAB. The effects of vitamin C and E on exercise-induced physiological adaptations: a systematic review and meta-analysis of randomised controlled trials. *Crit Rev Food Sci Nutr*. 2020;60(21):3669–79.

5698. Jackson MA, Jeffery IB, Beaumont M, et al. Signatures of early frailty in the gut microbiota. *Genome Med*. 2016;8(1):8.

5699. Ticinesi A, Nouvenne A, Cerundolo N, et al. Gut microbiota, muscle mass and function in aging: a focus on physical frailty and sarcopenia. *Nutrients*. 2019;11(7):E1633.

5700. van Tongeren SP, Slaets JPJ, Harmsen HJM, Welling GW. Fecal microbiota composition and frailty. *Appl Environ Microbiol*. 2005;71(10):6438–42.

5701. Montiel-Rojas D, Nilsson A, Santoro A, et al. Dietary fibre may mitigate sarcopenia risk: findings from the NU-AGE cohort of older European adults. *Nutrients*. 2020;12(4):E1075.

5702. Berendsen AAM, van de Rest O, Feskens EJM, et al. Changes in dietary intake and adherence to the NU-AGE diet following a one-year dietary intervention among European older adults—results of the NU-AGE randomized trial. Nutrients. 2018;10(12):E1905.

5703. Buigues C, Fernández-Garrido J, Pruimboom L, et al. Effect of a prebiotic formulation on frailty syndrome: a randomized, double-blind clinical trial. *Int J Mol Sci*. 2016;17(6):E932.

5704. Lee MC, Tu YT, Lee CC, et al. *Lactobacillus plantarum* TWK10 improves muscle mass and functional performance in frail older adults: a randomized, double-blind clinical trial. *Microorganisms*. 2021;9(7):1466.

5705. Yang HL, Feng P, Xu Y, Hou YY, Ojo O, Wang XH. The role of dietary fiber supplementation in regulating uremic toxins in patients with chronic kidney disease: a meta-analysis of randomized controlled trials. *J Ren Nutr*. 2021;31(5):438–47.

5706. Strasser B, Wolters M, Weyh C, Krüger K, Ticinesi A. The effects of lifestyle and diet on gut microbiota composition, inflammation and muscle performance in our aging society. *Nutrients*. 2021;13(6):2045.
5707. Enoki Y, Watanabe H, Arake R, et al. Indoxyl sulfate potentiates skeletal muscle atrophy by inducing the oxidative stress–mediated expression of myostatin and atrogin-1. *Sci Rep*. 2016;6:32084.
5708. Dawson-Hughes B, Castaneda-Sceppa C, Harris SS, et al. Impact of supplementation with bicarbonate on lower-extremity muscle performance in older men and women. *Osteoporos Int*. 2010;21(7):1171–9.
5709. Guder WG, Häussinger D, Gerok W. Renal and hepatic nitrogen metabolism in systemic acid base regulation. *J Clin Chem Clin Biochem*. 1987;25(8):457–66.
5710. Hamm LL, Ambühl PM, Alpern RJ. Role of glucocorticoids in acidosis. *Am J Kidney Dis*. 1999;34(5):960–5.
5711. Dawson-Hughes B, Harris SS, Ceglia L. Alkaline diets favor lean tissue mass in older adults. *Am J Clin Nutr*. 2008;87(3):662–5.
5712. Buehlmeier J, Remer T, Frings-Meuthen P, Maser-Gluth C, Heer M. Glucocorticoid activity and metabolism with NaCl-induced low-grade metabolic acidosis and oral alkalization: results of two randomized controlled trials. *Endocrine*. 2016;52(1):139–47.
5713. Dawson-Hughes B, Castaneda-Sceppa C, Harris SS, et al. Impact of supplementation with bicarbonate on lower-extremity muscle performance in older men and women. *Osteoporos Int*. 2010;21(7):1171–9.
5714. Caciano SL, Inman CL, Gockel-Blessing EE, Weiss EP. Effects of dietary acid load on exercise metabolism and anaerobic exercise performance. *J Sports Sci Med*. 2015;14(2):364–71.
5715. Trinchieri A. Development of a rapid food screener to assess the potential renal acid load of diet in renal stone formers (LAKE score). *Arch Ital Urol Androl*. 2012;84(1):36–8.
5716. Cosgrove K, Johnston CS. Examining the impact of adherence to a vegan diet on acid-base balance in healthy adults. *Plant Foods Hum Nutr*. 2017;72(3):308–13.
5717. Buehlmeier J, Remer T, Frings-Meuthen P, Maser-Gluth C, Heer M. Glucocorticoid activity and metabolism with NaCl-induced low-

grade metabolic acidosis and oral alkalization: results of two randomized controlled trials. *Endocrine*. 2016;52(1):139–47.

5718. Yoshida Y, Kosaki K, Sugasawa T, et al. High salt diet impacts the risk of sarcopenia associated with reduction of skeletal muscle performance in the Japanese population. *Nutrients*. 2020;12(11):3474.

5719. Appel LJ, Anderson CAM. Compelling evidence for public health action to reduce salt intake. *N Engl J Med*. 2010;362(7):650–2.

5720. Qian Q. Dietary influence on body fluid acid-base and volume balance: the deleterious "norm" furthers and cloaks subclinical pathophysiology. *Nutrients*. 2018;10(6):E778.

5721. Milajerdi A, Hassanzadeh Keshteli A, Haghighatdoost F, Azadbakht L, Esmaillzadeh A, Adibi P. Dietary acid load in relation to depression and anxiety in adults. *J Hum Nutr Diet*. 2020;33(1):48–55.

5722. Xue X, Liu Z, Li X, et al. The efficacy and safety of citrate mixture vs sodium bicarbonate on urine alkalization in Chinese primary gout patients with benzbromarone: a prospective, randomized controlled study. *Rheumatology (Oxford)*. 2021;60(6):2661–71.

5723. Sebastian A, Frassetto LA, Sellmeyer DE, Merriam RL, Morris RC. Estimation of the net acid load of the diet of ancestral preagricultural Homo sapiens and their hominid ancestors. *Am J Clin Nutr*. 2002;76(6):1308–16.

5724. Logozzi M, Mizzoni D, Di Raimo R, et al. *In vivo* antiaging effects of alkaline water supplementation. *J Enzyme Inhib Med Chem*. 35(1):657–64.

5725. Magro M, Corain L, Ferro S, et al. Alkaline water and longevity: a murine study. *Evid Based Complement Alternat Med*. 2016;2016:3084126.

5726. Wesson DE. Is NaHCO3 an antiaging elixir? *Am J Physiol Renal Physiol*. 2016;311(1):F182–3.

5727. Kim J, Lee Y, Kye S, Chung YS, Kim KM. Association of vegetables and fruits consumption with sarcopenia in older adults: the Fourth Korea National Health and Nutrition Examination Survey. *Age Ageing*. 2015;44(1):96–102.

5728. Koyanagi A, Veronese N, Solmi M, et al. Fruit and vegetable consumption and sarcopenia among older adults in low- and middle-

income countries. *Nutrients*. 2020;12(3):E706.
5729. García-Esquinas E, Rahi B, Peres K, et al. Consumption of fruit and vegetables and risk of frailty: a dose-response analysis of 3 prospective cohorts of community-dwelling older adults. *Am J Clin Nutr*. 2016;104(1):132–42.
5730. Sim M, Blekkenhorst LC, Lewis JR, et al. Vegetable and fruit intake and injurious falls risk in older women: a prospective cohort study. *Br J Nutr*. 2018;120(8):925–34.
5731. Schrager MA, Hilton J, Gould R, Kelly VE. Effects of blueberry supplementation on measures of functional mobility in older adults. *Appl Physiol Nutr Metab*. 2015;40(6):543–9.
5732. Sangouni AA, Azar MRMH, Alizadeh M. Effects of garlic powder supplementation on insulin resistance, oxidative stress, and body composition in patients with non-alcoholic fatty liver disease: a randomized controlled clinical trial. *Complement Ther Med*. 2020;51:102428.
5733. Pérez-Piñero S, Ávila-Gandía V, Rubio Arias JA, Muñoz-Carrillo JC, Losada-Zafrilla P, López-Román FJ. A 12-week randomized double-blind placebo-controlled clinical trial, evaluating the effect of supplementation with a spinach extract on skeletal muscle fitness in adults older than 50 years of age. *Nutrients*. 2021;13(12):4373.
5734. Dirks-Naylor AJ. The benefits of coffee on skeletal muscle. *Life Sci*. 2015;143:182–6.
5735. Sanchez AMJ, Bernardi H, Py G, Candau RB. Autophagy is essential to support skeletal muscle plasticity in response to endurance exercise. *Am J Physiol Regul Integr Comp Physiol*. 2014;307(8):R956–69.
5736. Marzetti E, Calvani R, Cesari M, et al. Mitochondrial dysfunction and sarcopenia of aging: from signaling pathways to clinical trials. *Int J Biochem Cell Biol*. 2013;45(10):2288–301.
5737. Guo Y, Niu K, Okazaki T, et al. Coffee treatment prevents the progression of sarcopenia in aged mice in vivo and in vitro. *Exp Gerontol*. 2014;50:1–8.
5738. Jyväkorpi SK, Urtamo A, Kivimäki M, Strandberg TE. Associations of coffee drinking with physical performance in the oldest-old

community-dwelling men The Helsinki Businessmen Study (HBS). *Aging Clin Exp Res*. 2021;33(5):1371–5.
5739. Iwasaka C, Yamada Y, Nishida Y, et al. Association between habitual coffee consumption and skeletal muscle mass in middle-aged and older Japanese people. *Geriatr Gerontol Int*. 2021;21(10):950–8.
5740. Wang T, Wu Y, Wang W, Zhang D. Association between coffee consumption and functional disability in older US adults. *Br J Nutr*. 2021;125(6):695–702.
5741. Chung H, Moon JH, Kim JI, Kong MH, Huh JS, Kim HJ. Association of coffee consumption with sarcopenia in Korean elderly men: analysis using the Korea National Health and Nutrition Examination Survey, 2008–2011. *Korean J Fam Med*. 2017;38(3):141–7.
5742. Wang T, Wu Y, Wang W, Zhang D. Association between coffee consumption and functional disability in older US adults. *Br J Nutr*. 2021;125(6):695–702.
5743. Grgic J, Grgic I, Pickering C, Schoenfeld BJ, Bishop DJ, Pedisic Z. Wake up and smell the coffee: caffeine supplementation and exercise performance—an umbrella review of 21 published meta-analyses. *Br J Sports Med*. 2020;54(11):681–8.
5744. Rivers WHR, Webber HN. The action of caffeine on the capacity for muscular work. *J Physiol*. 1907;36(1):33–47.
5745. Grgic J, Grgic I, Pickering C, Schoenfeld BJ, Bishop DJ, Pedisic Z. Wake up and smell the coffee: caffeine supplementation and exercise performance—an umbrella review of 21 published meta-analyses. *Br J Sports Med*. 2020;54(11):681–8.
5746. Duncan MJ, Clarke ND, Tallis J, Guimarães-Ferreira L, Leddington-Wright S. The effect of caffeine ingestion on functional performance in older adults. *J Nutr Health Aging*. 2014;18(10):883–7.
5747. Norager CB, Jensen MB, Madsen MR, Laurberg S. Caffeine improves endurance in 75-yr-old citizens: a randomized, double-blind, placebo-controlled, crossover study. *J Appl Physiol (1985)*. 2005;99(6):2302–6.
5748. Bakuradze T, Parra GAM, Riedel A, et al. Four-week coffee consumption affects energy intake, satiety regulation, body fat, and protects DNA integrity. *Food Res Int*. 2014;63:420–7.

5749. Jang YJ, Son HJ, Kim JS, et al. Coffee consumption promotes skeletal muscle hypertrophy and myoblast differentiation. *Food Funct*. 2018;9(2):1102–11.
5750. McDermott MM, Criqui MH, Domanchuk K, et al. Cocoa to improve walking performance in older people with peripheral artery disease: the COCOA-PAD pilot randomized clinical trial. *Circ Res*. 2020;126(5):589–99.
5751. Munguia L, Rubio-Gayosso I, Ramirez-Sanchez I, et al. High flavonoid cocoa supplement ameliorates plasma oxidative stress and inflammation levels while improving mobility and quality of life in older subjects: a double-blind randomized clinical trial. *J Gerontol A Biol Sci Med Sci*. 2019;74(10):1620–7.
5752. Navrátil T, Kohlíková E, Petr M, Pelclová D, Heyrovský M, Přistoupilová K. Supplemented creatine induces changes in human metabolism of thiocompounds and one- and two-carbon units. *Physiol Res*. 2010;59(3):431–42.
5753. Sumien N, Shetty RA, Gonzales EB. Creatine, creatine kinase, and aging. In: Harris JR, Korolchuk VI, eds. *Biochemistry and Cell Biology of Ageing: Part I Biomedical Science. Vol 90*. Springer; 2018:145–68.
5754. Balestrino M, Adriano E. Beyond sports: efficacy and safety of creatine supplementation in pathological or paraphysiological conditions of brain and muscle. *Med Res Rev*. 2019;39(6):2427–59.
5755. Kraemer WJ, Beeler MK, Post EM, et al. Physiological basis for creatine supplementation in skeletal muscle and the central nervous system. In: Sen CK, Nair S, Bagchi D, eds. *Nutrition and Enhanced Sports Performance: Muscle Building, Endurance, and Strength. 2nd ed*. Academic Press; 2019:581–94.
5756. Blancquaert L, Baguet A, Bex T, et al. Changing to a vegetarian diet reduces the body creatine pool in omnivorous women, but appears not to affect carnitine and carnosine homeostasis: a randomised trial. *Br J Nutr*. 2018;119(7):759–70.
5757. Solis MY, Painelli V de S, Artioli GG, Roschel H, Otaduy MC, Gualano B. Brain creatine depletion in vegetarians? A cross-sectional ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS) study. *Br J Nutr*. 2014;111(7):1272–4.

5758. Blancquaert L, Baguet A, Bex T, et al. Changing to a vegetarian diet reduces the body creatine pool in omnivorous women, but appears not to affect carnitine and carnosine homeostasis: a randomised trial. *Br J Nutr*. 2018;119(7):759–70.
5759. Shomrat A, Weinstein Y, Katz A. Effect of creatine feeding on maximal exercise performance in vegetarians. *Eur J Appl Physiol*. 2000;82(4):321–5.
5760. Steenge GR, Verhoef P, Greenhaff PL. The effect of creatine and resistance training on plasma homocysteine concentration in healthy volunteers. *Arch Intern Med*. 2001;161(11):1455–6.
5761. Chilibeck PD, Kaviani M, Candow DG, Zello GA. Effect of creatine supplementation during resistance training on lean tissue mass and muscular strength in older adults: a meta-analysis. *Open Access J Sports Med*. 2017;8:213–26.
5762. Buford TW, Kreider RB, Stout JR, et al. International Society of Sports Nutrition position stand: creatine supplementation and exercise. *J Int Soc Sports Nutr*. 2007;4:6.
5763. Riesberg LA, Weed SA, McDonald TL, Eckerson JM, Drescher KM. Beyond muscles: the untapped potential of creatine. *Int Immunopharmacol*. 2016;37:31–42.
5764. Antonio J, Candow DG, Forbes SC, et al. Common questions and misconceptions about creatine supplementation: what does the scientific evidence really show? *J Int Soc Sports Nutr*. 2021;18(1):13.
5765. Dolan E, Artioli GG, Pereira RMR, Gualano B. Muscular atrophy and sarcopenia in the elderly: is there a role for creatine supplementation? *Biomolecules*. 2019;9(11):E642.
5766. Syrotuik DG, Bell GJ, Burnham R, Sim LL, Calvert RA, Maclean IM. Absolute and relative strength performance following creatine monohydrate supplementation combined with periodized resistance training: *J Strength Cond Res*. 2000;14(2):182–90.
5767. Beaudart C, Dawson A, Shaw SC, et al. Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. *Osteoporos Int*. 2017;28(6):1817–33.
5768. Antonio J, Candow DG, Forbes SC, et al. Common questions and misconceptions about creatine supplementation: what does the scientific evidence really show? *J Int Soc Sports Nutr*. 2021;18(1):13.

5769. Chilibeck PD, Kaviani M, Candow DG, Zello GA. Effect of creatine supplementation during resistance training on lean tissue mass and muscular strength in older adults: a meta-analysis. *Open Access J Sports Med*. 2017;8:213–26.
5770. Gualano B, Rawson ES, Candow DG, Chilibeck PD. Creatine supplementation in the aging population: effects on skeletal muscle, bone and brain. *Amino Acids*. 2016;48(8):1793–805.
5771. Beaudart C, Dawson A, Shaw SC, et al. Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. *Osteoporos Int*. 2017;28(6):1817–33.
5772. Candow DG, Chilibeck PD, Chad KE, Chrusch MJ, Davison KS, Burke DG. Effect of ceasing creatine supplementation while maintaining resistance training in older men. *J Aging Phys Act*. 2004;12(3):219–31.
5773. Beaudart C, Rabenda V, Simmons M, et al. Effects of protein, essential amino acids, β-hydroxy β-methylbutyrate, creatine, dehydroepiandrosterone and fatty acid supplementation on muscle mass, muscle strength and physical performance in older people aged 60 years and over. A systematic review on the literature. *J Nutr Health Aging*. 2018;22(1):117–30.
5774. Candow DG, Forbes SC, Chilibeck PD, Cornish SM, Antonio J, Kreider RB. Effectiveness of creatine supplementation on aging muscle and bone: focus on falls prevention and inflammation. *J Clin Med*. 2019;8(4):E488.
5775. MacRae PG, Lacourse M, Moldavon R. Physical performance measures that predict faller status in community-dwelling older adults. *J Orthop Sports Phys Ther*. 1992;16(3):123–8.
5776. Dolan E, Artioli GG, Pereira RMR, Gualano B. Muscular atrophy and sarcopenia in the elderly: is there a role for creatine supplementation? *Biomolecules*. 2019;9(11):E642.
5777. Morley JE, Argiles JM, Evans WJ, et al. Nutritional recommendations for the management of sarcopenia. *J Am Med Dir Assoc*. 2010;11(6):391–6.
5778. Wu G. Important roles of dietary taurine, creatine, carnosine, anserine and 4-hydroxyproline in human nutrition and health. *Amino Acids*. 2020;52(3):329–60.

5779. Hultman E, Söderlund K, Timmons JA, Cederblad G, Greenhaff PL. Muscle creatine loading in men. *J Appl Physiol (1985)*. 1996;81(1):232–7.
5780. Stares A, Bains M. The additive effects of creatine supplementation and exercise training in an aging population: a systematic review of randomized controlled trials. *J Geriatr Phys Ther*. 2020;43(2):99–112.
5781. Ribeiro F, Longobardi I, Perim P, et al. Timing of creatine supplementation around exercise: a real concern? *Nutrients*. 2021;13(8):2844.
5782. Bender A, Beckers J, Schneider I, et al. Creatine improves health and survival of mice. *Neurobiol Aging*. 2008;29(9):1404–11.
5783. Korzun WJ. Oral creatine supplements lower plasma homocysteine concentrations in humans. *Clin Lab Sci*. 2004;17(2):102–6.
5784. Moret S, Prevarin A, Tubaro F. Levels of creatine, organic contaminants and heavy metals in creatine dietary supplements. *Food Chem*. 2011;126(3):1232–8.
5785. Cooperman T. Muscle & workout supplements review (creatine and branched-chain amino acids). ConsumerLab.com. https://www.consumerlab.com/reviews/review-creatine-bcaas/creatine/. Published January 23, 2017. Updated June 30, 2022. Accessed August 3, 2022.
5786. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. *Mov Disord*. 2010;25(5):534–41.
5787. Louis ED. Essential tremor then and now: how views of the most common tremor diathesis have changed over time. *Parkinsonism Relat Disord*. 2018;46(Suppl 1):S70–4.
5788. Hopfner F, Helmich RC. The etiology of essential tremor: genes versus environment. *Parkinsonism Relat Disord*. 2018;46 Suppl 1:S92–6.
5789. Pfau W, Skog K. Exposure to β-carbolines norharman and harman. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2004;802(1):115–26.
5790. Gibis M, Weiss J. Inhibitory effect of marinades with hibiscus extract on formation of heterocyclic aromatic amines and sensory quality of fried beef patties. *Meat Sci*. 2010;85(4):735–42.

5791. Busquets R, Puignou L, Galceran MT, Skog K. Effect of red wine marinades on the formation of heterocyclic amines in fried chicken breast. *J Agric Food Chem*. 2006;54(21):8376–84.
5792. Smith JS, Ameri F, Gadgil P. Effect of marinades on the formation of heterocyclic amines in grilled beef steaks. *J Food Sci*. 2008;73(6):T100–5.
5793. Khan MR, Busquets R, Azam M. Blueberry, raspberry, and strawberry extracts reduce the formation of carcinogenic heterocyclic amines in fried camel, beef and chicken meats. *Food Control*. 2021;123:107852.
5794. Abdulrahman AA, Faisal K, Meshref AAA, Arshaduddin M. Low-dose acute vanillin is beneficial against harmaline-induced tremors in rats. *Neurol Res*. 2017;39(3):264–70.
5795. Srinivasan S, Glover J, Tampi RR, Tampi DJ, Sewell DD. Sexuality and the older adult. *Curr Psychiatry Rep*. 2019;21(10):97.
5796. Doll GM. Sexuality in nursing homes: practice and policy. *J Gerontol Nurs*. 2013;39(7):30–7.
5797. Mishra BN. Secret of eternal youth; teaching from the centenarian hot spots ("blue zones"). *Indian J Community Med*. 2009;34(4):273–5.
5798. Morton L. Sexuality in the older adult. *Prim Care*. 2017;44(3):429–38.
5799. Gewirtz-Meydan A, Hafford-Letchfield T, Ayalon L, et al. How do older people discuss their own sexuality? A systematic review of qualitative research studies. *Cult Health Sex*. 2019;21(3):293–308.
5800. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. *N Engl J Med*. 2007;357(8):762–74.
5801. Srinivasan S, Glover J, Tampi RR, Tampi DJ, Sewell DD. Sexuality and the older adult. *Curr Psychiatry Rep*. 2019;21(10):97.
5802. Cao C, Yang L, Xu T, et al. Trends in sexual activity and associations with all-cause and cause-specific mortality among US adults. *J Sex Med*. 2020;17(10):1903–13.
5803. Cao C, Yang L, Xu T, et al. Trends in sexual activity and associations with all-cause and cause-specific mortality among US adults. *J Sex Med*. 2020;17(10):1903–13.

5804. Kay N, Allen J, Morley JE. Endorphins stimulate normal human peripheral blood lymphocyte natural killer activity. *Life Sci*. 1984;35(1):53–9.
5805. Cao C, Yang L, Xu T, et al. Trends in sexual activity and associations with all-cause and cause-specific mortality among US adults. *J Sex Med*. 2020;17(10):1903–13.
5806. Casazza K, Fontaine KR, Astrup A, et al. Myths, presumptions, and facts about obesity. *N Engl J Med*. 2013;368(5):446–54.
5807. Bohlen JG, Held JP, Sanderson MO, Patterson RP. Heart rate, rate-pressure product, and oxygen uptake during four sexual activities. *Arch Intern Med*. 1984;144(9):1745–8.
5808. Allen MS, Walter EE. Health-related lifestyle factors and sexual dysfunction: a meta-analysis of population-based research. *J Sex Med*. 2018;15(4):458–75.
5809. Maiorino MI, Bellastella G, Caputo M, et al. Effects of Mediterranean diet on sexual function in people with newly diagnosed type 2 diabetes: the MÈDITA trial. *J Diabetes Complications*. 2016;30(8):1519–24.
5810. Maiorino MI, Bellastella G, Chiodini P, et al. Primary prevention of sexual dysfunction with Mediterranean diet in type 2 diabetes: the MÈDITA randomized trial. *Diabetes Care*. 2016;39(9):e143–4.
5811. Pazzaglia M. Body and odors: not just molecules, after all. *Curr Dir Psychol Sci*. 2015;24(4):329–33.
5812. Herz RS, Inzlicht M. Sex differences in response to physical and social factors involved in human mate selection: the importance of smell for women. *Evol Hum Behav*. 2002;23(5):359–64.
5813. Habel U, Regenbogen C, Kammann C, Stickel S, Chechko N. Male brain processing of the body odor of ovulating women compared to that of pregnant women. *Neuroimage*. 2021;229:117733.
5814. Nishihira J, Nishimura M, Tanaka A, Yamaguchi A, Taira T. Effects of 4-week continuous ingestion of champignon extract on halitosis and body and fecal odor. *J Tradit Complement Med*. 2015;7(1):110–6.
5815. Nazzaro-Porro M, Passi S, Boniforti L, Belsito F. Effects of aging on fatty acids in skin surface lipids. *J Invest Dermatol*. 1979;73(1):112–7.

5816. Nishihira J, Nishimura M, Tanaka A, Yamaguchi A, Taira T. Effects of 4-week continuous ingestion of champignon extract on halitosis and body and fecal odor. *J Tradit Complement Med*. 2015;7(1):110–6.
5817. Agricultural Research Service, United States Department of Agriculture. Mushrooms, white, raw. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html?query=mushrooms&utf8=%E2%9C%93&affiliate=usda&commit=Search#/food-details/169251/nutrients. Published April 1, 2019. Accessed August 24, 2022.
5818. Kephart JC. Chlorophyll derivatives—their chemistry, commercial preparation and uses. *Econ Bot*. 1955;9(1):3–38.
5819. Bohn T, Walczyk T, Leisibach S, Hurrell RF. Chlorophyll-bound magnesium in commonly consumed vegetables and fruits: relevance to magnesium nutrition. *J Food Sci*. 2006;69(9):S347–50.
5820. Olsson MJ, Lundström JN, Kimball BA, et al. The scent of disease: human body odor contains an early chemosensory cue of sickness. *Psychol Sci*. 2014;25(3):817–23.
5821. Olsson MJ, Lundström JN, Kimball BA, et al. The scent of disease: human body odor contains an early chemosensory cue of sickness. *Psychol Sci*. 2014;25(3):817–23.
5822. Havlicek J, Lenochova P. The effect of meat consumption on body odor attractiveness. *Chem Senses*. 2006;31(8):747–52.
5823. Havlicek J, Lenochova P. The effect of meat consumption on body odor attractiveness. *Chem Senses*. 2006;31(8):747–52.
5824. Erridge C. The capacity of foodstuffs to induce innate immune activation of human monocytes *in vitro* is dependent on food content of stimulants of Toll-like receptors 2 and 4. *Br J Nutr*. 2011;105(1):15–23.
5825. Havlicek J, Lenochova P. The effect of meat consumption on body odor attractiveness. *Chem Senses*. 2006;31(8):747–52.
5826. Scavello I, Maseroli E, Di Stasi V, Vignozzi L. Sexual health in menopause. *Medicina (Kaunas)*. 2019;55(9):559.
5827. Tiefer L. Female sexual dysfunction: a case study of disease mongering and activist resistance. *PLoS Med*. 2006;3(4):e178.
5828. Angel K. The history of “Female Sexual Dysfunction” as a mental disorder in the 20th century. *Curr Opin Psychiatry*. 2010;23(6):536–

41.
5829. Meixel A, Yanchar E, Fugh-Berman A. Hypoactive sexual desire disorder: inventing a disease to sell low libido. *J Med Ethics.* 2015;41(10):859–62.
5830. Jaspers L, Feys F, Bramer WM, Franco OH, Leusink P, Laan ETM. Efficacy and safety of flibanserin for the treatment of hypoactive sexual desire disorder in women: a systematic review and meta-analysis. *JAMA Intern Med.* 2016;176(4):453–62.
5831. Woloshin S, Schwartz LM. US Food and Drug Administration approval of flibanserin: even the score does not add up. *JAMA Intern Med*. 2016;176(4):439–42.
5832. Fugh-Berman A. Advise against flibanserin. *Am J Nurs*. 2016;116(3):13.
5833. Moyad MA, Park K. What do most erectile dysfunction guidelines have in common? No evidence-based discussion or recommendation of heart-healthy lifestyle changes and/or *Panax ginseng*. *Asian J Androl*. 2012;14(6):830–41.
5834. Maravilla KR, Heiman JR, Garland PA, et al. Dynamic MR imaging of the sexual arousal response in women. *J Sex Marital Ther*. 2003;29 Suppl 1:71–6.
5835. Steinke EE. Sexual dysfunction in women with cardiovascular disease: what do we know? *J Cardiovasc Nurs*. 2010;25(2):151–8.
5836. Towe M, La J, El-Khatib F, Roberts N, Yafi FA, Rubin R. Diet and female sexual health. *Sex Med Rev*. 2020;8(2):256–64.
5837. Park K, Goldstein I, Andry C, Siroky MB, Krane RJ, Azadzoi KM. Vasculogenic female sexual dysfunction: the hemodynamic basis for vaginal engorgement insufficiency and clitoral erectile insufficiency. *Int J Impot Res*. 1997;9(1):27–37.
5838. Fishbeck DW, Sebastiani AM. *Comparative Anatomy: Manual of Vertebrate Dissection*. 3rd ed. Morton Publishing; 2015.
5839. Esposito K, Ciotola M, Maiorino MI, et al. Hyperlipidemia and sexual function in premenopausal women. *J Sex Med.* 2009;6(6):1696–703.
5840. Duncan LE, Lewis C, Jenkins P, Pearson TA. Does hypertension and its pharmacotherapy affect the quality of sexual function in women? *Am J Hypertens*. 2000;13(6 Pt 1):640–7.

5841. Baldassarre M, Alvisi S, Mancini I, et al. Impaired lipid profile is a risk factor for the development of sexual dysfunction in women. *J Sex Med*. 2016;13(1):46–54.
5842. Esposito K, Ciotola M, Giugliano F, et al. Mediterranean diet improves sexual function in women with the metabolic syndrome. *Int J Impot Res*. 2007;19(5):486–91.
5843. Levin RJ. The ins and outs of vaginal lubrication. *Sex Relation Ther*. 2003;18(4):509–13.
5844. Fisher NDL, Hughes M, Gerhard-Herman M, Hollenberg NK. Flavanol-rich cocoa induces nitric-oxide-dependent vasodilation in healthy humans. *J Hypertens*. 2003;21(12):2281–6.
5845. Salonia A, Fabbri F, Zanni G, et al. Chocolate and women's sexual health: an intriguing correlation. *J Sex Med*. 2006;3(3):476–82.
5846. Allouh MZ, Daradka HM, Al Barbarawi MM, Mustafa AG. Fresh onion juice enhanced copulatory behavior in male rats with and without paroxetine-induced sexual dysfunction. *Exp Biol Med (Maywood)*. 2014;239(2):177–82.
5847. Cai T, Gacci M, Mattivi F, et al. Apple consumption is related to better sexual quality of life in young women. *Arch Gynecol Obstet*. 2014;290(1):93–8.
5848. Esposito K, Ciotola M, Giugliano F, et al. Mediterranean diet improves sexual function in women with the metabolic syndrome. *Int J Impot Res*. 2007;19(5):486–91.
5849. Esposito K, Ciotola M, Giugliano F, et al. Mediterranean diet improves erectile function in subjects with the metabolic syndrome. *Int J Impot Res*. 2006;18(4):405–10.
5850. Wang F, Dai S, Wang M, Morrison H. Erectile dysfunction and fruit/vegetable consumption among diabetic Canadian men. *Urology*. 2013;82(6):1330–5.
5851. Maiorino MI, Bellastella G, Giugliano D, Esposito K. From inflammation to sexual dysfunctions: a journey through diabetes, obesity, and metabolic syndrome. *J Endocrinol Invest*. 2018;41(11):1249–58.
5852. Wadden TA, West DS, Delahanty LM, et al. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. *Obesity (Silver Spring)*. 2006;14(5):737–52.

5853. Belalcazar LM, Haffner SM, Lang W, et al. Lifestyle intervention and/or statins for the reduction of C-reactive protein in type 2 diabetes: from the Look AHEAD study. *Obesity (Silver Spring)*. 2013;21(5):944–50.
5854. Wing RR, Bond DS, Gendrano IN, et al. Effect of intensive lifestyle intervention on sexual dysfunction in women with type 2 diabetes: results from an ancillary Look AHEAD study. *Diabetes Care*. 2013;36(10):2937–44.
5855. Esposito K, Nappo F, Giugliano F, et al. Meal modulation of circulating interleukin 18 and adiponectin concentrations in healthy subjects and in patients with type 2 diabetes mellitus. *Am J Clin Nutr*. 2003;78(6):1135–40.
5856. Blankenberg S, Tiret L, Bickel C, et al. Interleukin-18 is a strong predictor of cardiovascular death in stable and unstable angina. *Circulation*. 2002;106(1):24–30.
5857. Levin RJ. The pharmacology of the human female orgasm—its biological and physiological backgrounds. *Pharmacol Biochem Behav*. 2014;121:62–70.
5858. Heath RG. Pleasure and brain activity in man. Deep and surface electroencephalograms during orgasm. *J Nerv Ment Dis*. 1972;154(1):3–18.
5859. Serrano SE, Braun J, Trasande L, Dills R, Sathyanarayana S. Phthalates and diet: a review of the food monitoring and epidemiology data. *Environ Health*. 2014;13(1):43.
5860. Main KM, Mortensen GK, Kaleva MM, et al. Human breast milk contamination with phthalates and alterations of endogenous reproductive hormones in infants three months of age. *Environ Health Perspect*. 2006;114(2):270–6.
5861. Swan SH, Liu F, Hines M, et al. Prenatal phthalate exposure and reduced masculine play in boys. *Int J Androl*. 2010;33(2):259–69.
5862. Watkins DJ, Téllez-Rojo MM, Ferguson KK, et al. In utero and peripubertal exposure to phthalates and BPA in relation to female sexual maturation. *Environ Res*. 2014;134:233–41.
5863. Chen FP, Chien MH. Lower concentrations of phthalates induce proliferation in human breast cancer cells. *Climacteric*. 2014;17(4):377–84.

5864. Desdoits-Lethimonier C, Albert O, Le Bizec B, et al. Human testis steroidogenesis is inhibited by phthalates. *Hum Reprod*. 2012;27(5):1451–9.
5865. Barrett ES, Parlett LE, Wang C, Drobnis EZ, Redmon JB, Swan SH. Environmental exposure to di-2-ethylhexyl phthalate is associated with low interest in sexual activity in premenopausal women. *Horm Behav*. 2014;66(5):787–92.
5866. Koch HM, Lorber M, Christensen KLY, Pälmke C, Koslitz S, Brüning T. Identifying sources of phthalate exposure with human biomonitoring: results of a 48h fasting study with urine collection and personal activity patterns. *Int J Hyg Environ Health*. 2013;216(6):672–81.
5867. Ji K, Lim Kho Y, Park Y, Choi K. Influence of a five-day vegetarian diet on urinary levels of antibiotics and phthalate metabolites: a pilot study with "Temple Stay" participants. *Environ Res*. 2010;110(4):375–82.
5868. Serrano SE, Braun J, Trasande L, Dills R, Sathyanarayana S. Phthalates and diet: a review of the food monitoring and epidemiology data. *Environ Health*. 2014;13(1):43.
5869. Schecter A, Lorber M, Guo Y, et al. Phthalate concentrations and dietary exposure from food purchased in New York State. *Environ Health Perspect*. 2013;121(4):473–9.
5870. Serrano SE, Braun J, Trasande L, Dills R, Sathyanarayana S. Phthalates and diet: a review of the food monitoring and epidemiology data. *Environ Health*. 2014;13(1):43.
5871. Koch HM, Lorber M, Christensen KLY, Pälmke C, Koslitz S, Brüning T. Identifying sources of phthalate exposure with human biomonitoring: results of a 48h fasting study with urine collection and personal activity patterns. *Int J Hyg Environ Health*. 2013;216(6):672–81.
5872. Braun JM, Sathyanarayana S, Hauser R. Phthalate exposure and children's health. *Curr Opin Pediatr*. 2013;25(2):247–54.
5873. CPSC prohibits certain phthalates in children's toys and child care products. United States Consumer Product Safety Commission. https://www.cpsc.gov/content/cpsc-prohibits-certain-phthalates-in-

children%E2%80%99s-toys-and-child-care-products. Published October 20, 2017. Accessed August 24, 2022.
5874. Nilsson NH, Malmgren-Hansen B, Bernth N, Pedersen E, Pommer K. Survey and health assesment of chemicals substances in sex toys. Survey of Chemical Substances in Consumer Products. https://www2.mst.dk/udgiv/publications/2006/87–7052–227–8/pdf/87–7052–228–6.pdf. Published September 8, 2006. Accessed August 24, 2022.
5875. Rao A, Steels E, Beccaria G, Inder WJ, Vitetta L. Influence of a specialized *Trigonella foenum-graecum* seed extract (libifem), on testosterone, estradiol and sexual function in healthy menstruating women, a randomised placebo controlled study. *Phytother Res*. 2015;29(8):1123–30.
5876. Laughlin GA, Barrett-Connor E, Kritz-Silverstein D, von Mühlen D. Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: the Rancho Bernardo Study. *J Clin Endocrinol Metab*. 2000;85(2):645–51.
5877. Simon JA, Kapner MD. The saga of testosterone for menopausal women at the Food and Drug Administration (FDA). *J Sex Med*. 2020;17(4):826–9.
5878. Randolph JF, Zheng H, Avis NE, Greendale GA, Harlow SD. Masturbation frequency and sexual function domains are associated with serum reproductive hormone levels across the menopausal transition. *J Clin Endocrinol Metab*. 2015;100(1):258–66.
5879. Smith T, Batur P. Prescribing testosterone and DHEA: the role of androgens in women. *Cleve Clin J Med*. 2021;88(1):35–43.
5880. Davis SR, Baber R, Panay N, et al. Global consensus position statement on the use of testosterone therapy for women. *Climacteric*. 2019;22(5):429–34.
5881. Pinkerton JV, Blackman I, Conner EA, Kaunitz AM. Risks of testosterone for postmenopausal women. *Endocrinol Metab Clin North Am*. 2021;50(1):139–50.
5882. Davis SR, Baber R, Panay N, et al. Global consensus position statement on the use of testosterone therapy for women. *Climacteric*. 2019;22(5):429–34.

5883. Fukui H, Yamashita M. The effects of music and visual stress on testosterone and cortisol in men and women. *Neuro Endocrinol Lett*. 2003;24(3–4):173–80.
5884. Akdoğan M, Tamer MN, Cüre E, Cüre MC, Köroğlu BK, Delibaş N. Effect of spearmint (Mentha spicata Labiatae) teas on androgen levels in women with hirsutism. Phytother Res. 2007;21(5):444-7.
5885. Nikjou R, Kazemzadeh R, Asadzadeh F, Fathi R, Mostafazadeh F. The effect of lavender aromatherapy on the symptoms of menopause. *J Natl Med Assoc*. 2018;110(3):265–9.
5886. Choi SY, Kang P, Lee HS, Seol GH. Effects of inhalation of essential oil of *Citrus aurantium* L. var. *amara* on menopausal symptoms, stress, and estrogen in postmenopausal women: a randomized controlled trial. *Evid Based Complement Alternat Med*. 2014;2014:796518.
5887. Ghorbani Z, Mirghafourvand M. A meta-analysis of the efficacy of panax ginseng on menopausal women's sexual function. *Int J Womens Health Reprod Sci*. 2018;7(1):124–33.
5888. Brooks NA, Wilcox G, Walker KZ, Ashton JF, Cox MB, Stojanovska L. Beneficial effects of *Lepidium meyenii* (Maca) on psychological symptoms and measures of sexual dysfunction in postmenopausal women are not related to estrogen or androgen content. *Menopause*. 2008;15(6):1157–62.
5889. Paul S, Chakraborty S, Anand U, et al. *Withania somnifera* (L.) Dunal (Ashwagandha): a comprehensive review on ethnopharmacology, pharmacotherapeutics, biomedicinal and toxicological aspects. *Biomed Pharmacother*. 2021;143:112175.
5890. Mandlik (Ingawale) DS, Namdeo AG. Pharmacological evaluation of Ashwagandha highlighting its healthcare claims, safety, and toxicity aspects. *J Diet Suppl*. 2021;18(2):183–226.
5891. Dongre S, Langade D, Bhattacharyya S. Efficacy and safety of ashwagandha (*Withania somnifera*) root extract in improving sexual function in women: a pilot study. *Biomed Res Int*. 2015;2015:284154.
5892. Ashwagandha. In: *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury.* National Institute of Diabetes and Digestive and Kidney Diseases; 2012.

5893. Simon JA, Lukas VA. Distressing sexual function at midlife: unmet needs, practical diagnoses, and available treatments. *Obstet Gynecol*. 2017;130(4):889–905.
5894. Portman DJ, Gass MLS, Kingsburg S, et al. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. *Menopause.* 2014;21(10):1063–8.
5895. Scavello I, Maseroli E, Di Stasi V, Vignozzi L. Sexual health in menopause. *Medicina (Kaunas)*. 2019;55(9):559.
5896. Minkin MJ. Menopause: hormones, lifestyle, and optimizing aging. *Obstet Gynecol Clin North Am*. 2019;46(3):501–14.
5897. Faubion SS, Sood R, Kapoor E. Genitourinary syndrome of menopause: management strategies for the clinician. *Mayo Clin Proc*. 2017;92(12):1842–9.
5898. Scavello I, Maseroli E, Di Stasi V, Vignozzi L. Sexual health in menopause. *Medicina (Kaunas)*. 2019;55(9):559.
5899. Faubion SS, Sood R, Kapoor E. Genitourinary syndrome of menopause: management strategies for the clinician. *Mayo Clin Proc*. 2017;92(12):1842–9.
5900. Herbenick D, Reece M, Hensel D, Sanders S, Jozkowski K, Fortenberry JD. Association of lubricant use with women's sexual pleasure, sexual satisfaction, and genital symptoms: a prospective daily diary study. *J Sex Med*. 2011;8(1):202–12.
5901. Mitchell CM, Reed SD, Diem S, et al. Efficacy of vaginal estradiol or vaginal moisturizer vs placebo for treating postmenopausal vulvovaginal symptoms: a randomized clinical trial. *JAMA Intern Med*. 2018;178(5):681–90.
5902. Huang AJ, Grady D. Rethinking the approach to managing postmenopausal vulvovaginal symptoms. *JAMA Intern Med*. 2018;178(5):690–1.
5903. Edwards D, Panay N. Treating vulvovaginal atrophy/genitourinary syndrome of menopause: how important is vaginal lubricant and moisturizer composition? *Climacteric*. 2016;19(2):151–61.
5904. Adriaens E, Remon JP. Mucosal irritation potential of personal lubricants relates to product osmolality as detected by the slug

mucosal irritation assay. *Sex Transm Dis*. 2008;35(5):512–6.
5905. Edwards D, Panay N. Treating vulvovaginal atrophy/genitourinary syndrome of menopause: how important is vaginal lubricant and moisturizer composition? *Climacteric*. 2016;19(2):151–61.
5906. Edwards D, Panay N. Treating vulvovaginal atrophy/genitourinary syndrome of menopause: how important is vaginal lubricant and moisturizer composition? *Climacteric*. 2016;19(2):151–61.
5907. Scavello I, Maseroli E, Di Stasi V, Vignozzi L. Sexual health in menopause. *Medicina (Kaunas)*. 2019;55(9):559.
5908. Faubion SS, Sood R, Kapoor E. Genitourinary syndrome of menopause: management strategies for the clinician. *Mayo Clin Proc*. 2017;92(12):1842–9.
5909. Cardozo L, Bachmann G, McClish D, Fonda D, Birgerson L. Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: second report of the Hormones and Urogenital Therapy Committee. *Obstet Gynecol*. 1998;92(4 Pt 2):722–7.
5910. Faubion SS, Sood R, Kapoor E. Genitourinary syndrome of menopause: management strategies for the clinician. *Mayo Clin Proc*. 2017;92(12):1842–9.
5911. Lethaby A, Ayeleke RO, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev*. 2016;(8):CD001500.
5912. Šimunić V, Banović I, Ciglar S, Jeren L, Pavičić Baldani D, Šprem M. Local estrogen treatment in patients with urogenital symptoms. *Int J Gynaecol Obstet*. 2003;82(2):187–97.
5913. Mitchell CM, Reed SD, Diem S, et al. Efficacy of vaginal estradiol or vaginal moisturizer vs placebo for treating postmenopausal vulvovaginal symptoms: a randomized clinical trial. *JAMA Intern Med*. 2018;178(5):681–90.
5914. Pinkerton JV. Hormone therapy for postmenopausal women. *N Engl J Med*. 2020;382(5):446–5.
5915. Premarin® Vaginal Cream Boxed Warning (conjugated estrogens). Pfizer. https://www.pfizermedicalinformation.com/en-us/premarin-vaginal-cream/boxed-warning. Updated September 2018. Accessed August 24, 2022.

5916. Pinkerton JV, Kaunitz AM, Manson JE. Vaginal estrogen in the treatment of genitourinary syndrome of menopause and risk of endometrial cancer: an assessment of recent studies provides reassurance. *Menopause*. 2017;24(12):1329–32.
5917. Bhupathiraju SN, Grodstein F, Stampfer MJ, et al. Vaginal estrogen use and chronic disease risk in the Nurses' Health Study. *Menopause*. 2018;26(6):603–10.
5918. Crandall CJ, Diamant A, Santoro N. Safety of vaginal estrogens: a systematic review. *Menopause*. 2020;27(3):339–60.
5919. Kelsey JL, LiVolsi VA, Holford TR, et al. A case-control study of cancer of the endometrium. *Am J Epidemiol*. 1982;116(2):333–42.
5920. Mørch LS, Kjaer SK, Keiding N, Løkkegaard E, Lidegaard Ø. The influence of hormone therapies on type I and II endometrial cancer: a nationwide cohort study. *Int J Cancer*. 2016;138(6):1506–15.
5921. Pinkerton JV, Kaunitz AM, Manson JE. Vaginal estrogen in the treatment of genitourinary syndrome of menopause and risk of endometrial cancer: an assessment of recent studies provides reassurance. *Menopause*. 2017;24(12):1329–32.
5922. Scavello I, Maseroli E, Di Stasi V, Vignozzi L. Sexual health in menopause. *Medicina (Kaunas)*. 2019;55(9):559.
5923. Eden JA. DHEA replacement for postmenopausal women: placebo or panacea? *Climacteric*. 2015;18(4):439–40.
5924. Elraiyah T, Sonbol MB, Wang Z, et al. Clinical review: the benefits and harms of systemic dehydroepiandrosterone (DHEA) in postmenopausal women with normal adrenal function: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2014;99(10):3536–42.
5925. U.S. Food and Drug Administration. FDA approves Intrarosa for postmenopausal women experiencing pain during sex. FDA.gov. https://www.fda.gov/news-events/press-announcements/fda-approves-intrarosa-postmenopausal-women-experiencing-pain-during-sex. Published November 17, 2016. Accessed Sept 26, 2022.
5926. Labrie F, Martel C, Bérubé R, et al. Intravaginal prasterone (DHEA) provides local action without clinically significant changes in serum concentrations of estrogens or androgens. *J Steroid Biochem Mol Biol*. 2013;138:359–67.

5927. Faubion SS, Sood R, Kapoor E. Genitourinary syndrome of menopause: management strategies for the clinician. *Mayo Clin Proc*. 2017;92(12):1842–9.
5928. Di Donato V, Schiavi MC, Iacobelli V, et al. Ospemifene for the treatment of vulvar and vaginal atrophy: a meta-analysis of randomized trials. Part II: evaluation of tolerability and safety. *Maturitas*. 2019;121:93–100.
5929. Gold EB. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40–55 years of age. *Am Journal Epidemiol*. 2000;152(5):463–73.
5930. Ghazanfarpour M, Roudsari RL, Treglia G, Sadeghi R. Topical administration of isoflavones for treatment of vaginal symptoms in postmenopausal women: a systematic review of randomised controlled trials. *J Obstet Gynaecol*. 2015;35(8):783–7.
5931. Lima SMRR, Bernardo BFA, Yamada SS, Reis BF, da Silva GMD, Galvão MAL. Effects of *Glycine max* (*L.) Merr*. soy isoflavone vaginal gel on epithelium morphology and estrogen receptor expression in postmenopausal women: a 12-week, randomized, double-blind, placebo-controlled trial. *Maturitas*. 2014;78(3):205–11.
5932. Lima SMRR, Yamada SS, Reis BF, Postigo S, Galvão da Silva MAL, Aoki T. Effective treatment of vaginal atrophy with isoflavone vaginal gel. *Maturitas*. 2013;74(3):252–8.
5933. Zhang J, Zhu Y, Pan L, Xia H, Ma J, Zhang A. Soy isoflavone improved female sexual dysfunction of mice via endothelial nitric oxide synthase pathway. *Sex Med*. 2019;7(3):345–51.
5934. Nikander E, Rutanen EM, Nieminen P, Wahlström T, Ylikorkala O, Tiitinen A. Lack of effect of isoflavonoids on the vagina and endometrium in postmenopausal women. *Fertil Steril*. 2005;83(1):137–42.
5935. Nourozi M, Haghollahi F, Ramezanzadeh F, Hanachi P. Effect of soy milk consumption on quality of life in Iranian postmenopausal women. *J Family Reprod Health*. 2015;9(2):93–100.
5936. Hanachi P, Golkho S. The effect of soymilk on menopausal symptoms and total antioxidant levels in menopausal women. *Malaysian J Med Health Sci*. 2008;4(1):33–40.

5937. Padmaqriya S, Kumar SS. Quality of life of postmenopausal women receiving plant-based phytoestrogens. *Int J Pharm Sci Res*. 2020;11(10):4998–5003.
5938. Amsterdam A, Abu-Rustum N, Carter J, Krychman M. Persistent sexual arousal syndrome associated with increased soy intake. *J Sex Med*. 2005;2(3):338–40.
5939. Omidvar S, Esmailzadeh S, Baradaran M, Basirat Z. Effect of fennel on pain intensity in dysmenorrhoea: a placebo-controlled trial. *Ayu*. 2012;33(2):311–3.
5940. Modaress Nejad V, Asadipour M. Comparison of the effectiveness of fennel and mefenamic acid on pain intensity in dysmenorrhoea. *East Mediterr Health J*. 2006;12(3–4):423–7.
5941. Ghazanfarpour M, Shokrollahi P, Khadivzadeh T, et al. Effect of *Foeniculum vulgare* (fennel) on vaginal atrophy in postmenopausal women: a double-blind, randomized, placebo-controlled trial. *Post Reprod Health*. 2017;23(4):171–6.
5942. Ghaffari P, Hosseininik M, Afrasiabifar A, et al. The effect of Fennel seed powder on estradiol levels, menopausal symptoms, and sexual desire in postmenopausal women. *Menopause*. 2020;27(11):1281–6.
5943. Yaralizadeh M, Abedi P, Najar S, Namjoyan F, Saki A. Effect of *Foeniculum vulgare* (fennel) vaginal cream on vaginal atrophy in postmenopausal women: a double-blind randomized placebo-controlled trial. *Maturitas*. 2016;84:75–80.
5944. Mazalzadeh F, Hekmat K, Namjouyan F, Saki A. Effect of *Trigonella foenum* (fenugreek) vaginal cream on vaginal atrophy in postmenopausal women. *J Family Med Prim Care*. 2020;9(6):2714–9.
5945. Abedi P, Najafian M, Yaralizadeh M, Namjoyan F. Effect of fennel vaginal cream on sexual function in postmenopausal women: a double blind randomized controlled trial. *J Med Life*. 2018;11(1):24–8.
5946. Poole C, Bushey B, Foster C, et al. The effects of a commercially available botanical supplement on strength, body composition, power output, and hormonal profiles in resistance-trained males. *J Int Soc Sports Nutr*. 2010;7:34.

5947. Mansoori A, Hosseini S, Zilaee M, Hormoznejad R, Fathi M. Effect of fenugreek extract supplement on testosterone levels in male: a meta-analysis of clinical trials. *Phytother Res*. 2020;34(7):1550–5.
5948. Rao A, Steels E, Inder WJ, Abraham S, Vitetta L. Testofen, a specialised *Trigonella foenum-graecum* seed extract reduces age-related symptoms of androgen decrease, increases testosterone levels and improves sexual function in healthy aging males in a double-blind randomised clinical study. *Aging Male*. 2016;19(2):134–42.
5949. Bahmani M, Shirzad H, Mirhosseini M, Mesripour A, Rafieian-Kopaei M. A review on ethnobotanical and therapeutic uses of fenugreek (*Trigonella foenum-graceum* L). *J Evid Based Complementary Altern Med*. 2016;21(1):53–62.
5950. Rao A, Steels E, Beccaria G, Inder WJ, Vitetta L. Influence of a specialized *Trigonella foenum-graecum* seed extract (libifem), on testosterone, estradiol and sexual function in healthy menstruating women, a randomised placebo controlled study. *Phytother Res*. 2015;29(8):1123–30.
5951. Steels E, Steele ML, Harold M, Coulson S. Efficacy of a proprietary *Trigonella foenum-graecum L.* de-husked seed extract in reducing menopausal symptoms in otherwise healthy women: a double-blind, randomized, placebo-controlled study. *Phytother Res*. 2017;31(9):1316–22.
5952. Safary M, Hakimi S, Mobaraki-Asl N, Amiri P, Tvassoli H, Delazar A. Comparison of the effects of fenugreek vaginal cream and ultra low-dose estrogen on atrophic vaginitis. *Curr Drug Deliv*. 2020;17(9):815–22.
5953. Pill-free ways to improve your sex life. Exercise, smoking cessation, and alcohol moderation can help bring sexual activity back into the bedroom. *Harv Health Lett*. 2014;39(10):4.
5954. Hall SA, Shackelton R, Rosen RC, Araujo AB. Sexual activity, erectile dysfunction, and incident cardiovascular events. *Am J Cardiol*. 2010;105(2):192–7.
5955. Davey Smith G, Frankel S, Yarnell J. Sex and death: are they related? Findings from the Caerphilly Cohort Study. *BMJ*. 1997;315(7123):1641–4.

5956. Fisher AD, Bandini E, Rastrelli G, et al. Sexual and cardiovascular correlates of male unfaithfulness. *J Sex Med*. 2012;9(6):1508–18.
5957. Maggi M, Corona G. Love protects lover's life. *J Sex Med*. 2011;8(4):931–5.
5958. Davey Smith G, Frankel S, Yarnell J. Sex and death: are they related? Findings from the Caerphilly Cohort Study. *BMJ*. 1997;315(7123):1641–4.
5959. Meldrum DR, Gambone JC, Morris MA, Meldrum DA, Esposito K, Ignarro LJ. The link between erectile and cardiovascular health: the canary in the coal mine. *Am J Cardiol.* 2011;108(4):599–606.
5960. Esposito K, Giugliano D. Lifestyle/dietary recommendations for erectile dysfunction and female sexual dysfunction. *Urol Clin North Am*. 2011;38(3):293–301.
5961. Dong JY, Zhang YH, Qin LQ. Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. *J Am Coll Cardiol*. 2011;58(13):1378–85.
5962. Ostfeld RJ, Allen KE, Aspry K, et al. Vasculogenic erectile dysfunction: the impact of diet and lifestyle. *Am J Med*. 2021;134(3):310–6.
5963. Kent KC, Zwolak RM, Egorova NN, et al. Analysis of risk factors for abdominal aortic aneurysm in a cohort of more than 3 million individuals. *J Vasc Surg*. 2010;52(3):539–48.
5964. Two-way street between erection problems and heart disease. Paying attention to heart health can be good for a man's sex life. *Harv Heart Lett*. 2011;21(9):4.
5965. Inman BA, Sauver JL, Jacobson DJ, et al. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. *Mayo Clin Proc*. 2009;84(2):108–13.
5966. Geerkens MJM, Al-Itejawi HHM, Nieuwenhuijzen JA, et al. Sexual dysfunction and bother due to erectile dysfunction in the healthy elderly male population: prevalence from a systematic review. *Eur Urol Focus*. 2020;6(4):776–90.
5967. Jackson G. Erectile dysfunction and coronary disease: evaluating the link. *Maturitas.* 2012;72(3):263–4.
5968. Carto C, Pagalavan M, Nackeeran S, et al. Consumption of a healthy plant-based diet is associated with a decreased risk of erectile

dysfunction: a cross-sectional study of the National Health and Nutrition Examination Survey. *Urology*. 2022;161:76–82.
5969. Bauer SR, Breyer BN, Stampfer MJ, Rimm EB, Giovannucci EL, Kenfield SA. Association of diet with erectile dysfunction among men in the Health Professionals Follow-Up Study. *JAMA Netw Open*. 2020;3(11):e2021701.
5970. Wang F, Dai S, Wang M, Morrison H. Erectile dysfunction and fruit/vegetable consumption among diabetic Canadian men. *Urology*. 2013;82(6):1330–5.
5971. Mykoniatis I, Grammatikopoulou MG, Bouras E, et al. Sexual dysfunction among young men: overview of dietary components associated with erectile dysfunction. *J Sex Med*. 2018;15(2):176–82.
5972. Gilbert SF, Zevit Z. Congenital human baculum deficiency: the generative bone of Genesis 2:21–23. *Am J Med Genet*. 2001;101(3):284–5.
5973. Dawkins R. The Selfish Gene. 30th Anniversary ed. Oxford University Press; 2006.
5974. Huynh LM, Liang K, Osman MM, et al. Organic diet and intermittent fasting are associated with improved erectile function. *Urology*. 2020;144:147–51.
5975. Burnett AL. Environmental erectile dysfunction: can the environment really be hazardous to your erectile health? *J Androl*. 2008;29(3):229–36.
5976. Espir ML, Hall JW, Shirreffs JG, Stevens DL. Impotence in farm workers using toxic chemicals. *Br Med J*. 1970;1(5693):423–5.
5977. Oliva A, Giami A, Multigner L. Environmental agents and erectile dysfunction: a study in a consulting population. *J Androl*. 2002;23(4):546–50.
5978. van de Vijver LPL, van Vliet MET. Health effects of an organic diet—consumer experiences in the Netherlands. *J Sci Food Agric*. 2012;92(14):2923–7.
5979. Li DK, Zhou Z, Miao M, et al. Relationship between urine bisphenol-A level and declining male sexual function. *J Androl*. 2010;31(5):500–6.
5980. Geens T, Aerts D, Berthot C, et al. A review of dietary and non-dietary exposure to bisphenol-A. *Food Chem Toxicol*.

2012;50(10):3725–40.
5981. Roberts R. BPA exposure and health effects: educating physicians and patients. *Am Fam Physician*. 2012;85(11):1040–4.
5982. Mirmira P, Evans-Molina C. Bisphenol A, obesity, and type 2 diabetes mellitus: genuine concern or unnecessary preoccupation? *Transl Res*. 2014;164(1):13–21.
5983. Feldman HA, Johannes CB, Derby CA, et al. Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts Male Aging Study. *Prev Med*. 2000;30(4):328–38.
5984. Juenemann KP, Lue TF, Luo JA, Benowitz NL, Abozeid M, Tanagho EA. The effect of cigarette smoking on penile erection. *J Urol*. 1987;138(2):438–41.
5985. Chan SSC, Leung DYP, Abdullah ASM, et al. Smoking-cessation and adherence intervention among Chinese patients with erectile dysfunction. *Am J Prev Med*. 2010;39(3):251–8.
5986. Pizzol D, Demurtas J, Stubbs B, et al. Relationship between cannabis use and erectile dysfunction: a systematic review and meta-analysis. *Am J Mens Health*. 2019;13(6):1557988319892464.
5987. Dallal RM, Chernoff A, O'Leary MP, Smith JA, Braverman JD, Quebbemann BB. Sexual dysfunction is common in the morbidly obese male and improves after gastric bypass surgery. *J Am Coll Surg*. 2008;207(6):859–64.
5988. Khoo J, Piantadosi C, Duncan R, et al. Comparing effects of a low-energy diet and a high-protein low-fat diet on sexual and endothelial function, urinary tract symptoms, and inflammation in obese diabetic men. *J Sex Med*. 2011;8(10):2868–75.
5989. Glina FPA, de Freitas Barboza JW, Nunes VM, Glina S, Bernardo WM. What is the impact of bariatric surgery on erectile function? A systematic review and meta-analysis. *Sex Med Rev*. 2017;5(3):393–402.
5990. Allen MS, Walter EE. Health-related lifestyle factors and sexual dysfunction: a meta-analysis of population-based research. *J Sex Med*. 2018;15(4):458–75.
5991. Silva AB, Sousa N, Azevedo LF, Martins C. Physical activity and exercise for erectile dysfunction: systematic review and meta-analysis. *Br J Sports Med*. 2017;51(19):1419–24.

5992. Li J, Peng L, Cao D, He L, Li Y, Wei Q. Avanafil for the treatment of men with erectile dysfunction: a systematic review and meta-analysis of randomized controlled trials. *Am J Mens Health*. 2019;13(5):1557988319880764.
5993. Gerbild H, Larsen CM, Graugaard C, Josefsson KA. Physical activity to improve erectile function: a systematic review of intervention studies. *Sex Med*. 2018;6(2):75–89.
5994. Michiels M, Van der Aa F. Bicycle riding and the bedroom: can riding a bicycle cause erectile dysfunction? *Urology*. 2015;85(4):725–30.
5995. Number of participants in bicycling in the United States from 2006 to 2020 (*in millions*). Statista. https://www.statista.com/statistics/191204/participants-in-bicycling-in-the-us-since-2006/. Published June 28, 2021. Accessed August 24, 2022.
5996. Gan ZS, Ehlers ME, Lin FC, Wright ST, Figler BD, Coward RM. Systematic review and meta-analysis of cycling and erectile dysfunction. *Sex Med Rev*. 2021;9(2):304–11.
5997. Michiels M, Van der Aa F. Bicycle riding and the bedroom: can riding a bicycle cause erectile dysfunction? *Urology*. 2015;85(4):725–30.
5998. Dettori JR, Koepsell TD, Cummings P, Corman JM. Erectile dysfunction after a long-distance cycling event: associations with bicycle characteristics. *J Urol*. 2004;172(2):637–41.
5999. Sommer F, Goldstein I, Korda JB. Bicycle riding and erectile dysfunction: a review. *J Sex Med*. 2010;7(7):2346–58.
6000. Michiels M, Van der Aa F. Bicycle riding and the bedroom: can riding a bicycle cause erectile dysfunction? *Urology*. 2015;85(4):725–30.
6001. Cai X, Tian Y, Wu T, Cao CX, Bu SY, Wang KJ. The role of statins in erectile dysfunction: a systematic review and meta-analysis. *Asian J Androl*. 2014;16(3):461–6.
6002. Williams P, McBain H, Amirova A, Newman S, Mulligan K. Men's beliefs about treatment for erectile dysfunction—what influences treatment use? A systematic review. *Int J Impot Res*. 2021;33(1):16–42.
6003. Goldstein I. The hour lecture that changed sexual medicine—the Giles Brindley injection story. *J Sex Med*. 2012;9(2):337–42.

6004. Barbas R, Llinas A, Prohens R. The solid state landscape of the sildenafil drug. *J Pharm Sci*. 2022;111(4):1104–9.
6005. Klotz L. How (not) to communicate new scientific information: a memoir of the famous Brindley lecture. *BJU Int.* 2005;96(7):956–7.
6006. Goldstein I. The hour lecture that changed sexual medicine—the Giles Brindley injection story. *J Sex Med*. 2012;9(2):337–42.
6007. Ghofrani HA, Osterloh IH, Grimminger F. Sildenafil: from angina to erectile dysfunction to pulmonary hypertension and beyond. *Nat Rev Drug Discov*. 2006;5(8):689–702.
6008. Williams P, McBain H, Amirova A, Newman S, Mulligan K. Men's beliefs about treatment for erectile dysfunction—what influences treatment use? A systematic review. *Int J Impot Res*. 2021;33(1):16–42.
6009. Souverein PC, Egberts ACG, Meuleman EJH, Urquhart J, Leufkens HGM. Incidence and determinants of sildenafil (dis)continuation: the Dutch cohort of sildenafil users. *Int J Impot Res*. 2002;14(4):259–65.
6010. Salonia A, Rigatti P, Montorsi F. Sildenafil in erectile dysfunction: a critical review. *Curr Med Res Opin*. 2003;19(4):241–62.
6011. Souverein PC, Egberts ACG, Meuleman EJH, Urquhart J, Leufkens HGM. Incidence and determinants of sildenafil (dis)continuation: the Dutch cohort of sildenafil users. *Int J Impot Res*. 2002;14(4):259–65.
6012. Le B, Burnett AL. Evolution of penile prosthetic devices. *Korean J Urol*. 2015;56(3):179–86.
6013. Schultheiss D, Gabouev AI, Jonas U. Nikolaj A. Bogoraz (1874–1952): pioneer of phalloplasty and penile implant surgery. *J Sex Med*. 2005;2(1):139–46.
6014. Jain S, Bhojwani A, Terry TR. The role of penile prosthetic surgery in the modern management of erectile dysfunction. *Postgrad Med J*. 2000;76(891):22–5.
6015. Ciftci H, Verit A, Savas M. Late complications of spontaneous urethral erosion of a malleable penile prosthesis in a young patient. *Singapore Med J*. 2012;53(6):e120–1.
6016. Le B, Burnett AL. Evolution of penile prosthetic devices. *Korean J Urol*. 2015;56(3):179–86.
6017. Chen L, Staubli SEL, Schneider MP, et al. Phosphodiesterase 5 inhibitors for the treatment of erectile dysfunction: a trade-off

network meta-analysis. *Eur Urol*. 2015;68(4):674–80.
6018. Matheeussen V, Maudens KE, Anseeuw K, Neels H. A non-fatal self-poisoning attempt with sildenafil. *J Anal Toxicol.* 2015;39(7):572–6.
6019. Chen SP, Singh K, Lin SC. Use of phosphodiesterase inhibitors and prevalence of self-reported glaucoma in the United States. *PLoS One*. 2017;12(8):e0183388.
6020. Kim SJ, Kim JH, Chang HK, Kim KH. Let's rethinking about the safety of phosphodiesterase type 5 inhibitor in the patients with erectile dysfunction after radical prostatectomy. *J Exerc Rehabil*. 2016;12(3):143–7.
6021. Mitra D, Robinson KC, Fisher DE. Melanoma and Viagra: an unexpected connection. *Pigment Cell Melanoma Res*. 2011;24(1):16–8.
6022. Arozarena I, Sanchez-Laorden B, Packer L, et al. Oncogenic BRAF induces melanoma cell invasion by downregulating the cGMP-specific phosphodiesterase PDE5A. *Cancer Cell*. 2011;19(1):45–57.
6023. Dhayade S, Kaesler S, Sinnberg T, et al. Sildenafil potentiates a cGMP-dependent pathway to promote melanoma growth. *Cell Rep*. 2016;14(11):2599–610.
6024. Yafi FA, Sharlip ID, Becher EF. Update on the safety of phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction. *Sex Med Rev*. 2018;6(2):242–52.
6025. Cohen PA, Venhuis BJ. Adulterated sexual enhancement supplements: more than mojo. *JAMA Intern Med*. 2013;173(13):1169–70.
6026. Poon WT, Lam YH, Lee HHC, et al. Outbreak of hypoglycaemia: sexual enhancement products containing oral hypoglycaemic agent. *Hong Kong Med J*. 2009;15(3):196–200.
6027. Jaksch F. Editorial: Are you concerned about the practice called "dry labbing" in the dietary supplement industry? *Altern Med Rev*. 2012;17(1):5.
6028. Robbins R. A supplement maker tried to silence this Harvard doctor —and put academic freedom on trial. STAT. https://www.statnews.com/2017/01/10/supplement-harvard-pieter-cohen/. Published January 10, 2017. Accessed August 24, 2022.

6029. Bagley N, Carroll AE, Cohen PA. Scientific trials—in the laboratories, not the courts. *JAMA Intern Med*. 2018;178(1):7–8.
6030. Cohen PA, Bloszies C, Yee C, Gerona R. An amphetamine isomer whose efficacy and safety in humans has never been studied, β-methylphenylethylamine (BMPEA), is found in multiple dietary supplements. *Drug Test Anal. 2016*;8(3–4):328–33.
6031. *Hi-Tech Pharms v Cohen*, 16–10660-WGY (D Mass 2016).
6032. Bagley N, Carroll AE, Cohen PA. Scientific trials—in the laboratories, not the courts. *JAMA Intern Med*. 2018;178(1):7–8.
6033. Bagley N, Carroll AE, Cohen PA. Scientific trials—in the laboratories, not the courts. *JAMA Intern Med*. 2018;178(1):7–8.
6034. Hall-Lipsy E, Malanga S. Defamation lawsuits: academic sword or shield? *EMBO Mol Med*. 2017;9(12):1623–5.
6035. Worner TM, Gordon GG, Leo MA, Lieber CS. Vitamin A treatment of sexual dysfunction in male alcoholics. *Am J Clin Nutr*. 1988;48(6):1431–5.
6036. Ng CF, Lee CP, Ho AL, Lee VWY. Effect of niacin on erectile function in men suffering erectile dysfunction and dyslipidemia. *J Sex Med*. 2011;8(10):2883–93.
6037. Biniaz V, Tayebi A, Ebadi A, Sadeghi S, Einollahi B. Effect of vitamin C supplementation on marital satisfaction in patients undergoing hemodialysis: a randomized, double-blind and placebo-controlled trial. *Saudi J Kidney Dis Transpl.* 2015;26(3):468–76.
6038. Ghanbari-Homaie S, Ataei-Almanghadim K, Mirghafourvand M. Effect of vitamins on sexual function: a systematic review. *Int J Vitam Nutr Res*. Published online March 29, 2021:1–10.
6039. Elshahid ARM, Shahein IM, Mohammed YF, Ismail NF, Zakarria HBAER, GamalEl Din SF. Folic acid supplementation improves erectile function in patients with idiopathic vasculogenic erectile dysfunction by lowering peripheral and penile homocysteine plasma levels: a case-control study. *Andrology*. 2020;8(1):148–53.
6040. Canguven O, Talib RA, El Ansari W, Yassin DJ, Al Naimi A. Vitamin D treatment improves levels of sexual hormones, metabolic parameters and erectile function in middle-aged vitamin D deficient men. *Aging Male*. 2017;20(1):9–16.

6041. Balasubramanian A, Thirumavalavan N, Srivatsav A, et al. An analysis of popular online erectile dysfunction supplements. *J Sex Med*. 2019;16(6):843–52.
6042. Srivatsav A, Balasubramanian A, Pathak UI, et al. Efficacy and safety of common ingredients in aphrodisiacs used for erectile dysfunction: a review. *Sex Med Rev*. 2020;8(3):431–42.
6043. Jang DJ, Lee MS, Shin BC, Lee YC, Ernst E. Red ginseng for treating erectile dysfunction: a systematic review. *Br J Clin Pharmacol*. 2008;66(4):444–50.
6044. Ichim MC, de Boer HJ. A review of authenticity and authentication of commercial ginseng herbal medicines and food supplements. *Front Pharmacol*. 2021;11:612071.
6045. West E, Krychman M. Natural aphrodisiacs—a review of selected sexual enhancers. *Sex Med Rev*. 2015;3(4):279–88.
6046. Zhu L, Han X, Zhu J, Du L, Liu L, Gong W. Severe acute intoxication with yohimbine: four simultaneous poisoning cases. *Forensic Sci Int*. 2021;320:110705.
6047. Muncey W, Sellke N, Kim T, Mishra K, Thirumavalavan N, Loeb A. Alternative treatment for erectile dysfunction: a growing arsenal in men's health. *Curr Urol Rep*. 2021;22(2):11.
6048. Burnett AL, Nehra A, Breau RH, et al. Erectile dysfunction: AUA guideline. *J Urol*. 2018;200(3):633–41.
6049. Hatzimouratidis K, Amar E, Eardley I, et al. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. *Eur Urol*. 2010;57(5):804–14.
6050. Maio G, Saraeb S, Marchiori A. Physical activity and PDE5 inhibitors in the treatment of erectile dysfunction: results of a randomized controlled study. *J Sex Med*. 2010;7(6):2201–8.
6051. Esposito K, Ciotola M, Giugliano F, et al. Mediterranean diet improves erectile function in subjects with the metabolic syndrome. *Int J Impot Res*. 2006;18(4):405–10.
6052. Meldrum DR, Gambone JC, Morris MA, Meldrum DAN, Esposito K, Ignarro LJ. The link between erectile and cardiovascular health: the canary in the coal mine. *Am J Cardiol*. 2011;108(4):599–606.
6053. Gupta BP, Murad MH, Clifton MM, Prokop L, Nehra A, Kopecky SL. The effect of lifestyle modification and cardiovascular risk factor

reduction on erectile dysfunction: a systematic review and meta-analysis. *Arch Intern Med*. 2011;171(20):1797–803.
6054. Esselstyn CB. Resolving the coronary artery disease epidemic through plant-based nutrition. *Prev Cardiol*. 2001;4(4):171–7.
6055. Barnett TD, Barnard ND, Radak TL. Development of symptomatic cardiovascular disease after self-reported adherence to the Atkins diet. *J Am Diet Assoc*. 2009;109(7):1263–5.
6056. Ramírez R, Pedro-Botet J, García M, et al. Erectile dysfunction and cardiovascular risk factors in a Mediterranean diet cohort. *Intern Med J*. 2016;46(1):52–6.
6057. Aldemir M, Okulu E, Neşelioğlu S, Erel O, Kayigil O. Pistachio diet improves erectile function parameters and serum lipid profiles in patients with erectile dysfunction. *Int J Impot Res*. 2011;23(1):32–8.
6058. Salas-Huetos A, Moraleda R, Giardina S, et al. Effect of nut consumption on semen quality and functionality in healthy men consuming a Western-style diet: a randomized controlled trial. *Am J Clin Nutr*. 2018;108(5):953–62.
6059. Salas-Huetos A, Muralidharan J, Galiè S, Salas-Salvadó J, Bulló M. Effect of nut consumption on erectile and sexual function in healthy males: a secondary outcome analysis of the FERTINUTS randomized controlled trial. *Nutrients*. 2019;11(6):E1372.
6060. Aldemir M, Okulu E, Neşelioğlu S, Erel O, Kayıgil O. Pistachio diet improves erectile function parameters and serum lipid profiles in patients with erectile dysfunction. *Int J Impot Res*. 2011;23(1):32–8.
6061. Salas-Huetos A, Muralidharan J, Galiè S, Salas-Salvadó J, Bulló M. Effect of nut consumption on erectile and sexual function in healthy males: a secondary outcome analysis of the FERTINUTS randomized controlled trial. *Nutrients*. 2019;11(6):E1372.
6062. Ohebshalom M, Mulhall JP. Transdermal and topical pharmacotherapy for male sexual dysfunction. *Expert Opin Drug Deliv*. 2005;2(1):115–20.
6063. Bhupathiraju SN, Wedick NM, Pan A, et al. Quantity and variety in fruit and vegetable intake and risk of coronary heart disease. *Am J Clin Nutr*. 2013;98(6):1514–23.
6064. Tamakoshi A, Tamakoshi K, Lin Y, Yagyu K, Kikuchi S. Healthy lifestyle and preventable death: findings from the Japan Collaborative

Cohort (JACC) Study. *Prev Med*. 2009;48(5):486–92.
6065. Wang F, Dai S, Wang M, Morrison H. Erectile dysfunction and fruit/vegetable consumption among diabetic Canadian men. *Urology*. 2013;82(6):1330–5.
6066. Presley TD, Morgan AR, Bechtold E, et al. Acute effect of a high nitrate diet on brain perfusion in older adults. *Nitric Oxide*. 2011;24(1):34–42.
6067. Rhim HC, Kim MS, Park YJ, et al. The potential role of arginine supplements on erectile dysfunction: a systemic review and meta-analysis. *J Sex Med*. 2019;16(2):223–34.
6068. Grimble GK. Adverse gastrointestinal effects of arginine and related amino acids. *J Nutr*. 2007;137(6 Suppl 2):1693S-701S.
6069. Rimando AM, Perkins-veazie PM. Determination of citrulline in watermelon rind. *J Chromatogr A.* 2005;1078(1–2):196–200.
6070. Cormio L, De siati M, Lorusso F, et al. Oral L-citrulline supplementation improves erection hardness in men with mild erectile dysfunction. *Urology*. 2011;77(1):119–22.
6071. Pfizer Annual Meeting of Shareholders 2014 Financial Report. http://www.pfizer.com/system/files/presentation/2014_Pfizer_Financial_Report.pdf. Accessed May 16, 2015.
6072. Johnson G. Watermelon board approves officers, budget, marketing plan. The Packer. http://www.thepacker.com/news/watermelon-board-approves-officers-budget-marketing-plan. February 24, 2015. Accessed May 16, 2015.
6073. Lopresti AL, Drummond PD. Saffron (*Crocus sativus*) for depression: a systematic review of clinical studies and examination of underlying antidepressant mechanisms of action. *Hum Psychopharmacol*. 2014;29(6):517–27.
6074. Talaei A, Hassanpour Moghadam M, Sajadi Tabassi SA, Mohajeri SA. Crocin, the main active saffron constituent, as an adjunctive treatment in major depressive disorder: a randomized, double-blind, placebo-controlled, pilot clinical trial. *J Affect Disord*. 2015;174:51–6.
6075. Lopresti AL, Drummond PD. Saffron (*Crocus sativus*) for depression: a systematic review of clinical studies and examination of underlying

antidepressant mechanisms of action. *Hum Psychopharmacol*. 2014;29(6):517–27.
6076. Higgins A, Nash M, Lynch AM. Antidepressant-associated sexual dysfunction: impact, effects, and treatment. *Drug Healthc Patient Saf*. 2010;2:141–50.
6077. Hu XH, Bull SA, Hunkeler EM, et al. Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate. *J Clin Psychiatry*. 2004;65(7):959–65.
6078. Csoka AB, Shipko S. Persistent sexual side effects after SSRI discontinuation. *Psychother Psychosom*. 2006;75(3):187–8.
6079. Modabbernia A, Sohrabi H, Nasehi AA, et al. Effect of saffron on fluoxetine-induced sexual impairment in men: randomized double-blind placebo-controlled trial. *Psychopharmacology (Berl)*. 2012;223(4):381–8.
6080. Kashani L, Raisi F, Saroukhani S, et al. Saffron for treatment of fluoxetine-induced sexual dysfunction in women: randomized double-blind placebo-controlled study. *Hum Psychopharmacol*. 2013;28(1):54–60.
6081. Giesbers AAGM, Bruins JL, Kramer AEJL, Jonas U. New methods in the diagnosis of impotence: RigiScan® penile tumescence and rigidity monitoring and diagnostic papaverine hydrochloride injection. *World J Urol*. 1987;5(3):173–6.
6082. Mohammadzadeh-Moghadam H, Nazari SM, Shamsa A, et al. Effects of a topical saffron (*Crocus sativus* L) gel on erectile dysfunction in diabetics: a randomized, parallel-group, double-blind, placebo-controlled trial. *J Evid Based Complementary Altern Med*. 2015;20(4):283–6.
6083. La J, Roberts NH, Yafi FA. Diet and men's sexual health. *Sex Med Rev*. 2018;6(1):54–68.
6084. Springmann M, Clark MA, Rayner M, Scarborough P, Webb P. The global and regional costs of healthy and sustainable dietary patterns: a modelling study. *Lancet Planet Health*. 2021;5(11):e797–807.
6085. Flynn MM, Schiff AR. Economical healthy diets (2012): including lean animal protein costs more than using extra virgin olive oil. *J Hunger Environ Nutr*. 2015;10(4):467–82.

6086. Ahmed IA, Mikail MA, Zamakshshari N, Abdullah ASH. Natural anti-aging skincare: role and potential. *Biogerontology*. 2020;21(3):293–310.
6087. Gu Y, Han J, Jiang C, Zhang Y. Biomarkers, oxidative stress and autophagy in skin aging. *Ageing Res Rev*. 2020;59:101036.
6088. Lowry WE. Its written all over your face: the molecular and physiological consequences of aging skin. *Mech Ageing Dev*. 2020;190:111315.
6089. Ahmed IA, Mikail MA, Zamakshshari N, Abdullah ASH. Natural anti-aging skincare: role and potential. *Biogerontology*. 2020;21(3):293–310.
6090. Makrantonaki E, Zouboulis CC. The skin as a mirror of the aging process in the human organism—state of the art and results of the aging research in the German National Genome Research Network 2 (NGFN-2). *Exp Gerontol*. 2007;42(9):879–86.
6091. Ahmed IA, Mikail MA, Zamakshshari N, Abdullah ASH. Natural anti-aging skincare: role and potential. *Biogerontology*. 2020;21(3):293–310.
6092. Makrantonaki E, Zouboulis CC. The skin as a mirror of the aging process in the human organism—state of the art and results of the aging research in the German National Genome Research Network 2 (NGFN-2). *Exp Gerontol*. 2007;42(9):879–86.
6093. Chaudhary M, Khan A, Gupta M. Skin ageing: pathophysiology and current market treatment approaches. *Curr Aging Sci*. 2020;13(1):22–30.
6094. Malik A, Hoenig LJ. Can aging be slowed down? *Clin Dermatol*. 2019;37(4):306–11.
6095. Nikolakis G, Makrantonaki E, Zouboulis CC. Skin mirrors human aging. *Horm Mol Biol Clin Investig*. 2013;16(1):13–28.
6096. Huang S, Haiminen N, Carrieri AP, et al. Human skin, oral, and gut microbiomes predict chronological age. *mSystems*. 2020;5(1):e00630–19.
6097. Rinnerthaler M, Bischof J, Streubel MK, Trost A, Richter K. Oxidative stress in aging human skin. *Biomolecules*. 2015;5(2):545–89.

6098. Ahmed IA, Mikail MA, Zamakshshari N, Abdullah ASH. Natural anti-aging skincare: role and potential. *Biogerontology*. 2020;21(3):293–310.
6099. Nikolakis G, Makrantonaki E, Zouboulis CC. Skin mirrors human aging. *Horm Mol Biol Clin Investig*. 2013;16(1):13–28.
6100. Singh G. Can we prevent skin aging? *Indian J Dermatol Venereol Leprol*. 2009;75(5):447–51.
6101. Gu Y, Han J, Jiang C, Zhang Y. Biomarkers, oxidative stress and autophagy in skin aging. *Ageing Res Rev*. 2020;59:101036.
6102. Silveira JEPS, Pedroso DMM. UV light and skin aging. *Rev Environ Health*. 2014;29(3):243–54.
6103. Singh G. Can we prevent skin aging? *Indian J Dermatol Venereol Leprol*. 2009;75(5):447–51.
6104. Ahmed IA, Mikail MA, Zamakshshari N, Abdullah ASH. Natural anti-aging skincare: role and potential. *Biogerontology*. 2020;21(3):293–310.
6105. Gordon JRS, Brieva JC. Images in clinical medicine. Unilateral dermatoheliosis. *N Engl J Med*. 2012;366(16):e25.
6106. Gunn DA, Dick JL, van Heemst D, et al. Lifestyle and youthful looks. *Br J Dermatol*. 2015;172(5):1338–45.
6107. Malik A, Hoenig LJ. Can aging be slowed down? *Clin Dermatol*. 2019;37(4):306–11.
6108. Singh G. Can we prevent skin aging? *Indian J Dermatol Venereol Leprol*. 2009;75(5):447–51.
6109. Elsner P, Fluhr JW, Gehring W, et al. Anti-aging data and support claims—consensus statement. *J Dtsch Dermatol Ges.* 2011;9 Suppl 3:S1–32.
6110. Gunn DA, Dick JL, van Heemst D, et al. Lifestyle and youthful looks. *Br J Dermatol*. 2015;172(5):1338–45.
6111. Ahmed IA, Mikail MA, Zamakshshari N, Abdullah ASH. Natural anti-aging skincare: role and potential. *Biogerontology*. 2020;21(3):293–310.
6112. Nikolakis G, Makrantonaki E, Zouboulis CC. Skin mirrors human aging. *Horm Mol Biol Clin Investig*. 2013;16(1):13–28.
6113. Burford O, Jiwa M, Carter O, Parsons R, Hendrie D. Internet-based photoaging within Australian pharmacies to promote smoking

cessation: randomized controlled trial. *J Med Internet Res*. 2013;15(3):e64.

6114. Mahler HIM, Kulik JA, Gerrard M, Gibbons FX. Long-term effects of appearance-based interventions on sun protection behaviors. *Health Psychol*. 2007;26(3):350–60.

6115. Misra BB. The chemical exposome of human aging. *Front Genet*. 2020;11:574936.

6116. Wong QYA, Chew FT. Defining skin aging and its risk factors: a systematic review and meta-analysis. *Sci Rep*. 2021;11(1):22075.

6117. Qiao Y, Li Q, Du HY, Wang QW, Huang Y, Liu W. Airborne polycyclic aromatic hydrocarbons trigger human skin cells aging through aryl hydrocarbon receptor. *Biochem Biophys Res Commun*. 2017;488(3):445–52.

6118. Krutmann J, Liu W, Li L, et al. Pollution and skin: from epidemiological and mechanistic studies to clinical implications. *J Dermatol Sci*. 2014;76(3):163–8.

6119. Van Rooij JG, Veeger MM, Bodelier-Bade MM, Scheepers PT, Jongeneelen FJ. Smoking and dietary intake of polycyclic aromatic hydrocarbons as sources of interindividual variability in the baseline excretion of 1-hydroxypyrene in urine. *Int Arch Occup Environ Health*. 1994;66(1):55–65.

6120. Ramesh A, Walker SA, Hood DB, Guillén MD, Schneider K, Weyand EH. Bioavailability and risk assessment of orally ingested polycyclic aromatic hydrocarbons. *Int J Toxicol*. 2004;23(5):301–33.

6121. Harris KL, Banks LD, Mantey JA, Huderson AC, Ramesh A. Bioaccessibility of polycyclic aromatic hydrocarbons: relevance to toxicity and carcinogenesis. *Expert Opin Drug Metab Toxicol*. 2013;9(11):1465–80.

6122. Crinnion WJ. The role of persistent organic pollutants in the worldwide epidemic of type 2 diabetes mellitus and the possible connection to farmed Atlantic salmon (*Salmo salar*). *Altern Med Rev*. 2011;16(4):301–13.

6123. Li Z, Romanoff L, Bartell S, et al. Excretion profiles and half-lives of ten urinary polycyclic aromatic hydrocarbon metabolites after dietary exposure. *Chem Res Toxicol*. 2012;25(7):1452–61.

6124. Solway J, McBride M, Haq F, Abdul W, Miller R. Diet and dermatology: the role of a whole-food, plant-based diet in preventing and reversing skin aging—a review. *J Clin Aesthet Dermatol*. 2020 May;13(5):38–43.
6125. Pontius AT, Smith PW. How to successfully incorporate antiaging and wellness into your practice: things you should know. *Facial Plast Surg*. 2010;26(1):12–5.
6126. Smirnova MH. A will to youth: the woman's anti-aging elixir. *Soc Sci Med*. 2012;75(7):1236–43.
6127. Plastic Surgery Statistics Report: ASPS National Clearinghouse of Plastic Surgery Procedural Statistics 2020. American Society of Plastic Surgeons. https://www.plasticsurgery.org/documents/News/Statistics/2020/plastic-surgery-statistics-full-report-2020.pdf. Published 2020. Accessed August 31, 2022.
6128. Barrett DM, Gerecci D, Wang TD. Facelift controversies. *Facial Plast Surg Clin North Am*. 2016;24(3):357–66.
6129. Chopan M, Samant S, Mast BA. Contemporary analysis of rhytidectomy using the Tracking Operations and Outcomes for Plastic Surgeons database with 13,346 patients. *Plast Reconstr Surg*. 2020;145(6):1402–8.
6130. Chopan M, Samant S, Mast BA. Contemporary analysis of rhytidectomy using the Tracking Operations and Outcomes for Plastic Surgeons database with 13,346 patients. *Plast Reconstr Surg*. 2020;145(6):1402–8.
6131. Truswell WH. Approaches to reducing risk in rhytidectomy surgery. *Facial Plast Surg Clin North Am*. 2020;28(3):419–27.
6132. Plastic Surgery Statistics Report: ASPS National Clearinghouse of Plastic Surgery Procedural Statistics 2020. American Society of Plastic Surgeons. https://www.plasticsurgery.org/documents/News/Statistics/2020/plastic-surgery-statistics-full-report-2020.pdf. Published 2020. Accessed August 31, 2022.
6133. Lee KC, Pascal AB, Halepas S, Koch A. What are the most commonly reported complications with cosmetic botulinum toxin type A treatments? *J Oral Maxillofac Surg*. 2020;78(7):1190.e1–9.

6134. Giordano CN, Matarasso SL, Ozog DM. Injectable and topical neurotoxins in dermatology: indications, adverse events, and controversies. *J Am Acad Dermatol*. 2017;76(6):1027–42.
6135. Lee KC, Pascal AB, Halepas S, Koch A. What are the most commonly reported complications with cosmetic botulinum toxin type A treatments? *J Oral Maxillofac Surg*. 2020;78(7):1190.e1–9.
6136. Plastic Surgery Statistics Report: ASPS National Clearinghouse of Plastic Surgery Procedural Statistics 2020. American Society of Plastic Surgeons. https://www.plasticsurgery.org/documents/News/Statistics/2020/plastic-surgery-statistics-full-report-2020.pdf. Published 2020. Accessed August 31, 2022.
6137. DeVictor S, Ong AA, Sherris DA. Complications secondary to nonsurgical rhinoplasty: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg*. 2021;165(5):611–6.
6138. Vanaman M, Fabi SG, Carruthers J. Complications in the cosmetic dermatology patient: a review and our experience (Part 1). *Dermatol Surg*. 2016;42(1):1–11.
6139. Tran AQ, Staropoli P, Rong AJ, Lee WW. Filler-associated vision loss. *Facial Plast Surg Clin North Am*. 2019;27(4):557–64.
6140. Rayess HM, Svider PF, Hanba C, et al. A cross-sectional analysis of adverse events and litigation for injectable fillers. *JAMA Facial Plast Surg*. 2018;20(3):207–14.
6141. Woodward J, Khan T, Martin J. Facial filler complications. *Facial Plast Surg Clin North Am*. 2015;23(4):447–58.
6142. Plastic Surgery Statistics Report: ASPS National Clearinghouse of Plastic Surgery Procedural Statistics 2020. American Society of Plastic Surgeons. https://www.plasticsurgery.org/documents/News/Statistics/2020/plastic-surgery-statistics-full-report-2020.pdf. Published 2020. Accessed August 31, 2022.
6143. Shah AR, Kennedy PM. The aging face. *Med Clin North Am*. 2018;102(6):1041–54.
6144. Ganceviciene R, Liakou AI, Theodoridis A, Makrantonaki E, Zouboulis CC. Skin anti-aging strategies. *Dermatoendocrinol*. 2012;4(3):308–19.

6145. Manríquez JJ, Cataldo K, Vera-Kellet C, Harz-Fresno I. Wrinkles. *BMJ Clin Evid*. 2014;2014:1711.
6146. Neill US. Skin care in the aging female: myths and truths. *J Clin Invest*. 2012;122(2):473–7.
6147. Vanaman M, Fabi SG, Carruthers J. Complications in the cosmetic dermatology patient: a review and our experience (Part 2). *Dermatol Surg*. 2016;42(1):12–20.
6148. Ganceviciene R, Liakou AI, Theodoridis A, Makrantonaki E, Zouboulis CC. Skin anti-aging strategies. *Dermatoendocrinol*. 2012;4(3):308–19.
6149. Sillanpää S, Salminen J-P, Eeva T. Breeding success and lutein availability in great tit (*Parus major*). *Acta Oecologica.* 2009;35(6):805–10.
6150. Whitehead RD, Coetzee V, Ozakinci G, Perrett DI. Cross-cultural effects of fruit and vegetable consumption on skin color. *Am J Public Health.* 2012;102(2):212–3.
6151. Stephen ID, Law Smith MJ, Stirrat MR, Perrett DI. Facial skin coloration affects perceived health of human faces. *Int J Primatol.* 2009;30(6):845–57.
6152. Whitehead RD, Re D, Xiao D, Ozakinci G, Perrett DI. You are what you eat: within-subject increases in fruit and vegetable consumption confer beneficial skin-color changes. *PLoS One.* 2012;7(3):e32988.
6153. Stahl W, Heinrich U, Jungmann H, et al. Increased dermal carotenoid levels assessed by noninvasive reflection spectrophotometry correlate with serum levels in women ingesting Betatene. *J Nutr*. 1998;128(5):903–7.
6154. Stephen ID, Law Smith MJ, Stirrat MR, Perrett DI. Facial skin coloration affects perceived health of human faces. *Int J Primatol*. 2009;30(6):845–57.
6155. Lefevre CE, Perrett DI. Fruit over sunbed: carotenoid skin colouration is found more attractive than melanin colouration. *Q J Exp Psychol (Hove)*. 2015;68(2):284–93.
6156. Pezdirc K, Hutchesson M, Whitehead R, Ozakinci G, Perrett D, Collins CE. Can dietary intake influence perception of and measured appearance? A systematic review. *Nutr Res*. 2015;35(3):175–97.

6157. Greens to be gorgeous: why eating your five fruit and veg a day makes you sexy. Daily Mail. http://www.dailymail.co.uk/health/article-1228348/Eating-fruit-veg-makes-attractive-opposite-sex.html. November 17, 2009. Accessed September 7, 2022.
6158. Mitic V, Jovanovic VS, Dimitrijevic M, Cvetkovic J, Stojanovic G. Effect of food preparation technique on antioxidant activity and plant pigment content in some vegetables species. *J Food Nutr Res*. 2013;1(6):121–7.
6159. Meinke MC, Nowbary CK, Schanzer S, Vollert H, Lademann J, Darvin ME. Influences of orally taken carotenoid-rich curly kale extract on collagen I/elastin index of the skin. *Nutrients*. 2017;9(7):775.
6160. Shoji T, Masumoto S, Moriichi N, Ohtake Y, Kanda T. Administration of apple polyphenol supplements for skin conditions in healthy women: a randomized, double-blind, placebo-controlled clinical trial. *Nutrients*. 2020;12(4):1071.
6161. Nobile V, Michelotti A, Cestone E, et al. Skin photoprotective and antiageing effects of a combination of rosemary (*Rosmarinus officinalis*) and grapefruit (*Citrus paradisi*) polyphenols. *Food Nutr Res*. 2016;60:31871.
6162. Stahl W, Heinrich U, Wiseman S, Eichler O, Sies H, Tronnier H. Dietary tomato paste protects against ultraviolet light-induced erythema in humans. *J Nutr*. 2001;131(5):1449–51.
6163. Palombo P, Fabrizi G, Ruocco V, et al. Beneficial long-term effects of combined oral/topical antioxidant treatment with the carotenoids lutein and zeaxanthin on human skin: a double-blind, placebo-controlled study. *Skin Pharmacol Physiol*. 2007;20(4):199–210.
6164. Köpcke W, Krutmann J. Protection from sunburn with β-carotene—a meta-analysis. *Photochem Photobiol*. 2008;84(2):284–8.
6165. Darvin M, Patzelt A, Gehse S, et al. Cutaneous concentration of lycopene correlates significantly with the roughness of the skin. *Eur J Pharm Biopharm*. 2008;69(3):943–7.
6166. Hughes MCB, Williams GM, Pageon H, Fourtanier A, Green AC. Dietary antioxidant capacity and skin photoaging: a 15-year longitudinal study. *J Invest Dermatol*. 2021;141(4S):1111–8.e2.

6167. Sundelin T, Lekander M, Kecklund G, Van Someren EJW, Olsson A, Axelsson J. Cues of fatigue: effects of sleep deprivation on facial appearance. *Sleep*. 2013;36(9):1355–60.
6168. Axelsson J, Sundelin T, Ingre M, Van Someren EJW, Olsson A, Lekander M. Beauty sleep: experimental study on the perceived health and attractiveness of sleep deprived people. *BMJ*. 2010;341:c6614.
6169. Atrooz F, Salim S. Sleep deprivation, oxidative stress and inflammation. *Adv Protein Chem Struct Biol*. 2020;119:309–36.
6170. Lee CM, Watson REB, Kleyn CE. The impact of perceived stress on skin ageing. *J Eur Acad Dermatol Venereol*. 2020;34(1):54–8.
6171. Noordam R, Gunn DA, Tomlin CC, et al. Cortisol serum levels in familial longevity and perceived age: the Leiden Longevity Study. *Psychoneuroendocrinology*. 2012;37(10):1669–75.
6172. Smith S. The graying of the presidents. Boston.com. http://archive.boston.com/news/politics/2008/articles/2009/01/04/the_graying_of_the_presidents/. Published January 4, 2009. Accessed August 31, 2022.
6173. Agrigoroaei S, Attardo AL, Lachman ME. Stress and subjective age: those with greater financial stress look older. *Res Aging*. 2017;39(10):1075–99.
6174. Mukamal KJ. Alcohol consumption and self-reported sunburn: a cross-sectional, population-based survey. *J Am Acad Dermatol*. 2006;55(4):584–9.
6175. Darvin ME, Sterry W, Lademann J, Patzelt A. Alcohol consumption decreases the protection efficiency of the antioxidant network and increases the risk of sunburn in human skin. *Skin Pharmacol Physiol*. 2013;26(1):45–51.
6176. Darvin ME, Sterry W, Lademann J, Patzelt A. Alcohol consumption decreases the protection efficiency of the antioxidant network and increases the risk of sunburn in human skin. *Skin Pharmacol Physiol*. 2013;26(1):45–51.
6177. Castelo-Branco C, Figueras F, Martínez de Osaba MJ, Vanrell JA. Facial wrinkling in postmenopausal women. Effects of smoking status and hormone replacement therapy. *Maturitas*. 1998;29(1):75–86.

6178. Wong QYA, Chew FT. Defining skin aging and its risk factors: a systematic review and meta-analysis. *Sci Rep*. 2021;11(1):22075.
6179. Walsh NP, Fortes MB, Raymond-Barker P, et al. Is whole-body hydration an important consideration in dry eye? *Invest Ophthalmol Vis Sci*. 2012;53(10):6622–7.
6180. Sharma A, Hindman HB. Aging: a predisposition to dry eyes. *J Ophthalmol*. 2014;2014:781683.
6181. Akdeniz M, Tomova-Simitchieva T, Dobos G, Blume-Peytavi U, Kottner J. Does dietary fluid intake affect skin hydration in healthy humans? A systematic literature review. *Skin Res Technol*. 2018;24(3):459–65.
6182. Clarke KA, Dew TP, Watson REB, et al. Green tea catechins and their metabolites in human skin before and after exposure to ultraviolet radiation. *J Nutr Biochem*. 2016;27:203–10.
6183. Fukushima Y, Takahashi Y, Hori Y, et al. Skin photoprotection and consumption of coffee and polyphenols in healthy middle-aged Japanese females. *Int J Dermatol*. 2015;54(4):410–8.
6184. Fukushima Y, Takahashi Y, Kishimoto Y, et al. Consumption of polyphenols in coffee and green tea alleviates skin photoaging in healthy Japanese women. *Clin Cosmet Investig Dermatol*. 2020;13:165–72.
6185. Chiu AE, Chan JL, Kern DG, Kohler S, Rehmus WE, Kimball AB. Double-blinded, placebo-controlled trial of green tea extracts in the clinical and histologic appearance of photoaging skin. *Dermatol Surg*. 2005;31(7 Pt 2):855–60.
6186. Jeon HY, Kim JK, Kim WG, Lee SJ. Effects of oral epigallocatechin gallate supplementation on the minimal erythema dose and UV-induced skin damage. *Skin Pharmacol Physiol*. 2009;22(3):137–41.
6187. Heinrich U, Moore CE, De Spirt S, Tronnier H, Stahl W. Green tea polyphenols provide photoprotection, increase microcirculation, and modulate skin properties of women. *J Nutr*. 2011;141(6):1202–8.
6188. Farrar MD, Nicolaou A, Clarke KA, et al. A randomized controlled trial of green tea catechins in protection against ultraviolet radiation–induced cutaneous inflammation. *Am J Clin Nutr*. 2015;102(3):608–15.

6189. Janjua R, Munoz C, Gorell E, et al. A two-year, double-blind, randomized placebo-controlled trial of oral green tea polyphenols on the long-term clinical and histologic appearance of photoaging skin. *Dermatol Surg*. 2009;35(7):1057–65.
6190. Tjeerdsma F, Jonkman MF, Spoo JR. Temporary arrest of basal cell carcinoma formation in a patient with basal cell naevus syndrome (BCNS) since treatment with a gel containing various plant extracts. *J Eur Acad Dermatol Venereol*. 2011;25(2):244–5.
6191. Camouse MM, Domingo DS, Swain FR, et al. Topical application of green and white tea extracts provides protection from solar-simulated ultraviolet light in human skin. *Exp Dermatol*. 2009;18(6):522–6.
6192. Chiu AE, Chan JL, Kern DG, Kohler S, Rehmus WE, Kimball AB. Double-blinded, placebo-controlled trial of green tea extracts in the clinical and histologic appearance of photoaging skin. *Dermatol Surg*. 2005;31(7 Pt 2):855–60.
6193. Kessels J, Voeten L, Nelemans P, et al. Topical sinecatechins, 10%, ointment for superficial basal cell carcinoma: a randomized clinical trial. *JAMA Dermatol*. 2017;153(10):1061–3.
6194. Petrova A, Davids LM, Rautenbach F, Marnewick JL. Photoprotection by honeybush extracts, hesperidin and mangiferin against UVB-induced skin damage in SKH-1 mice. *J Photochem Photobiol B*. 2011;103(2):126–39.
6195. Choi SY, Hong JY, Ko EJ, et al. Protective effects of fermented honeybush (*Cyclopia intermedia*) extract (HU-018) against skin aging: a randomized, double-blinded, placebo-controlled study. *J Cosmet Laser Ther*. 2018;20(5):313–8.
6196. Neukam K, Stahl W, Tronnier H, Sies H, Heinrich U. Consumption of flavanol-rich cocoa acutely increases microcirculation in human skin. *Eur J Nutr*. 2007;46(1):53–6.
6197. Heinrich U, Neukam K, Tronnier H, Sies H, Stahl W. Long-term ingestion of high flavanol cocoa provides photoprotection against UV-induced erythema and improves skin condition in women. *J Nutr*. 2006;136(6):1565–9.
6198. Yoon HS, Kim JR, Park GY, et al. Cocoa flavanol supplementation influences skin conditions of photo-aged women: a 24-week double-blind, randomized, controlled trial. *J Nutr*. 2016;146(1):46–50.

6199. Anson G, Kane MAC, Lambros V. Sleep wrinkles: facial aging and facial distortion during sleep. *Aesthet Surg J*. 2016;36(8):931–40.
6200. Kligman AM, Zheng P, Lavker RM. The anatomy and pathogenesis of wrinkles. *Br J Dermatol*. 1985;113(1):37–42.
6201. Hillebrand GG, Liang Z, Yan X, Yoshii T. New wrinkles on wrinkling: an 8-year longitudinal study on the progression of expression lines into persistent wrinkles. *Br J Dermatol*. 2010;162(6):1233–41.
6202. Vogeley C, Esser C, Tüting T, Krutmann J, Haarmann-Stemmann T. Role of the aryl hydrocarbon receptor in environmentally induced skin aging and skin carcinogenesis. *Int J Mol Sci*. 2019;20(23):6005.
6203. Mekić S, Jacobs LC, Hamer MA, et al. A healthy diet in women is associated with less facial wrinkles in a large Dutch population-based cohort. *J Am Acad Dermatol*. 2019;80(5):1358–63.e2.
6204. Cosgrove MC, Franco OH, Granger SP, Murray PG, Mayes AE. Dietary nutrient intakes and skin-aging appearance among middle-aged American women. *Am J Clin Nutr*. 2007;86(4):1225–31.
6205. Foolad N, Vaughn AR, Rybak I, et al. Prospective randomized controlled pilot study on the effects of almond consumption on skin lipids and wrinkles. *Phytother Res*. 2019;33(12):3212–7.
6206. De Spirt S, Stahl W, Tronnier H, et al. Intervention with flaxseed and borage oil supplements modulates skin condition in women. *Br J Nutr*. 2009;101(3):440–5.
6207. Izumi T, Saito M, Obata A, Arii M, Yamaguchi H, Matsuyama A. Oral intake of soy isoflavone aglycone improves the aged skin of adult women. *J Nutr Sci Vitaminol (Tokyo)*. 2007;53(1):57–62.
6208. Oyama A, Ueno T, Uchiyama S, et al. The effects of natural *S*-equol supplementation on skin aging in postmenopausal women: a pilot randomized placebo-controlled trial. *Menopause*. 2012;19(2):202–10.
6209. Fam VW, Holt RR, Keen CL, Sivamani RK, Hackman RM. Prospective evaluation of mango fruit intake on facial wrinkles and erythema in postmenopausal women: a randomized clinical pilot study. *Nutrients*. 2020;12(11):3381.
6210. Katta R, Sanchez A, Tantry E. An anti-wrinkle diet: nutritional strategies to combat oxidation, inflammation and glycation. *Skin Therapy Lett*. 2020;25(2):3–7.

6211. Solway J, McBride M, Haq F, Abdul W, Miller R. Diet and dermatology: the role of a whole-food, plant-based diet in preventing and reversing skin aging—a review. *J Clin Aesthet Dermatol*. 2020;13(5):38–43.
6212. Pacifico A, Conic RRZ, Cristaudo A, et al. Diet-related phototoxic reactions in psoriatic patients undergoing phototherapy: results from a multicenter prospective study. *Nutrients*. 2021;13(9):2934.
6213. Fusano M, Zane C, Calzavara-Pinton P, Bencini PL. Photodynamic therapy for actinic keratosis in vegan and omnivore patients: the role of diet on skin healing. *J Dermatolog Treat*. 2021;32(1):78–83.
6214. Fusano M, Galimberti MG, Bencini PL. Laser removal of tattoos in vegan and omnivore patients. *J Cosmet Dermatol*. 2022;21(2):674–8.
6215. Fusano M, Bencini PL, Fusano I, et al. Ultrapulsed CO_2 resurfacing of photodamaged facial skin in vegan and omnivore patients: a multicentric study. *Lasers Surg Med*. 2021;53(10):1370–5.
6216. Fusano M, Fusano I, Galimberti MG, Bencini M, Bencini PL. Comparison of postsurgical scars between vegan and omnivore patients. *Dermatol Surg*. 2020;46(12):1572–6.
6217. Galimberti MG, Guida S, Pellacani G, Bencini PL. Hyaluronic acid filler for skin rejuvenation: the role of diet on outcomes. A pilot study. *Dermatol Ther*. 2018;31(4):e12646.
6218. Fusano M, Galimberti MG, Bencini M, Fusano I, Bencini PL. Comparison of microfocused ultrasound with visualization for skin laxity among vegan and omnivore patients. *J Cosmet Dermatol*. 2021;20(9):2769–74.
6219. Karlic H, Schuster D, Varga F, et al. Vegetarian diet affects genes of oxidative metabolism and collagen synthesis. *Ann Nutr Metab*. 2008;53(1):29–32.
6220. Fusano M, Zane C, Calzavara-Pinton P, Bencini PL. Photodynamic therapy for actinic keratosis in vegan and omnivore patients: the role of diet on skin healing. *J Dermatolog Treat*. 2021;32(1):78–83.
6221. Fusano M, Galimberti MG, Bencini PL. Laser removal of tattoos in vegan and omnivore patients. *J Cosmet Dermatol*. 2022;21(2):674–8.
6222. Fusano M, Bencini PL, Fusano I, et al. Ultrapulsed CO_2 resurfacing of photodamaged facial skin in vegan and omnivore patients: a

multicentric study. *Lasers Surg Med*. 2021;53(10):1370–5.
6223. Fusano M, Fusano I, Galimberti MG, Bencini M, Bencini PL. Comparison of postsurgical scars between vegan and omnivore patients. *Dermatol Surg*. 2020;46(12):1572–6.
6224. Fusano M, Galimberti MG, Bencini M, Fusano I, Bencini PL. Comparison of microfocused ultrasound with visualization for skin laxity among vegan and omnivore patients. *J Cosmet Dermatol*. 2021;20(9):2769–74.
6225. Kang AH, Trelstad RL. A collagen defect in homocystinuria. *J Clin Invest*. 1973;52(10):2571–8.
6226. Rao VH, Bose SM. Effect of vitamin B_{12} on the formation of collagen and nucleic acids in the albino rat skins and granulomas. *J Vitaminol (Kyoto)*. 1970;16(4):253–8.
6227. Findlay CW. Effect of vitamin B_{12} on wound healing. *Proc Soc Exp Biol Med*. 1953;82(3):492–5.
6228. Tuz MA, Mitchell A. The influence of anaemia on pressure ulcer healing in elderly patients. *Br J Nurs*. 2021;30(15):S32–8.
6229. Kang AH, Trelstad RL. A collagen defect in homocystinuria. *J Clin Invest*. 1973;52(10):2571–8.
6230. Makris EA, Responte DJ, Paschos NK, Hu JC, Athanasiou KA. Developing functional musculoskeletal tissues through hypoxia and lysyl oxidase-induced collagen cross-linking. *Proc Natl Acad Sci U S A*. 2014;111(45):E4832–41.
6231. National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance, Haesler E, ed. *Prevention and Treatment of Pressure Ulcers: Quick Reference Guide*. Cambridge Medi; 2014.
6232. Smith MEB, Totten A, Hickam DH, et al. Pressure ulcer treatment strategies: a systematic comparative effectiveness review. *Ann Intern Med*. 2013;159(1):39–50.
6233. Mariotti F, Gardner CD. Dietary protein and amino acids in vegetarian diets—a review. *Nutrients*. 2019;11(11):2661.
6234. Berryman CE, Lieberman HR, Fulgoni VL, Pasiakos SM. Protein intake trends and conformity with the Dietary Reference Intakes in the United States: analysis of the National Health and Nutrition

Examination Survey, 2001–2014. *Am J Clin Nutr*. 2018;108(2):405–13.
6235. Jhawar N, Wang JV, Saedi N. Oral collagen supplementation for skin aging: a fad or the future? *J Cosmet Dermatol*. 2020;19(4):910–2.
6236. de Lange C. Can a drink really make skin look younger? The Guardian. https://www.theguardian.com/science/2015/sep/27/nutricosmetics-drink-make-skin-look-younger-science. Published September 27, 2015. Accessed August 31, 2022.
6237. Albornoz CA, Shah S, Murgia RD, Wang JV, Saedi N. Understanding aesthetic interest in oral collagen peptides: a 5-year national assessment. *J Cosmet Dermatol*. 2021;20(2):566–8.
6238. de Miranda RB, Weimer P, Rossi RC. Effects of hydrolyzed collagen supplementation on skin aging: a systematic review and meta-analysis. *Int J Dermatol*. 2021;60(12):1449–61.
6239. Albornoz CA, Shah S, Murgia RD, Wang JV, Saedi N. Understanding aesthetic interest in oral collagen peptides: a 5-year national assessment. *J Cosmet Dermatol*. 2021;20(2):566–8.
6240. Jhawar N, Wang JV, Saedi N. Oral collagen supplementation for skin aging: a fad or the future? *J Cosmet Dermatol*. 2020;19(4):910–2.
6241. Rustad AM, Nickles MA, McKenney JE, Bilimoria SN, Lio PA. Myths and media in oral collagen supplementation for the skin, nails, and hair: a review. *J Cosmet Dermatol.* 2022 Feb;21(2):438–43.
6242. Spiro A, Lockyer S. Nutraceuticals and skin appearance: is there any evidence to support this growing trend? *Nutr Bull*. 2018;43(1):10–45.
6243. Hujoel PP, Hujoel MLA. Vitamin C and scar strength: analysis of a historical trial and implications for collagen-related pathologies. *Am J Clin Nutr*. 2022;115(1):8–17.
6244. Vitamin C: factsheet for health professionals. National Institutes of Health. https://ods.od.nih.gov/factsheets/VitaminC-HealthProfessional/. Updated March 26, 2021. Accessed September 7, 2022.
6245. Albornoz CA, Shah S, Murgia RD, Wang JV, Saedi N. Understanding aesthetic interest in oral collagen peptides: a 5-year national assessment. *J Cosmet Dermatol*. 2021;20(2):566–8.

6246. Perez-Sanchez AC, Burns EK, Perez VM, Tantry EK, Prabhu S, Katta R. Safety concerns of skin, hair and nail supplements in retail stores. *Cureus*. 12(7):e9477.
6247. Avila-Rodríguez MI, Rodríguez Barroso LG, Sánchez ML. Collagen: a review on its sources and potential cosmetic applications. *J Cosmet Dermatol*. 2018;17(1):20–6.
6248. Sionkowska A, Adamiak K, Musiał K, Gadomska M. Collagen based materials in cosmetic applications: a review. *Materials*. 2020;13(19):4217.
6249. Perez-Sanchez AC, Burns EK, Perez VM, Tantry EK, Prabhu S, Katta R. Safety concerns of skin, hair and nail supplements in retail stores. *Cureus*. 12(7):e9477.
6250. Rustad AM, Nickles MA, McKenney JE, Bilimoria SN, Lio PA. Myths and media in oral collagen supplementation for the skin, nails, and hair: a review. *J Cosmet Dermatol*. 2022;21(2):438–43.
6251. Cao C, Xiao Z, Wu Y, Ge C. Diet and skin aging—from the perspective of food nutrition. *Nutrients*. 2020;12(3):870.
6252. Cooperman T. Collagen supplements. ConsumerLab.com. https://www.consumerlab.com/reviews/collagen-supplements-review-peptides-hydrolysate/collagen/. Published September 28, 2019. Updated June 6, 2022. Accessed August 31, 2022.
6253. Seror J, Stern M, Zarka R, Orr N. The potential use of novel plant-derived recombinant human collagen in aesthetic medicine. *Plast Reconstr Surg*. 2021;148(6S):32S-8S.
6254. Huang CK, Miller TA. The truth about over-the-counter topical anti-aging products: a comprehensive review. *Aesthet Surg J*. 2007;27(4):402–12.
6255. Neill US. Skin care in the aging female: myths and truths. *J Clin Invest*. 2012;122(2):473–7.
6256. Elsner P, Fluhr JW, Gehring W, et al. Anti-aging data and support claims—consensus statement. *J Dtsch Dermatol Ges.* 2011;9 Suppl 3:S1–32.
6257. Huang CK, Miller TA. The truth about over-the-counter topical anti-aging products: a comprehensive review. *Aesthet Surg J*. 2007;27(4):402–12.

6258. Elsner P, Fluhr JW, Gehring W, et al. Anti-aging data and support claims—consensus statement. *J Dtsch Dermatol Ges.* 2011;9 Suppl 3:S1–32.
6259. Mayes AE, Murray PG, Gunn DA, et al. Environmental and lifestyle factors associated with perceived facial age in Chinese women. *PLoS One*. 2010;5(12):e15270.
6260. Gunn DA, Dick JL, van Heemst D, et al. Lifestyle and youthful looks. *Br J Dermatol*. 2015;172(5):1338–45.
6261. Huang CK, Miller TA. The truth about over-the-counter topical anti-aging products: a comprehensive review. *Aesthet Surg J*. 2007;27(4):402–12.
6262. Neill US. Skin care in the aging female: myths and truths. *J Clin Invest*. 2012;122(2):473–7.
6263. Draelos ZD. Active agents in common skin care products. *Plast Reconstr Surg*. 2010;125(2):719–24.
6264. Ramos-e-Silva M, Celem LR, Ramos-e-Silva S, Fucci-da-Costa AP. Anti-aging cosmetics: facts and controversies. *Clin Dermatol*. 2013;31(6):750–8.
6265. Draelos ZD. Active agents in common skin care products. *Plast Reconstr Surg*. 2010;125(2):719–24.
6266. Neill US. Skin care in the aging female: myths and truths. *J Clin Invest*. 2012;122(2):473–7.
6267. Draelos ZD. Active agents in common skin care products. *Plast Reconstr Surg*. 2010;125(2):719–24.
6268. Sunder S. Relevant topical skin care products for prevention and treatment of aging skin. *Facial Plast Surg Clin North Am*. 2019;27(3):413–8.
6269. Bergstrom KG. Carrots before sticks: appealing to vanity promotes sun protection. *J Drugs Dermatol*. 2013;12(8):952–3.
6270. Hughes MCB, Williams GM, Baker P, Green AC. Sunscreen and prevention of skin aging: a randomized trial. *Ann Intern Med*. 2013;158(11):781–90.
6271. Draelos ZD. Active agents in common skin care products. *Plast Reconstr Surg*. 2010;125(2):719–24.
6272. Neill US. Skin care in the aging female: myths and truths. *J Clin Invest*. 2012;122(2):473–7.

6273. Lupo MP, Cole AL. Cosmeceutical peptides. *Dermatol Ther*. 2007;20(5):343–9.
6274. Sunder S. Relevant topical skin care products for prevention and treatment of aging skin. *Facial Plast Surg Clin North Am*. 2019;27(3):413–8.
6275. Ramos-e-Silva M, Celem LR, Ramos-e-Silva S, Fucci-da-Costa AP. Anti-aging cosmetics: facts and controversies. *Clin Dermatol*. 2013;31(6):750–8.
6276. Zussman J, Ahdout J, Kim J. Vitamins and photoaging: do scientific data support their use? *J Am Acad Dermatol*. 2010;63(3):507–25.
6277. Darlenski R, Surber C, Fluhr JW. Topical retinoids in the management of photodamaged skin: from theory to evidence-based practical approach. *Br J Dermatol*. 2010;163(6):1157–65.
6278. Elmets CA. Long term topical tretinoin and excess mortality in older patients. NEJM Journal Watch. https://www.jwatch.org/jd200901300000001/2009/01/30/long-term-topical-tretinoin-and-excess-mortality. Published January 20, 2009. Accessed August 31, 2022.
6279. Imhof L, Leuthard D. Topical over-the-counter antiaging agents: an update and systematic review. *Dermatology*. 2021;237(2):217–29.
6280. Tran D, Townley JP, Barnes TM, Greive KA. An antiaging skin care system containing alpha hydroxy acids and vitamins improves the biomechanical parameters of facial skin. *Clin Cosmet Investig Dermatol*. 2015;8:9–17.
6281. Bilal M, Iqbal HMN. An insight into toxicity and human-health-related adverse consequences of cosmeceuticals—a review. *Sci Total Environ*. 2019;670:555–68.
6282. Neill US. Skin care in the aging female: myths and truths. *J Clin Invest*. 2012;122(2):473–7.
6283. Bissett DL, Miyamoto K, Sun P, Li J, Berge CA. Topical niacinamide reduces yellowing, wrinkling, red blotchiness, and hyperpigmented spots in aging facial skin. *Int J Cosmet Sci*. 2004;26(5):231–8.
6284. Levin J, Del Rosso JQ, Momin SB. How much do we really know about our favorite cosmeceutical ingredients? *J Clin Aesthet Dermatol*. 2010;3(2):22–41.

6285. Imhof L, Leuthard D. Topical over-the-counter antiaging agents: an update and systematic review. *Dermatology*. 2021;237(2):217–29.
6286. Sivamani RK, Jagdeo JR, Elsner P, Maibach HI, eds. *Cosmeceuticals and Active Cosmetics*. 3rd ed. CRC Press; 2016.
6287. Bissett DL, Miyamoto K, Sun P, Li J, Berge CA. Topical niacinamide reduces yellowing, wrinkling, red blotchiness, and hyperpigmented spots in aging facial skin. *Int J Cosmet Sci*. 2004;26(5):231–8.
6288. Hunt KJ, Hung SK, Ernst E. Botanical extracts as anti-aging preparations for the skin: a systematic review. *Drugs Aging*. 2010;27(12):973–85.
6289. Bissett DL, Miyamoto K, Sun P, Li J, Berge CA. Topical niacinamide reduces yellowing, wrinkling, red blotchiness, and hyperpigmented spots in aging facial skin. *Int J Cosmet Sci*. 2004;26(5):231–8.
6290. Bissett DL, Oblong JE, Berge CA. Niacinamide: A B vitamin that improves aging facial skin appearance. *Dermatol Surg*. 2005;31(7 Pt 2):860–5; discussion 865.
6291. Bissett DL, Oblong JE, Berge CA. Niacinamide: A B vitamin that improves aging facial skin appearance. *Dermatol Surg*. 2005;31(7 Pt 2):860–5.
6292. Zussman J, Ahdout J, Kim J. Vitamins and photoaging: do scientific data support their use? *J Am Acad Dermatol*. 2010;63(3):507–25.
6293. Chiu P-C, Chan C-C, Lin H-M, Chiu H-C. The clinical anti-aging effects of topical kinetin and niacinamide in Asians: a randomized, double-blind, placebo-controlled, split-face comparative trial. *J Cosmet Dermatol*. 2007;6(4):243–9.
6294. Kawada A, Konishi N, Oiso N, Kawara S, Date A. Evaluation of anti-wrinkle effects of a novel cosmetic containing niacinamide. *J Dermatol*. 2008;35(10):637–42.
6295. Burke KE, Clive J, Combs GF, Commisso J, Keen CL, Nakamura RM. Effects of topical and oral vitamin E on pigmentation and skin cancer induced by ultraviolet irradiation in Skh:2 hairless mice. *Nutr Cancer*. 2000;38(1):87–97.
6296. Sunder S. Relevant topical skin care products for prevention and treatment of aging skin. *Facial Plast Surg Clin North Am*. 2019;27(3):413–8.

6297. Imhof L, Leuthard D. Topical over-the-counter antiaging agents: an update and systematic review. *Dermatology*. 2021;237(2):217–29.
6298. Inui M, Ooe M, Fujii K, Matsunaka H, Yoshida M, Ichihashi M. Mechanisms of inhibitory effects of CoQ10 on UVB-induced wrinkle formation *in vitro* and *in vivo*. *Biofactors*. 2008;32(1–4):237–43.
6299. Elsner P, Fluhr JW, Gehring W, et al. Anti-aging data and support claims—consensus statement. *J Dtsch Dermatol Ges.* 2011;9 Suppl 3:S1–32.
6300. Nusgens BV, Humbert P, Rougier A, et al. Topically applied vitamin C enhances the mRNA level of collagens I and III, their processing enzymes and tissue inhibitor of matrix metalloproteinase 1 in the human dermis. *J Invest Dermatol*. 2001;116(6):853–9.
6301. Traikovich SS. Use of topical ascorbic acid and its effects on photodamaged skin topography. *Arch Otolaryngol Head Neck Surg*. 1999;125(10):1091–8.
6302. Sivamani RK, Jagdeo JR, Elsner P, Maibach HI, eds. *Cosmeceuticals and Active Cosmetics*. 3rd ed. CRC Press; 2016.
6303. Traikovich SS. Use of topical ascorbic acid and its effects on photodamaged skin topography. *Arch Otolaryngol Head Neck Surg*. 1999;125(10):1091–8.
6304. Raschke T, Koop U, Düsing HJ, et al. Topical activity of ascorbic acid: from in vitro optimization to in vivo efficacy. *Skin Pharmacol Physiol*. 2004;17(4):200–6.
6305. Humbert PG, Haftek M, Creidi P, et al. Topical ascorbic acid on photoaged skin. Clinical, topographical and ultrastructural evaluation: double-blind study vs. placebo. *Exp Dermatol*. 2003;12(3):237–44.
6306. High potency serum. Cellex-C. https://www.cellexcusa.com/products/high-potency-serum. Accessed September 7, 2022.
6307. Sunder S. Relevant topical skin care products for prevention and treatment of aging skin. *Facial Plast Surg Clin North Am*. 2019;27(3):413–8.
6308. Huang CK, Miller TA. The truth about over-the-counter topical anti-aging products: a comprehensive review. *Aesthet Surg J*. 2007;27(4):402–12.

6309. Alpha hydroxy acids. U.S. Food & Drug Administration. https://www.fda.gov/cosmetics/cosmetic-ingredients/alpha-hydroxy-acids#q6. Updated February 25, 2022. Accessed September 7, 2022.
6310. Gordon R. Skin cancer: an overview of epidemiology and risk factors. *Semin Oncol Nurs*. 2013;29(3):160–9.
6311. Garcovich S, Colloca G, Sollena P, et al. Skin cancer epidemics in the elderly as an emerging issue in geriatric oncology. *Aging Dis*. 2017;8(5):643–61.
6312. Strauss DG, Michele TM. Skin cancer prevention and sunscreen safety: commentary on American Society of Clinical Oncology policy statement on skin cancer prevention. *JCO Oncol Pract*. 2020;16(8):436–8.
6313. Johnson MM, Leachman SA, Aspinwall LG, et al. Skin cancer screening: recommendations for data-driven screening guidelines and a review of the US Preventive Services Task Force controversy. *Melanoma Manag*. 2017;4(1):13–37.
6314. Wernli KJ, Henrikson NB, Morrison CC, Nguyen M, Pocobelli G, Blasi PR. Screening for skin cancer in adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2016;316(4):436–47.
6315. Katalinic A, Waldmann A, Weinstock MA, et al. Does skin cancer screening save lives?: an observational study comparing trends in melanoma mortality in regions with and without screening. *Cancer*. 2012;118(21):5395–402.
6316. Boniol M, Autier P, Gandini S. Melanoma mortality following skin cancer screening in Germany. *BMJ Open*. 2015;5(9):e008158.
6317. Brenner H. Mortality from malignant melanoma in an era of nationwide skin cancer screening. *Dtsch Arztebl Int*. 2015;112(38):627–8.
6318. Boniol M, Autier P, Gandini S. Melanoma mortality following skin cancer screening in Germany. *BMJ Open*. 2015;5(9):e008158.
6319. Wernli KJ, Henrikson NB, Morrison CC, Nguyen M, Pocobelli G, Blasi PR. Screening for skin cancer in adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2016;316(4):436–47.

6320. Halpern AC, Marghoob AA, Reiter O. Melanoma warning signs: what you need to know about early signs of skin cancer. Skin Cancer Foundation. https://www.skincancer.org/skin-cancer-information/melanoma/melanoma-warning-signs-and-images/. Updated January 2021. Accessed September 7, 2022.
6321. Linos E, Katz KA, Colditz GA. Skin cancer—the importance of prevention. *JAMA Intern Med*. 2016;176(10):1435–6.
6322. Burke KE, Clive J, Combs GF, Commisso J, Keen CL, Nakamura RM. Effects of topical and oral vitamin E on pigmentation and skin cancer induced by ultraviolet irradiation in Skh:2 hairless mice. *Nutr Cancer*. 2000;38(1):87–97.
6323. Stern RS, Weinstein MC, Baker SG. Risk reduction for nonmelanoma skin cancer with childhood sunscreen use. *Arch Dermatol*. 1986;122(5):537–45.
6324. Strauss DG, Michele TM. Skin cancer prevention and sunscreen safety: commentary on American Society of Clinical Oncology policy statement on skin cancer prevention. *JCO Oncol Pract*. 2020;16(8):436–8.
6325. Li H, Colantonio S, Dawson A, Lin X, Beecker J. Sunscreen application, safety, and sun protection: the evidence. *J Cutan Med Surg*. 2019;23(4):357–69.
6326. Strauss DG, Michele TM. Skin cancer prevention and sunscreen safety: commentary on American Society of Clinical Oncology policy statement on skin cancer prevention. *JCO Oncol Pract*. 2020;16(8):436–8.
6327. Li H, Colantonio S, Dawson A, Lin X, Beecker J. Sunscreen application, safety, and sun protection: the evidence. *J Cutan Med Surg*. 2019;23(4):357–69.
6328. Boo YC. Mechanistic basis and clinical evidence for the applications of nicotinamide (niacinamide) to control skin aging and pigmentation. *Antioxidants (Basel)*. 2021;10(8):1315.
6329. Surjana D, Halliday GM, Martin AJ, Moloney FJ, Damian DL. Oral nicotinamide reduces actinic keratoses in phase II double-blinded randomized controlled trials. *J Invest Dermatol*. 2012;132(5):1497–500.

6330. Chen AC, Martin AJ, Choy B, et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. *N Engl J Med*. 2015;373(17):1618–26.
6331. Byrne SN. How much sunlight is enough? *Photochem Photobiol Sci*. 2014;13(6):840–52.
6332. Tsai J, Chien AL. Photoprotection for skin of color. *Am J Clin Dermatol*. 2022;23(2):195–205.
6333. Strauss DG, Michele TM. Skin cancer prevention and sunscreen safety: commentary on American Society of Clinical Oncology policy statement on skin cancer prevention. *JCO Oncol Pract*. 2020;16(8):436–8.
6334. Purdue MP, Beane Freeman LE, Anderson WF, Tucker MA. Recent trends in incidence of cutaneous melanoma among US Caucasian young adults. *J Invest Dermatol*. 2008;128(12):2905–8.
6335. Boniol M, Autier P, Boyle P, Gandini S. Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. *BMJ*. 2012;345:e4757.
6336. Weinstock MA, Moses AM. Skin cancer meets vitamin D: the way forward for dermatology and public health. *J Am Acad Dermatol*. 2009;61(4):720–4.
6337. Dahl MV. Sun exposure, vitamin D metabolism, and skin cancer. *Mayo Clin Proc*. 2004;79(5):699–700.
6338. Grant WB, Garland CF, Holick MF. Comparisons of estimated economic burdens due to insufficient solar ultraviolet irradiance and vitamin D and excess solar UV irradiance for the United States. *Photochem Photobiol*. 2005;81(6):1276–86.
6339. Grant WB. In defense of the sun: an estimate of changes in mortality rates in the United States if mean serum 25-hydroxyvitamin D levels were raised to 45 ng/mL by solar ultraviolet-B irradiance. *Dermatoendocrinol*. 2009;1(4):207–14.
6340. Dahl MV. Sun exposure, vitamin D metabolism, and skin cancer. *Mayo Clin Proc*. 2004;79(5):699–700.
6341. Gilchrest BA. Sun protection and vitamin D: three dimensions of obfuscation. *J Steroid Biochem Mol Biol*. 2007;103(3–5):655–63.
6342. Citrin DL, Bloom DL, Grutsch JF, Mortensen SJ, Lis CG. Beliefs and perceptions of women with newly diagnosed breast cancer who

refused conventional treatment in favor of alternative therapies. *Oncologist*. 2012;17(5):607–12.
6343. Li H, Colantonio S, Dawson A, Lin X, Beecker J. Sunscreen application, safety, and sun protection: the evidence. *J Cutan Med Surg*. 2019;23(4):357–69.
6344. Phillips TJ, Bhawan J, Yaar M, Bello Y, Lopiccolo D, Nash JF. Effect of daily versus intermittent sunscreen application on solar simulated UV radiation-induced skin response in humans. *J Am Acad Dermatol*. 2000;43(4):610–8.
6345. Krutmann J, Berking C, Berneburg M, Diepgen TL, Dirschka T, Szeimies M. New strategies in the prevention of actinic keratosis: a critical review. *Skin Pharmacol Physiol*. 2015;28(6):281–9.
6346. Krutmann J, Berking C, Berneburg M, Diepgen TL, Dirschka T, Szeimies M. New strategies in the prevention of actinic keratosis: a critical review. *Skin Pharmacol Physiol*. 2015;28(6):281–9.
6347. Ramos-e-Silva M, Celem LR, Ramos-e-Silva S, Fucci-da-Costa AP. Anti-aging cosmetics: facts and controversies. *Clin Dermatol*. 2013;31(6):750–8.
6348. Buller DB, Andersen PA, Walkosz BJ, et al. Compliance with sunscreen advice in a survey of adults engaged in outdoor winter recreation at high-elevation ski areas. *J Am Acad Dermatol*. 2012;66(1):63–70.
6349. Isedeh P, Osterwalder U, Lim HW. Teaspoon rule revisited: proper amount of sunscreen application: Letter to the Editor. *Photodermatol Photoimmunol Photomed*. 2013;29(1):55–6.
6350. Li H, Colantonio S, Dawson A, Lin X, Beecker J. Sunscreen application, safety, and sun protection: the evidence. *J Cutan Med Surg*. 2019;23(4):357–69.
6351. Kligman LH, Akin FJ, Kligman AM. Sunscreens prevent ultraviolet photocarcinogenesis. *J Am Acad Dermatol*. 1980;3(1):30–5.
6352. Calbó J, Pagès D, González JA. Empirical studies of cloud effects on UV radiation: a review. *Rev Geophys*. 2005;43(2).
6353. de Gálvez MV, Aguilera J, Buendía EA, Sánchez-Roldán C, Herrera-Ceballos E. Time required for a standard sunscreen to become effective following application: a UV photography study. *J Eur Acad Dermatol Venereol*. 2018;32(4):e123–4.

6354. Stokes RP, Diffey BL. The water resistance of sunscreen and day-care products. *Br J Dermatol*. 1999;140(2):259–63.
6355. Stokes RP, Diffey BL. A novel *ex vivo* technique to assess the sand/rub resistance of sunscreen products. *Int J Cosmet Sci*. 2000;22(5):329–34.
6356. Tsai J, Chien AL. Photoprotection for skin of color. *Am J Clin Dermatol*. 2022;23(2):195–205.
6357. Kaidbey KH, Agin PP, Sayre RM, Kligman AM. Photoprotection by melanin—a comparison of black and Caucasian skin. *J Am Acad Dermatol*. 1979;1(3):249–60.
6358. Sander M, Sander M, Burbidge T, Beecker J. The efficacy and safety of sunscreen use for the prevention of skin cancer. *CMAJ*. 2020;192(50):E1802–8.
6359. National Cancer Institute. Sun-protective behavior. Cancer Trends Progress Report. https://progressreport.cancer.gov/prevention/sun_protection. Updated April 2022. Accessed Nov 19, 2022.
6360. Tsai J, Chien AL. Photoprotection for skin of color. *Am J Clin Dermatol*. 2022;23(2):195–205.
6361. Taylor SC, Alexis AF, Armstrong AW, Chiesa Fuxench ZC, Lim HW. Misconceptions of photoprotection in skin of color. *J Am Acad Dermatol*. 2022;86(3S):S9–17.
6362. Tsai J, Chien AL. Photoprotection for skin of color. *Am J Clin Dermatol*. 2022;23(2):195–205.
6363. Sander M, Sander M, Burbidge T, Beecker J. The efficacy and safety of sunscreen use for the prevention of skin cancer. *CMAJ*. 2020;192(50):E1802–8.
6364. Barr J. Spray-on sunscreens need a good rub. *J Am Acad Dermatol*. 2005;52(1):180–1.
6365. Sander M, Sander M, Burbidge T, Beecker J. The efficacy and safety of sunscreen use for the prevention of skin cancer. *CMAJ*. 2020;192(50):E1802–8.
6366. Pearce K, Goldsmith WT, Greenwald R, Yang C, Mainelis G, Wright C. Characterization of an aerosol generation system to assess inhalation risks of aerosolized nano-enabled consumer products. *Inhal Toxicol*. 2019;31(9–10):357–67.

6367. Food and Drug Administration, Department of Health and Human Services. 21 CFR parts 201, 310, 347, and 352. Sunscreen drug products for over-the-counter human use. *Federal Register*. 2019;84(38):6205–75.
6368. Black HS, Lenger WA, Gerguis J, Thornby JI. Relation of antioxidants and level of dietary lipid to epidermal lipid peroxidation and ultraviolet carcinogenesis. *Cancer Res*. 1985;45(12 Pt 1):6254–9.
6369. Ibiebele TI, van der Pols JC, Hughes MC, Marks GC, Williams GM, Green AC. Dietary pattern in association with squamous cell carcinoma of the skin: a prospective study. *Am J Clin Nutr*. 2007;85(5):1401–8.
6370. Black HS, Thornby JI, Wolf JE Jr, et al. Evidence that a low-fat diet reduces the occurrence of non-melanoma skin cancer. *Int J Cancer*. 1995;62(2):165–9.
6371. Lumley E, Phillips P, Aber A, Buckley-Woods H, Jones GL, Michaels JA. Experiences of living with varicose veins: a systematic review of qualitative research. *J Clin Nurs*. 2019;28(7–8):1085–99.
6372. Meissner MH. What is the medical rationale for the treatment of varicose veins? *Phlebology*. 2012;27(Suppl 1):27–33.
6373. Raetz J, Wilson M, Collins K. Varicose veins: diagnosis and treatment. *Am Fam Physician*. 2019;99(11):682–8.
6374. Atik D, Atik C, Karatepe C. The effect of external apple vinegar application on varicosity symptoms, pain, and social appearance anxiety: a randomized controlled trial. *Evid Based Complement Alternat Med*. 2016;2016:6473678.
6375. Montgomery L, Seys J, Mees J. To pee, or not to pee: a review on envenomation and treatment in European jellyfish species. *Mar Drugs*. 2016;14(7):127.
6376. Wilcox CL, Headlam JL, Doyle TK, Yanagihara AA. Assessing the efficacy of first-aid measures in *Physalia* sp. Envenomation, using solution- and blood agarose-based models. *Toxins (Basel)*. 2017;9(5):149.
6377. Luu LA, Flowers RH, Kellams AL, et al. Apple cider vinegar soaks [0.5%] as a treatment for atopic dermatitis do not improve skin barrier integrity. *Pediatr Dermatol*. 2019;36(5):634–9.

6378. Feldstein S, Afshar M, Krakowski AC. Chemical burn from vinegar following an internet-based protocol for self-removal of nevi. *J Clin Aesthet Dermatol*. 2015;8(6):50.
6379. Kroeger CM, Brown AW, Allison DB. Differences in Nominal Significance (DINS) Error leads to invalid conclusions: letter regarding, “Diet enriched with fresh coconut decreases blood glucose levels and body weight in normal adults.” *J Complement Integr Med*. 2019;16(2):/j/jcim.2019.16.issue-2/jcim-2018–0037/jcim-2018–0037.xml.
6380. Richardson JB, Dixon M. Varicose veins in tropical Africa. *Lancet*. 1977;1(8015):791–2.
6381. O’Keefe SJD, Chung D, Mahmoud N, et al. Why do African Americans get more colon cancer than Native Africans? *J Nutr*. 2007;137(1 Suppl):175S-82S.
6382. Tuohy KM, Gougoulias C, Shen Q, Walton G, Fava F, Ramnani P. Studying the human gut microbiota in the trans-omics era—focus on metagenomics and metabonomics. *Curr Pharm Des*. 2009;15(13):1415–27.
6383. Burkitt DP. Two blind spots in medical knowledge. *Nurs Times*. 1976;72(1):24–7.
6384. Crowe FL, Appleby PN, Allen NE, Key TJ. Diet and risk of diverticular disease in Oxford cohort of European Prospective Investigation into Cancer and Nutrition (EPIC): prospective study of British vegetarians and non-vegetarians. *BMJ*. 2011;343:d4131.
6385. Knutsen SF. Lifestyle and the use of health services. *Am J Clin Nutr*. 1994;59(5 Suppl):1171S-5S.
6386. Eddy TP, Taylor GF. Sublingual varicosities and vitamin C in elderly vegetarians. *Age Ageing*. 1977;6(1):6–13.
6387. Reinecke JK, Hinshaw MA. Nail health in women. *Int J Womens Dermatol*. 2020;6(2):73–9.
6388. Halteh P, Scher RK, Lipner SR. Over-the-counter and natural remedies for onychomycosis: do they really work? *Cutis*. 2016;98(5):E16–25.
6389. Halteh P, Scher RK, Lipner SR. Over-the-counter and natural remedies for onychomycosis: do they really work? *Cutis*. 2016;98(5):E16–25.

6390. Murdan S. Nail disorders in older people, and aspects of their pharmaceutical treatment. *Int J Pharm*. 2016;512(2):405–11.
6391. Iorizzo M. Tips to treat the 5 most common nail disorders: brittle nails, onycholysis, paronychia, psoriasis, onychomycosis. *Dermatol Clin*. 2015;33(2):175–83.
6392. Maddy AJ, Tosti A. Hair and nail diseases in the mature patient. *Clin Dermatol*. 2018;36(2):159–66.
6393. Iorizzo M. Tips to treat the 5 most common nail disorders: brittle nails, onycholysis, paronychia, psoriasis, onychomycosis. *Dermatol Clin*. 2015;33(2):175–83.
6394. Murdan S. Nail disorders in older people, and aspects of their pharmaceutical treatment. *Int J Pharm*. 2016;512(2):405–11.
6395. Gupta AK, Konnikov N, Lynde CW. Single-blind, randomized, prospective study on terbinafine and itraconazole for treatment of dermatophyte toenail onychomycosis in the elderly. *J Am Acad Dermatol*. 2001;44(3):479–84.
6396. Murdan S. Nail disorders in older people, and aspects of their pharmaceutical treatment. *Int J Pharm*. 2016;512(2):405–11.
6397. Gupta AK, Daigle D, Foley KA. Network meta-analysis of onychomycosis treatments. *Skin Appendage Disord*. 2015;1(2):74–81.
6398. Murdan S. Nail disorders in older people, and aspects of their pharmaceutical treatment. *Int J Pharm*. 2016;512(2):405–11.
6399. Iorizzo M. Tips to treat the 5 most common nail disorders: brittle nails, onycholysis, paronychia, psoriasis, onychomycosis. *Dermatol Clin*. 2015;33(2):175–83.
6400. Murdan S. Nail disorders in older people, and aspects of their pharmaceutical treatment. *Int J Pharm*. 2016;512(2):405–11.
6401. Sleven R, Lanckacker E, Delputte P, Maes L, Cos P. Evaluation of topical antifungal products in an *in vitro* onychomycosis model. *Mycoses*. 2016;59(5):327–30.
6402. Kelly S, Liu D, Wang T, Rajpara A, Franano C, Aires D. Vinegar sock soak for tinea pedis or onychomycosis. *J Am Acad Dermato*l. Published online September 22, 2017:S0190–9622(17)32448–9.
6403. Satchell AC, Saurajen A, Bell C, Barnetson RSC. Treatment of dandruff with 5% tea tree oil shampoo. *J Am Acad Dermatol*.

2002;47(6):852–5.
6404. Satchell AC, Saurajen A, Bell C, Barnetson RSC. Treatment of interdigital tinea pedis with 25% and 50% tea tree oil solution: a randomized, placebo-controlled, blinded study. *Australas J Dermatol*. 2002;43(3):175–8.
6405. Buck DS, Nidorf DM, Addino JG. Comparison of two topical preparations for the treatment of onychomycosis: *Melaleuca alternifolia* (tea tree) oil and clotrimazole. *J Fam Pract*. 1994;38(6):601–5.
6406. Murdan S. Nail disorders in older people, and aspects of their pharmaceutical treatment. *Int J Pharm*. 2016;512(2):405–11.
6407. Maddy AJ, Tosti A. Hair and nail diseases in the mature patient. *Clin Dermatol*. 2018;36(2):159–66.
6408. Ingrown toenails. American Academy of Family Physicians. https://www.aafp.org/dam/brand/aafp/pubs/afp/issues/2019/0801/p158-s1.pdf. Updated August 2019. Accessed September 1, 2022.
6409. Reinecke JK, Hinshaw MA. Nail health in women. *Int J Womens Dermatol*. 2020;6(2):73–9.
6410. Ilfeld FW. Ingrown toenail treated with cotton collodion insert. *Foot Ankle*. 1991;11(5):312–3.
6411. Ingrown toenails. American Academy of Family Physicians. https://www.aafp.org/dam/brand/aafp/pubs/afp/issues/2019/0801/p158-s1.pdf. Updated August 2019. Accessed September 1, 2022.
6412. Ingrown toenails. American Academy of Family Physicians. https://www.aafp.org/dam/brand/aafp/pubs/afp/issues/2019/0801/p158-s1.pdf. Updated August 2019. Accessed September 1, 2022.
6413. Ilfeld FW. Ingrown toenail treated with cotton collodion insert. *Foot Ankle*. 1991;11(5):312–3.
6414. Gutiérrez-Mendoza D, De Anda-Juárez M, Ávalos VF, Martínez GR, Domínguez-Cherit J. “Cotton nail cast”: a simple solution for mild and painful lateral and distal nail embedding. *Dermatol Surg*. 2015;41(3):411–4.
6415. Reinecke JK, Hinshaw MA. Nail health in women. *Int J Womens Dermatol*. 2020;6(2):73–9.
6416. Maddy AJ, Tosti A. Hair and nail diseases in the mature patient. *Clin Dermatol*. 2018;36(2):159–66.

6417. Klafke GB, da Silva RA, de Pellegrin KT, Xavier MO. Analysis of the role of nail polish in the transmission of onychomycosis. *An Bras Dermatol*. 2018;93:930–1.
6418. Shemer A, Trau H, Davidovici B, Grunwald MH, Amichai B. Onycomycosis due to artificial nails. *J Eur Acad Dermatol Venereol*. 2008;22(8):998–1000.
6419. Kechijian P. Dangers of acrylic fingernails. *JAMA*.1990;263(3):458
6420. Dimitris R, Ralph D. Management of simple brittle nails. *Dermatol Ther*. 2012;25(6):569–73.
6421. Buck DS, Nidorf DM, Addino JG. Comparison of two topical preparations for the treatment of onychomycosis: *Melaleuca alternifolia* (tea tree) oil and clotrimazole. *J Fam Pract*. 1994;38(6):601–5.
6422. Kuo PT, Whereat AF, Horwitz O. The effect of lipemia upon coronary and peripheral arterial circulation in patients with essential hyperlipemia. *Am J Med*. 1959;26(1):68–75.
6423. Reinecke JK, Hinshaw MA. Nail health in women. *Int J Womens Dermatol*. 2020;6(2):73–9.
6424. Reinecke JK, Hinshaw MA. Nail health in women. *Int J Womens Dermatol*. 2020;6(2):73–9.
6425. Nail care products. U.S. Food & Drug Administration. https://www.fda.gov/cosmetics/cosmetic-products/nail-care-products#forma. Published February 25, 2022. Accessed September 7, 2022.
6426. Reinecke JK, Hinshaw MA. Nail health in women. *Int J Womens Dermatol*. 2020;6(2):73–9.
6427. van de Kerkhof PCM, Pasch MC, Scher RK, et al. Brittle nail syndrome: a pathogenesis-based approach with a proposed grading system. *J Am Acad Dermatol*. 2005;53(4):644–51.
6428. Reinecke JK, Hinshaw MA. Nail health in women. *Int J Womens Dermatol*. 2020;6(2):73–9.
6429. Cashman MW, Sloan SB. Nutrition and nail disease. *Clin Dermatol*. 2010;28(4):420–5.
6430. Maddy AJ, Tosti A. Hair and nail diseases in the mature patient. *Clin Dermatol*. 2018;36(2):159–66.

6431. Reinecke JK, Hinshaw MA. Nail health in women. *Int J Womens Dermatol*. 2020;6(2):73–9.
6432. Stern DK, Diamantis S, Smith E, et al. Water content and other aspects of brittle versus normal fingernails. *J Am Acad Dermatol*. 2007;57(1):31–6.
6433. Stern DK, Diamantis S, Smith E, et al. Water content and other aspects of brittle versus normal fingernails. *J Am Acad Dermatol*. 2007;57(1):31–6.
6434. Dimitris R, Ralph D. Management of simple brittle nails. *Dermatol Ther*. 2012;25(6):569–73.
6435. Stern DK, Diamantis S, Smith E, et al. Water content and other aspects of brittle versus normal fingernails. *J Am Acad Dermatol*. 2007;57(1):31–6.
6436. Dimitris R, Ralph D. Management of simple brittle nails. *Dermatol Ther*. 2012;25(6):569–73.
6437. Yousif J, Farshchian M, Potts GA. Oral nail growth supplements: a comprehensive review. *Int J Dermatol*. 2022;61(8):916–22.
6438. Lipner SR, Scher RK. Biotin for the treatment of nail disease: what is the evidence? *J Dermatolog Treat*. 2018;29(4):411–4.
6439. Reinecke JK, Hinshaw MA. Nail health in women. *Int J Womens Dermatol*. 2020;6(2):73–9.
6440. Patel DP, Swink SM, Castelo-Soccio L. A review of the use of biotin for hair loss. *Skin Appendage Disord*. 2017;3(3):166–9.
6441. Reilly JD, Cottrell DF, Martin RJ, Cuddeford DJ. Effect of supplementary dietary biotin on hoof growth and hoof growth rate in ponies: a controlled trial. *Equine Vet J Suppl*. 1998;(26):51–7.
6442. Floersheim GL. [Treatment of brittle fingernails with biotin]. *Z Hautkr*. 1989;64(1):41–8.
6443. Colombo VE, Gerber F, Bronhofer M, Floersheim GL. Treatment of brittle fingernails and onychoschizia with biotin: scanning electron microscopy. *J Am Acad Dermatol*. 1990;23(6 Pt 1):1127–32.
6444. Chiavetta A, Mazzurco S, Secolo MP, Tomarchio G, Milani M. Treatment of brittle nail with a hydroxypropyl chitosan-based lacquer, alone or in combination with oral biotin: a randomized, assessor-blinded trial. *Dermatol Ther*. 2019;32(5):e13028.

6445. Bowen R, Benavides R, Colón-Franco JM, et al. Best practices in mitigating the risk of biotin interference with laboratory testing. *Clin Biochem*. 2019;74:1–11.
6446. Lipner SR. Update on biotin therapy in dermatology: time for a change. *J Drugs Dermatol*. 2020;19(12):1264–5.
6447. John JJ, Cooley V, Lipner SR. Assessment of biotin supplementation among patients in an outpatient dermatology clinic. *J Am Acad Dermatol*. 2019;81(2):620–1.
6448. Waqas B, Wu A, Yim E, Lipner SR. A survey-based study of physician practices regarding biotin supplementation. *J Dermatolog Treat*. 2022;33(1):573–4.
6449. Reinecke JK, Hinshaw MA. Nail health in women. *Int J Womens Dermatol*. 2020;6(2):73–9.
6450. Yousif J, Farshchian M, Potts GA. Oral nail growth supplements: a comprehensive review. *Int J Dermatol*. 2022;61(8):916–22.
6451. Eke PI, Dye BA, Wei L, et al. Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. *J Periodontol*. 2015;86(5):611–22.
6452. Nascimento GG, Leite FRM, Conceição DA, Ferrúa CP, Singh A, Demarco FF. Is there a relationship between obesity and tooth loss and edentulism? A systematic review and meta-analysis. *Obes Rev*. 2016;17(7):587–98.
6453. Kotronia E, Brown H, Papacosta AO, et al. Poor oral health and the association with diet quality and intake in older people in two studies in the UK and USA. *Br J Nutr*. 2021;126(1):118–30.
6454. Antoniadou M, Varzakas T. Breaking the vicious circle of diet, malnutrition and oral health for the independent elderly. *Crit Rev Food Sci Nutr*. 2021;61(19):3233–55.
6455. Gaewkhiew P, Sabbah W, Bernabé E. Does tooth loss affect dietary intake and nutritional status? A systematic review of longitudinal studies. *J Dent*. 2017;67:1–8.
6456. Romandini M, Baima G, Antonoglou G, Bueno J, Figuero E, Sanz M. Periodontitis, edentulism, and risk of mortality: a systematic review with meta-analyses. *J Dent Res*. 2021;100(1):37–49.
6457. Liljestrand JM, Havulinna AS, Paju S, Männistö S, Salomaa V, Pussinen PJ. Missing teeth predict incident cardiovascular events,

diabetes, and death. *J Dent Res*. 2015;94(8):1055–62.
6458. Friedman PK, Lamster IB. Tooth loss as a predictor of shortened longevity: exploring the hypothesis. *Periodontol 2000*. 2016;72(1):142–52.
6459. Kaufman LB, Setiono TK, Doros G, et al. An oral health study of centenarians and children of centenarians. *J Am Geriatr Soc*. 2014;62(6):1168–73.
6460. Liljestrand JM, Havulinna AS, Paju S, Männistö S, Salomaa V, Pussinen PJ. Missing teeth predict incident cardiovascular events, diabetes, and death. *J Dent Res*. 2015;94(8):1055–62.
6461. Romandini M, Baima G, Antonoglou G, Bueno J, Figuero E, Sanz M. Periodontitis, edentulism, and risk of mortality: a systematic review with meta-analyses. *J Dent Res*. 2021;100(1):37–49.
6462. Liljestrand JM, Havulinna AS, Paju S, Männistö S, Salomaa V, Pussinen PJ. Missing teeth predict incident cardiovascular events, diabetes, and death. *J Dent Res*. 2015;94(8):1055–62.
6463. Kellesarian SV, Kellesarian TV, Ros Malignaggi V, et al. Association between periodontal disease and erectile dysfunction: a systematic review. *Am J Mens Health*. 2018;12(2):338–46.
6464. Nascimento PC, Castro MML, Magno MB, et al. Association between periodontitis and cognitive impairment in adults: a systematic review. *Front Neurol*. 2019;10:323.
6465. Fang WL, Jiang MJ, Gu BB, et al. Tooth loss as a risk factor for dementia: systematic review and meta-analysis of 21 observational studies. *BMC Psychiatry*. 2018;18(1):345.
6466. Weijenberg RAF, Delwel S, Ho BV, van der Maarel-Wierink CD, Lobbezoo F. Mind your teeth—the relationship between mastication and cognition. *Gerodontology*. 2019;36(1):2–7.
6467. Chen J, Ren CJ, Wu L, et al. Tooth loss is associated with increased risk of dementia and with a dose-response relationship. *Front Aging Neurosci*. 2018;10:415.
6468. De Cicco V, Barresi M, Tramonti Fantozzi MP, Cataldo E, Parisi V, Manzoni D. Oral implant-prostheses: new teeth for a brighter brain. *PLoS One*. 2016;11(2):e0148715.
6469. Banu R F, Veeravalli PT, Kumar V A. Comparative evaluation of changes in brain activity and cognitive function of edentulous

patients, with dentures and two-implant supported mandibular overdenture-pilot study. *Clin Implant Dent Relat Res*. 2016;18(3):580–7.

6470. Awadalla HI, Ragab MH, Bassuoni MW, Fayed MT, Abbas MO. A pilot study of the role of green tea use on oral health. *Int J Dent Hyg*. 2011;9(2):110–6.

6471. Balappanavar AY, Sardana V, Singh M. Comparison of the effectiveness of 0.5% tea, 2% neem and 0.2% chlorhexidine mouthwashes on oral health: a randomized control trial. *Indian J Dent Res*. 2013;24(1):26–34.

6472. Hasan S, Danishuddin M, Adil M, Singh K, Verma PK, Khan AU. Efficacy of *E. officinalis* on the cariogenic properties of *Streptococcus mutans*: a novel and alternative approach to suppress quorum-sensing mechanism. *PLoS One*. 2012;7(7):e40319.

6473. Stoy PJ. Dental disease and civilization. *Ulster Med J*. 1951;20(2):144–58.

6474. Marcenes W, Kassebaum NJ, Bernabé E, et al. Global burden of oral conditions in 1990–2010: a systematic analysis. *J Dent Res*. 2013;92(7):592–7.

6475. Sheiham A, James WPT. Diet and dental caries: the pivotal role of free sugars reemphasized. *J Dent Res*. 2015;94(10):1341–7.

6476. Kearns CE, Apollonio D, Glantz SA. Sugar industry sponsorship of germ-free rodent studies linking sucrose to hyperlipidemia and cancer: an historical analysis of internal documents. *PLoS Biol*. 2017;15(11):e2003460.

6477. Harris JL, Schwartz MB, Brownell KD, et al. Cereal FACTS 2012: limited progress in the nutrition quality and marketing of children's cereals. Yale Rudd Center for Food Policy & Obesity; 2012.

6478. Policy statement on beverage vending machines in schools. American Academy of Pediatric Dentists. https://www.aapd.org/assets/news/upload/2002/118.pdf. Published May 2022. Accessed September 10, 2022.

6479. Jacobson MF. Lifting the veil of secrecy: corporate support for health and environmental professional associations, charities, and industry front groups. Center for Science in the Public Interest.

https://www.cspinet.org/sites/default/files/attachment/lift_the_veil_intro.pdf. Published June 2003. Accessed September 10, 2022.

6480. AAPD leadership perspective on the AAPD Foundation's collaboration with the Coca-Cola Foundation. American Academy of Pediatric Dentists. https://www.aapd.org/globalassets/assets/news/upload/2003/197.pdf. Accessed September 10, 2022.

6481. Jacobson MF. Lifting the veil of secrecy: corporate support for health and environmental professional associations, charities, and industry front groups. Center for Science in the Public Interest. https://www.cspinet.org/sites/default/files/attachment/lift_the_veil_intro.pdf. Published June 2003. Accessed September 10, 2022.

6482. Sheiham A, James WPT. A reappraisal of the quantitative relationship between sugar intake and dental caries: the need for new criteria for developing goals for sugar intake. *BMC Public Health*. 2014;14(1):863.

6483. Gibson SA. Breakfast cereal consumption in young children: associations with non-milk extrinsic sugars and caries experience: further analysis of data from the UK National Diet and Nutrition Survey of children aged 1.5–4.5 years. *Public Health Nutr*. 2000;3(2):227–32.

6484. Curzon MEJ. Dietary carbohydrate and dental caries. In: Dobbing J, ed. *A Balanced Diet?*. Springer London, 1988: 57–75.

6485. Cottrell RC. Letter to the editor, "Effect on caries of restricting sugars intake: systematic review to inform WHO guidelines." *J Dent Res*. 2014;93(5):530.

6486. Redberg RF. Cancer risks and radiation exposure from computed tomographic scans: how can we be sure that the benefits outweigh the risks? *Arch Intern Med*. 2009;169(22):2049–50.

6487. Memon A, Rogers I, Paudyal P, Sundin J. Dental x-rays and the risk of thyroid cancer and meningioma: a systematic review and meta-analysis of current epidemiological evidence. *Thyroid*. 2019;29(11):1572–93.

6488. Food and Drug Administration. Dental radiography: doses and film speed. https://www.fda.gov/radiation-emitting-products/nationwide-

evaluation-x-ray-trendsnext/dental-radiography-doses-and-film-speed. Updated December 2, 2017. Accessed January 12, 2023.
6489. Memon A, Rogers I, Paudyal P, Sundin J. Dental x-rays and the risk of thyroid cancer and meningioma: a systematic review and meta-analysis of current epidemiological evidence. *Thyroid*. 2019;29(11):1572–93.
6490. American Dental Association Council on Scientific Affairs. The use of dental radiographs: update and recommendations. *J Am Dent Assoc*. 2006;137(9):1304–12.
6491. White SC, Mallya SM. Update on the biological effects of ionizing radiation, relative dose factors and radiation hygiene. *Aust Dent J*. 2012;57 Suppl 1:2–8.
6492. Staufenbiel I, Weinspach K, Förster G, Geurtsen W, Günay H. Periodontal conditions in vegetarians: a clinical study. *Eur J Clin Nutr*. 2013;67(8):836–40.
6493. Macri E, Lifshitz F, Ramos C, et al. Atherogenic cholesterol-rich diet and periodontal disease. *Arch Oral Biol*. 2014;59(7):679–86.
6494. Kondo K, Ishikado A, Morino K, et al. A high-fiber, low-fat diet improves periodontal disease markers in high-risk subjects: a pilot study. *Nutr Res*. 2014;34(6):491–8.
6495. Laine MA, Tolvanen M, Pienihäkkinen K, et al. The effect of dietary intervention on paraffin-stimulated saliva and dental health of children participating in a randomized controlled trial. *Arch Oral Biol*. 2014;59(2):217–25.
6496. Wälti A, Lussi A, Seemann R. The effect of a chewing-intensive, high-fiber diet on oral halitosis: a clinical controlled study. *Swiss Dent J*. 2016;126(9):782–95.
6497. Sambunjak D, Nickerson JW, Poklepovic T, et al. Flossing for the management of periodontal diseases and dental caries in adults. *Cochrane Database Syst Rev*. 2011;(12):CD008829.
6498. Vernon LT, Da Silva APB, Seacat JD. In defense of flossing: part II—can we agree it's premature to claim flossing is ineffective to help prevent periodontal diseases? *J Evid Based Dent Pract*. 2017;17(3):149–58.
6499. Terézhalmy GT, Bartizek RD, Biesbrock AR. Plaque-removal efficacy of four types of dental floss. *J Periodontol*. 2008;79(2):245–

51.
6500. Mazhari F, Boskabady M, Moeintaghavi A, Habibi A. The effect of toothbrushing and flossing sequence on interdental plaque reduction and fluoride retention: a randomized controlled clinical trial. *J Periodontol*. 2018;89(7):824–32.
6501. Baumgartner S, Imfeld T, Schicht O, Rath C, Persson RE, Persson GR. The impact of the Stone Age diet on gingival conditions in the absence of oral hygiene. *J Periodontol*. 2009;80(5):759–68.
6502. Shi J, Maguer ML. Lycopene in tomatoes: chemical and physical properties affected by food processing. *Crit Rev Food Sci Nutr*. 2000;40(1):1–42.
6503. Chandra RV, Prabhuji MLV, Roopa DA, Ravirajan S, Kishore HC. Efficacy of lycopene in the treatment of gingivitis: a randomised, placebo-controlled clinical trial. *Oral Health Prev Dent*. 2007;5(4):327–36.
6504. Arora N, Avula H, Avula JK. The adjunctive use of systemic antioxidant therapy (lycopene) in nonsurgical treatment of chronic periodontitis: a short-term evaluation. *Quintessence Int*. 2013;44(6):395–405.
6505. Belludi SA, Verma S, Banthia R, et al. Effect of lycopene in the treatment of periodontal disease: a clinical study. *J Contemp Dent Pract*. 2013;14(6):1054–9.
6506. Benjamin N, Pattullo S, Weller R, Smith L, Ormerod A. Wound licking and nitric oxide. *Lancet*. 1997;349(9067):1776.
6507. Jockel-Schneider Y, Goßner SK, Petersen N, et al. Stimulation of the nitrate-nitrite-NO-metabolism by repeated lettuce juice consumption decreases gingival inflammation in periodontal recall patients: a randomized, double-blinded, placebo-controlled clinical trial. *J Clin Periodontol*. 2016;43(7):603–8.
6508. Burnett CL, Bergfeld WF, Belsito DV, et al. Final report on the safety assessment of *Cocos nucifera* (coconut) oil and related ingredients. *Int J Toxicol*. 2011;30(3 Suppl):5S-16S.
6509. Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. *Circulation.* 2017;136(3):e1–23.

6510. Freeman AM, Morris PB, Barnard N, et al. Trending cardiovascular nutrition controversies. *J Am Coll Cardiol*. 2017;69(9):1172–87.
6511. Emissions of volatile aldehydes from heated cooking oils. *Food Chem*. 2010;120(1):59–65.
6512. Bekeleski GM, McCombs G, Melvin W. Oil pulling: an ancient practice for a modern time. *J Int Oral Health*. 2012;4(3):1–10.
6513. Shanbhag VKL. Oil pulling for maintaining oral hygiene—a review. *J Tradit Complement Med*. 2017;7(1):106–9.
6514. Cheema R, Sharma R, Choudhary E, Sharma S. A clinical investigation to test the efficacy of oil pulling, in reducing dentin hypersensitivity, as compared to a desensitizing tooth paste. *Int J Sci Study*. 2014;1(6):22–6.
6515. Hannig C, Wagenschwanz C, Pötschke S, et al. Effect of safflower oil on the protective properties of the in situ formed salivary pellicle. *Caries Res*. 2012;46(5):496–506.
6516. Wheater M, Friedl Z. Effect of oil pulling on tooth whitening in vitro. *J Adv Oral Res*. 2016;7(1):20–3.
6517. The practice of oil pulling. American Dental Association (ADA). https://web.archive.org/web/20140819060804/http:/www.ada.org/en/science-research/science-in-the-news/the-practice-of-oil-pulling. Published May 14, 2014. Accessed September 10, 2022.
6518. Wheater M, Friedl Z. Effect of oil pulling on tooth whitening in vitro. *J Adv Oral Res*. 2016;7(1):20–3.
6519. Smits KPJ, Listl S, Jevdjevic M. Vegetarian diet and its possible influence on dental health: a systematic literature review. *Community Dent Oral Epidemiol*. 2020;48(1):7–13.
6520. Ginter E. Vegetarian diets, chronic diseases and longevity. *Bratisl Lek Listy*. 2008;109(10):463–6.
6521. Menzel J, Jabakhanji A, Biemann R, Mai K, Abraham K, Weikert C. Systematic review and meta-analysis of the associations of vegan and vegetarian diets with inflammatory biomarkers. *Sci Rep*. 2020;10(1):21736.
6522. Hirayama T. An epidemiological study of oral and pharyngeal cancer in Central and South-East Asia. *Bull World Health Organ*. 1966;34(1):41–69.

6523. Rao DN, Ganesh B, Rao RS, Desai PB. Risk assessment of tobacco, alcohol and diet in oral cancer—a case-control study. *Int J Cancer*. 1994;58(4):469–73.
6524. Gangane N, Chawla S, Anshu, Subodh A, Gupta SS, Sharma SM. Reassessment of risk factors for oral cancer. *Asian Pac J Cancer Prev*. 2007;8(2):243–8.
6525. Mishra A. Head and neck cancer in India—review of practices for prevention policy. *Oral Dis*. 2009;15(7):454–65.
6526. Chainani-Wu N, Epstein J, Touger-Decker R. Diet and prevention of oral cancer: strategies for clinical practice. *J Am Dent Assoc*. 2011;142(2):166–9.
6527. Smits KPJ, Listl S, Jevdjevic M. Vegetarian diet and its possible influence on dental health: a systematic literature review. *Community Dent Oral Epidemiol*. 2020;48(1):7–13.
6528. Herman K, Czajczyńska-Waszkiewicz A, Kowalczyk-Zając M, Dobrzyński M. Assessment of the influence of vegetarian diet on the occurrence of erosive and abrasive cavities in hard tooth tissues. *Postepy Hig Med Dosw*. 2011;65:764–9.
6529. Chu CH, Pang KKL, Lo ECM. Dietary behavior and knowledge of dental erosion among Chinese adults. *BMC Oral Health*. 2010;10:13.
6530. Attin T, Siegel S, Buchalla W, Lennon AM, Hannig C, Becker K. Brushing abrasion of softened and remineralised dentin: an in situ study. *Caries Res*. 2004;38(1):62–6.
6531. Staufenbiel I, Adam K, Deac A, Geurtsen W, Günay H. Influence of fruit consumption and fluoride application on the prevalence of caries and erosion in vegetarians—a controlled clinical trial. *Eur J Clin Nutr*. 2015;69(10):1156–60.
6532. Walsh T, Worthington HV, Glenny AM, Marinho VC, Jeroncic A. Fluoride toothpastes of different concentrations for preventing dental caries. *Cochrane Database Syst Rev*. 2019;3:CD007868.
6533. Centers for Disease Control and Prevention (CDC). Ten great public health achievements—United States, 1900–1999. *MMWR Morb Mortal Wkly Rep*. 1999;48(12):241–3.
6534. Bellinger DC. Is fluoride potentially neurotoxic? *JAMA Pediatr*. 2019;173(10):915–7.

6535. Valdez Jiménez L, López Guzmán OD, Cervantes Flores M, et al. In utero exposure to fluoride and cognitive development delay in infants. *Neurotoxicology*. 2017;59:65–70.
6536. Needleman HL, Gatsonis CA. Low-level lead exposure and the IQ of children. A meta-analysis of modern studies. *JAMA*. 1990;263(5):673–8.
6537. Unde MP, Patil RU, Dastoor PP. The untold story of fluoridation: revisiting the changing perspectives. *Indian J Occup Environ Med*. 2018;22(3):121–7.
6538. Walchuk C, Suh M. Nutrition and the aging retina: a comprehensive review of the relationship between nutrients and their role in age-related macular degeneration and retina disease prevention. *Adv Food Nutr Res*. 2020;93:293–332.
6539. Ruan Y, Jiang S, Gericke A. Age-related macular degeneration: role of oxidative stress and blood vessels. *Int J Mol Sci*. 2021;22(3):1296.
6540. Glickman RD. Ultraviolet phototoxicity to the retina. *Eye Contact Lens*. 2011;37(4):196–205.
6541. Abokyi S, To CH, Lam TT, Tse DY. Central role of oxidative stress in age-related macular degeneration: evidence from a review of the molecular mechanisms and animal models. *Oxid Med Cell Longev*. 2020;2020:7901270.
6542. Abokyi S, To CH, Lam TT, Tse DY. Central role of oxidative stress in age-related macular degeneration: evidence from a review of the molecular mechanisms and animal models. *Oxid Med Cell Longev*. 2020;2020:7901270.
6543. Blasiak J, Glowacki S, Kauppinen A, Kaarniranta K. Mitochondrial and nuclear DNA damage and repair in age-related macular degeneration. *Int J Mol Sci*. 2013;14(2):2996–3010.
6544. Totan Y, Yağci R, Bardak Y, et al. Oxidative macromolecular damage in age-related macular degeneration. *Curr Eye Res*. 2009;34(12):1089–93.
6545. Abokyi S, To CH, Lam TT, Tse DY. Central role of oxidative stress in age-related macular degeneration: evidence from a review of the molecular mechanisms and animal models. *Oxid Med Cell Longev*. 2020;2020:7901270.

6546. Heesterbeek TJ, Lorés-Motta L, Hoyng CB, Lechanteur YTE, den Hollander AI. Risk factors for progression of age-related macular degeneration. *Ophthalmic Physiol Opt*. 2020;40(2):140–70.
6547. Sin HPY, Liu DTL, Lam DSC. Lifestyle modification, nutritional and vitamins supplements for age-related macular degeneration. *Acta Ophthalmol*. 2013;91(1):6–11.
6548. Jia YP, Sun L, Yu HS, et al. The pharmacological effects of lutein and zeaxanthin on visual disorders and cognition diseases. *Molecules*. 2017;22(4):E610.
6549. Wegner A, Khoramnia R. Cataract is a self-defence reaction to protect the retina from oxidative damage. *Med Hypotheses*. 2011;76(5):741–4.
6550. Kanter M. Lutein, zeaxanthin and eye health. Egg Nutrition Center. https://www.ee-staging.eggnutritioncenter.org/articles/lutein-zeaxanthin-and-eye-health/. Published May 16, 2022. Accessed September 15, 2022.
6551. Agricultural Research Service, United States Department of Agriculture. Kale, 113 g serving. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html#/food-details/1602525/nutrients. Published March 19, 2021. Accessed February 24, 2023.
6552. Agricultural Research Service, United States Department of Agriculture. Spinach, frozen, chopped or leaf, cooked, boiled, drained, without salt. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html#/food-details/169288/nutrients. Published April 1, 2019. Accessed February 24, 2023.
6553. Agricultural Research Service, United States Department of Agriculture. Component search: lutein + zeaxanthin (µg). FoodData Central https://fdc.nal.usda.gov/fdc-app.html#/?component=1123. Accessed January 25, 2023.
6554. Wenzel AJ, Gerweck C, Barbato D, Nicolosi RJ, Handelman GJ, Curran-Celentano J. A 12-wk egg intervention increases serum zeaxanthin and macular pigment optical density in women. *J Nutr*. 2006;136(10):2568–73.
6555. Hammond BR, Johnson EJ, Russell RM, et al. Dietary modification of human macular pigment density. *Invest Ophthalmol Vis Sci*.

1997;38(9):1795–801.
6556. Abdel-Aal ESM, Akhtar H, Zaheer K, Ali R. Dietary sources of lutein and zeaxanthin carotenoids and their role in eye health. *Nutrients*. 2013;5(4):1169–85.
6557. Eisenhauer B, Natoli S, Liew G, Flood VM. Lutein and zeaxanthin—food sources, bioavailability and dietary variety in age-related macular degeneration protection. *Nutrients*. 2017;9(2):E120.
6558. Cheng CY, Chung WY, Szeto YT, Benzie IFF. Fasting plasma zeaxanthin response to *Fructus barbarum* L. (wolfberry; kei tze) in a food-based human supplementation trial. *Br J Nutr*. 2005;93(1):123–30.
6559. Neelam K, Dey S, Sim R, Lee J, Au Eong KG. *Fructus lycii*: a natural dietary supplement for amelioration of retinal diseases. *Nutrients*. 2021;13(1):246.
6560. Unlu NZ, Bohn T, Clinton SK, Schwartz SJ. Carotenoid absorption from salad and salsa by humans is enhanced by the addition of avocado or avocado oil. *J Nutr*. 2005;135(3):431–6.
6561. Eriksen JN, Luu AY, Dragsted LO, Arrigoni E. *In vitr*o liberation of carotenoids from spinach and Asia salads after different domestic kitchen procedures. *Food Chem*. 2016;203:23–7.
6562. Eriksen JN, Luu AY, Dragsted LO, Arrigoni E. *In vitr*o liberation of carotenoids from spinach and Asia salads after different domestic kitchen procedures. *Food Chem*. 2016;203:23–7.
6563. Gorusupudi A, Nelson K, Bernstein PS. The Age-Related Eye Disease 2 Study: micronutrients in the treatment of macular degeneration. *Adv Nutr*. 2017;8(1):40–53.
6564. Gorusupudi A, Nelson K, Bernstein PS. The Age-Related Eye Disease 2 Study: micronutrients in the treatment of macular degeneration. *Adv Nutr*. 2017;8(1):40–53.
6565. Gorusupudi A, Nelson K, Bernstein PS. The Age-Related Eye Disease 2 Study: micronutrients in the treatment of macular degeneration. *Adv Nutr*. 2017;8(1):40–53.
6566. Chew EY, Clemons TE, SanGiovanni JP, et al. Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. *JAMA Ophthalmol*. 2014;132(2):142–9.

6567. Lawrenson JG, Evans JR, Downie LE. A critical appraisal of national and international clinical practice guidelines reporting nutritional recommendations for age-related macular degeneration: are recommendations evidence-based? *Nutrients*. 2019;11(4):E823.
6568. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. *Cochrane Database Syst Rev*. 2017;7:CD000253.
6569. Broadhead GK, Grigg JR, Chang AA, McCluskey P. Dietary modification and supplementation for the treatment of age-related macular degeneration. *Nutr Rev*. 2015;73(7):448–62.
6570. Rhone M, Basu A. Phytochemicals and age-related eye diseases. *Nutr Rev*. 2008;66(8):465–72.
6571. Hammond BR, Fuld K, Snodderly DM. Iris color and macular pigment optical density. *Exp Eye Res*. 1996;62(3):293–7.
6572. Stringham JM, Bovier ER, Wong JC, Hammond BR. The influence of dietary lutein and zeaxanthin on visual performance. *J Food Sci*. 2010;75(1):R24–9.
6573. Hammond BR, Fletcher LM, Roos F, Wittwer J, Schalch W. A double-blind, placebo-controlled study on the effects of lutein and zeaxanthin on photostress recovery, glare disability, and chromatic contrast. *Invest Ophthalmol Vis Sci*. 2014;55(12):8583–9.
6574. Rinninella E, Mele MC, Merendino N, et al. The role of diet, micronutrients and the gut microbiota in age-related macular degeneration: new perspectives from the gut–retina axis. *Nutrients*. 2018;10(11):E1677.
6575. Hammond BR, Fletcher LM, Roos F, Wittwer J, Schalch W. A double-blind, placebo-controlled study on the effects of lutein and zeaxanthin on photostress recovery, glare disability, and chromatic contrast. *Invest Ophthalmol Vis Sci*. 2014;55(12):8583–9.
6576. Sorond FA, Lipsitz LA, Hollenberg NK, Fisher NDL. Cerebral blood flow response to flavanol-rich cocoa in healthy elderly humans. *Neuropsychiatr Dis Treat*. 2008;4(2):433–40.
6577. Rabin JC, Karunathilake N, Patrizi K. Effects of milk vs dark chocolate consumption on visual acuity and contrast sensitivity within 2 hours: a randomized clinical trial. *JAMA Ophthalmol*. 2018;136(6):678–81.

6578. Westenskow PD. Nicotinamide: a novel treatment for age-related macular degeneration? *Stem Cell Investig*. 2017;4:86.
6579. Dinu M, Pagliai G, Casini A, Sofi F. Food groups and risk of age-related macular degeneration: a systematic review with meta-analysis. *Eur J Nutr*. 2019;58(5):2123–43.
6580. Mares-Perlman JA, Brady WE, Klein R, VandenLangenberg GM, Klein BE, Palta M. Dietary fat and age-related maculopathy. *Arch Ophthalmol*. 1995;113(6):743–8.
6581. Ban N, Lee TJ, Sene A, et al. Impaired monocyte cholesterol clearance initiates age-related retinal degeneration and vision loss. *JCI Insight*. 2018;3(17):120824.
6582. Rodriguez IR, Clark ME, Lee JW, Curcio CA. 7-ketocholesterol accumulates in ocular tissues as a consequence of aging and is present in high levels in drusen. *Exp Eye Res*. 2014;128:151–5.
6583. Yin L, Shi Y, Liu X, et al. A rat model for studying the biological effects of circulating LDL in the choriocapillaris-BrM-RPE complex. *Am J Pathol*. 2012;180(2):541–9.
6584. Gehlbach P, Li T, Hatef E. Statins for age-related macular degeneration. *Cochrane Database Syst Rev*. 2016;(8):CD006927.
6585. Rhone M, Basu A. Phytochemicals and age-related eye diseases. *Nutr Rev*. 2008;66(8):465–72.
6586. Park CY, Gu N, Lim CY, et al. The effect of *Vaccinium uliginosum* extract on tablet computer-induced asthenopia: randomized placebo-controlled study. *BMC Complement Altern Med*. 2016;16:296.
6587. Kalt W, McDonald JE, Fillmore SAE, Tremblay F. Blueberry effects on dark vision and recovery after photobleaching: placebo-controlled crossover studies. *J Agric Food Chem*. 2014;62(46):11180–9.
6588. Broadhead GK, Grigg JR, McCluskey P, Hong T, Schlub TE, Chang AA. Saffron therapy for the treatment of mild/moderate age-related macular degeneration: a randomised clinical trial. *Graefes Arch Clin Exp Ophthalmol*. 2019;257(1):31–40.
6589. Tribble JR, Hui F, Jöe M, et al. Targeting diet and exercise for neuroprotection and neurorecovery in glaucoma. *Cells*. 2021;10(2):295.
6590. Han B, Song M, Li L, Sun X, Lei Y. The application of nitric oxide for ocular hypertension treatment. *Molecules*. 2021;26(23):7306.

6591. Han B, Song M, Li L, Sun X, Lei Y. The application of nitric oxide for ocular hypertension treatment. *Molecules*. 2021;26(23):7306.
6592. Bastia E, Toris C, Bukowski JM, et al. NCX 1741, a novel nitric oxide-donating phosphodiesterase-5 inhibitor, exerts rapid and long-lasting intraocular pressure-lowering in cynomolgus monkeys. *J Ocul Pharmacol Ther*. 2021;37(4):215–22.
6593. Coleman AL, Stone KL, Kodjebacheva G, et al. Glaucoma risk and the consumption of fruits and vegetables among older women in the study of osteoporotic fractures. *Am J Ophthalmol*. 2008;145(6):1081–9.
6594. Giaconi JA, Yu F, Stone KL, et al. The association of consumption of fruits/vegetables with decreased risk of glaucoma among older African-American women in the study of osteoporotic fractures. *Am J Ophthalmol*. 2012;154(4):635–44.
6595. Bao Y, Bertoia ML, Lenart EB, et al. Origin, methods, and evolution of the three Nurses' Health Studies. *Am J Public Health*. 2016;106(9):1573–81.
6596. Health Professionals Follow-up Study. Harvard T.H. Chan School of Public Health. https://sites.sph.harvard.edu/hpfs/questions-and-answers/. Accessed September 15, 2022.
6597. Kang JH, Willett WC, Rosner BA, Buys E, Wiggs JL, Pasquale LR. Association of dietary nitrate intake with primary open-angle glaucoma: a prospective analysis from the Nurses' Health Study and Health Professionals Follow-up Study. *JAMA Ophthalmol*. 2016;134(3):294–303.
6598. Zhu MM, Lai JSM, Choy BNK, et al. Physical exercise and glaucoma: a review on the roles of physical exercise on intraocular pressure control, ocular blood flow regulation, neuroprotection and glaucoma-related mental health. *Acta Ophthalmol*. 2018;96(6):e676–91.
6599. Passo MS, Elliot DL, Goldberg L. Long-term effects of exercise conditioning on intraocular pressure in glaucoma suspects. *J Glaucoma*. 1992;1(1):39–41.
6600. Chorich LJ III, Davidorf FH, Chambers RB, Weber PA. Bungee cord-associated ocular injuries. *Am J Ophthalmol*. 1998;125(2):270–2.

6601. Kalthoff H, John S. [Intraocular pressure in snorkling and diving (author's transl)]. *Klin Monbl Augenheilkd*. 1976;168(02):253–7.
6602. Jasien JV, Jonas JB, de Moraes CG, Ritch R. Intraocular pressure rise in subjects with and without glaucoma during four common yoga positions. *PLoS One*. 2015;10(12):e0144505.
6603. Williams PT. Relationship of incident glaucoma versus physical activity and fitness in male runners. *Med Sci Sports Exerc*. 2009;41(8):1566–72.
6604. Ramulu PY, Maul E, Hochberg C, Chan ES, Ferrucci L, Friedman DS. Real-world assessment of physical activity in glaucoma using an accelerometer. *Ophthalmology*. 2012;119(6):1159–66.
6605. Ohguro H, Ohguro I, Katai M, Tanaka S. Two-year randomized, placebo-controlled study of black currant anthocyanins on visual field in glaucoma. *Ophthalmologica*. 2012;228(1):26–35.
6606. McGlynnP. Welcome back black currants: forbidden fruit making a comeback in New York. Cornell Chronicle. https://news.cornell.edu/stories/2006/07/welcome-back-black-currants-forbidden-fruit-making-ny-comeback. Published July 26, 2006. Accessed February 25, 2006.
6607. Sari MD. Ginkgo biloba extract effect on oxidative stress marker malonildialdehyde, redox enzyme gluthation peroxidase, visual field damage, and retinal nerve fiber layer thickness in primary open angle glaucoma. InnoPharm2 Second International Conference on Innovations in Pharmaceutical Medical and Bio Science. Innovare Academic Sciences. http://repository.usu.ac.id/handle/123456789/65446. Published February 11–12, 2017. Accessed September 15, 2022.
6608. Quaranta L, Bettelli S, Uva MG, Semeraro F, Turano R, Gandolfo E. Effect of *Ginkgo biloba* extract on preexisting visual field damage in normal tension glaucoma. *Ophthalmology*. 2003;110(2):359–62.
6609. Guo X, Kong X, Huang R, et al. Effect of Ginkgo biloba on visual field and contrast sensitivity in Chinese patients with normal tension glaucoma: a randomized, crossover clinical trial. *Invest Ophthalmol Vis Sci*. 2014;55(1):110–6.
6610. Bent S, Goldberg H, Padula A, Avins AL. Spontaneous bleeding associated with *Ginkgo biloba*: a case report and systematic review of

the literature. *J Gen Intern Med*. 2005;20(7):657–61.
6611. Hui F, Tang J, Williams PA, et al. Improvement in inner retinal function in glaucoma with nicotinamide (vitamin B3) supplementation: a crossover randomized clinical trial. *Clin Exp Ophthalmol*. 2020;48(7):903–14.
6612. De Moraes CG, John SWM, Williams PA, Blumberg DM, Cioffi GA, Liebmann JM. Nicotinamide and pyruvate for neuroenhancement in open-angle glaucoma: a phase 2 randomized clinical trial. *JAMA Ophthalmol*. 2022;140(1):11–8.
6613. Liu YC, Wilkins M, Kim T, Malyugin B, Mehta JS. Cataracts. *Lancet*. 2017;390(10094):600–12.
6614. Liu YC, Wilkins M, Kim T, Malyugin B, Mehta JS. Cataracts. *Lancet*. 2017;390(10094):600–12.
6615. Stephenson M. Dysphotopsia: not just black and white. Review of Ophthalmology. https://www.reviewofophthalmology.com/article/dysphotopsia-not-just-black-and-white. Published November 7, 2022. Accessed September 15, 2022.
6616. Liu YC, Wilkins M, Kim T, Malyugin B, Mehta JS. Cataracts. *Lancet*. 2017;390(10094):600–12.
6617. Liu YC, Wilkins M, Kim T, Malyugin B, Mehta JS. Cataracts. *Lancet*. 2017;390(10094):600–12.
6618. Thorn DC, Grosas AB, Mabbitt PD, Ray NJ, Jackson CJ, Carver JA. The structure and stability of the disulfide-linked γs-crystallin dimer provide insight into oxidation products associated with lens cataract formation. *J Mol Biol*. 2019;431(3):483–97.
6619. Weikel KA, Garber C, Baburins A, Taylor A. Nutritional modulation of cataract. *Nutr Rev*. 2014;72(1):30–47.
6620. Westenskow PD. Nicotinamide: a novel treatment for age-related macular degeneration? *Stem Cell Investig*. 2017;4:86.
6621. Weikel KA, Garber C, Baburins A, Taylor A. Nutritional modulation of cataract. *Nutr Rev*. 2014;72(1):30–47.
6622. Hah YS, Chung HJ, Sontakke SB, et al. Ascorbic acid concentrations in aqueous humor after systemic vitamin C supplementation in patients with cataract: pilot study. *BMC Ophthalmol*. 2017;17(1):121.

6623. Mares J. Food antioxidants to prevent cataract. *JAMA*. 2015;313(10):1048–9.
6624. Sideri O, Tsaousis KT, Li HJ, Viskadouraki M, Tsinopoulos IT. The potential role of nutrition on lens pathology: a systematic review and meta-analysis. *Surv Ophthalmol*. 2019;64(5):668–78.
6625. Wei L, Liang G, Cai C, Lv J. Association of vitamin C with the risk of age-related cataract: a meta-analysis. *Acta Ophthalmol*. 2016;94(3):e170–6.
6626. Weikel KA, Garber C, Baburins A, Taylor A. Nutritional modulation of cataract. *Nutr Rev*. 2014;72(1):30–47.
6627. Ma L, Hao Zx, Liu Rr, Yu RB, Shi Q, Pan JP. A dose-response meta-analysis of dietary lutein and zeaxanthin intake in relation to risk of age-related cataract. *Graefes Arch Clin Exp Ophthalmol*. 2014;252(1):63–70.
6628. Christen WG, Glynn RJ, Sesso HD, et al. Age-related cataract in a randomized trial of vitamins E and C in men. *Arch Ophthalmol*. 2010;128(11):1397–405.
6629. Kassoff A, Kassoff J, Buehler JA, et al. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. *Arch Ophthalmol*. 2001;119(10):1439–52.
6630. Gritz DC, Srinivasan M, Smith SD, et al. The antioxidants in prevention of cataracts study: effects of antioxidant supplements on cataract progression in South India. *Br J Ophthalmol*. 2006;90(7):847–51.
6631. Jiang H, Yin Y, Wu CR, et al. Dietary vitamin and carotenoid intake and risk of age-related cataract. *Am J Clin Nutr*. 2019;109(1):43–54.
6632. Barker FM. Dietary supplementation: effects on visual performance and occurrence of AMD and cataracts. *Curr Med Res Opin*. 2010;26(8):2011–23.
6633. Christen W, Glynn R, Sperduto R, Chew E, Buring J. Age-related cataract in a randomized trial of beta-carotene in women. *Ophthalmic Epidemiol*. 2004;11(5):401–12.
6634. Chew EY, SanGiovanni JP, Ferris FL et al. Lutein/zeaxanthin for the treatment of age-related cataract: AREDS2 randomized trial report no. 4. *JAMA Ophthalmol*. 2013;131(7):843–50.

6635. Maraini G, Williams SL, Camparini M, et al. A randomized, double-masked, placebo-controlled clinical trial of multivitamin supplementation for age-related lens opacities: Clinical Trial of Nutritional Supplements and Age-Related Cataract report no. 3. *Ophthalmology*. 2008;115(4):599–607.e1.
6636. Mares J. Food antioxidants to prevent cataract. *JAMA*. 2015;313(10):1048–9.
6637. Shivappa N, Hébert JR, Rashidkhani B, Ghanavati M. Inflammatory potential of diet is associated with increased odds of cataract in a case-control study from Iran. *Int J Vitam Nutr Res*. 2017;87(1–2):17–24.
6638. Semba RD, Nicklett EJ, Ferrucci L. Does accumulation of advanced glycation end products contribute to the aging phenotype? *J Gerontol A Biol Sci Med Sci*. 2010;65(9):963–75.
6639. Wu C, Han X, Yan X, et al. Impact of diet on the incidence of cataract surgery among diabetic patients: findings from the 45 and Up Study. *Curr Eye Res*. 2019;44(4):385–92.
6640. Tan AG, Flood VM, Kifley A, et al. Wholegrain and legume consumption and the 5-year incidence of age-related cataract in the Blue Mountains Eye Study. *Br J Nutr*. 2020;124(3):306–15.
6641. Appleby PN, Allen NE, Key TJ. Diet, vegetarianism, and cataract risk. *Am J Clin Nutr*. 2011;93(5):1128–35.
6642. Appleby PN, Allen NE, Key TJ. Diet, vegetarianism, and cataract risk. *Am J Clin Nutr*. 2011;93(5):1128–35.
6643. Fraser GE. Vegetarian diets: what do we know of their effects on common chronic diseases? *Am J Clin Nutr*. 2009;89(5):1607S-12S.
6644. Chiu THT, Chang CC, Lin CL, Lin MN. A vegetarian diet is associated with a lower risk of cataract, particularly among individuals with overweight: a prospective study. *J Acad Nutr Diet*. 2021;121(4):669–77.e1.
6645. Mitchell HS, Dodge WM. Cataract in rats fed on high lactose rations. *J Nutr*. 1935;9(1):37–49.
6646. Richter CP, Duke JR. Cataracts produced in rats by yogurt. *Science*. 1970;168(3937):1372–4.
6647. Kinoshita JH. Cataracts in galactosemia. The Tonas S. Friedenwald Memorial Lecture. *Invest Ophthalmol*. 1965;4(5):786–99.

6648. Couet C, Jan P, Debry G. Lactose and cataract in humans: a review. *J Am Coll Nutr*. 1991;10(1):79–86.
6649. Wilson WA, Donnell GN. Cataracts in galactosemia. *AMA Arch Ophthalmol*. 1958;60(2):215–22.
6650. Mustafa OM, Daoud YJ. Is dietary milk intake associated with cataract extraction history in older adults? An analysis from the US population. *J Ophthalmol*. 2020;2020:2562875.
6651. Mustafa OM, Daoud YJ. Is dietary milk intake associated with cataract extraction history in older adults? An analysis from the US population. *J Ophthalmol*. 2020;2020:2562875.
6652. Jacques PF, Phillips J, Hartz SC, Chylack LT. Lactose intake, galactose metabolism and senile cataract. *Nutr Res*. 1990;10(3):255–65.
6653. Couet C, Jan P, Debry G. Lactose and cataract in humans: a review. *J Am Coll Nutr*. 1991;10(1):79–86.
6654. Smith R. A good death. An important aim for health services and for us all. *BMJ*. 2000;320(7228):129–30.
6655. Broad JB, Gott M, Kim H, Boyd M, Chen H, Connolly MJ. Where do people die? An international comparison of the percentage of deaths occurring in hospital and residential aged care settings in 45 populations, using published and available statistics. *Int J Public Health*. 2013;58(2):257–67.
6656. Hetzler PT III, Dugdale LS. How do medicalization and rescue fantasy prevent healthy dying? *AMA J Ethics*. 2018;20(8):E766–73.
6657. Quickstats: percentage distribution of deaths, by place of death—United States, 2000–2014. *MMWR Morb Mortal Wkly Rep*. 2016;65(13):357.
6658. Wright AA, Keating NL, Balboni TA, Matulonis UA, Block SD, Prigerson HG. Place of death: correlations with quality of life of patients with cancer and predictors of bereaved caregivers' mental health. *J Clin Oncol*. 2010;28(29):4457–64.
6659. Mills M, Davies HT, Macrae WA. Care of dying patients in hospital. *BMJ*. 1994;309(6954):583–6.
6660. Smith R. A good death. An important aim for health services and for us all. *BMJ*. 2000;320(7228):129–30.

6661. Quill TE, Ganzini L, Truog RD, Pope TM. Voluntarily stopping eating and drinking among patients with serious advanced illness—clinical, ethical, and legal aspects. *JAMA Intern Med*. 2018;178(1):123–7.
6662. 2020 Edition: Hospice Facts and Figures. National Hospice and Palliative Care Organization. www.nhpco.org/factsfigures. Published August 20, 2020. Accessed September 20, 2022.
6663. Connor SR, Pyenson B, Fitch K, Spence C, Iwasaki K. Comparing hospice and nonhospice patient survival among patients who die within a three-year window. *J Pain Symptom Manage*. 2007;33(3):238–46.
6664. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med.* 2010;363(8):733–42.
6665. Kelley AS, Meier DE. Palliative care—a shifting paradigm. *N Engl J Med*. 2010;363(8):781–2.
6666. Irwin KE, Greer JA, Khatib J, Temel JS, Pirl WF. Early palliative care and metastatic non-small cell lung cancer: potential mechanisms of prolonged survival. *Chron Respir Dis*. 2013;10(1):35–47.
6667. Winyard G, Macdonald L. The limits of palliative care. *BMJ*. 2014;349:g4285.
6668. Ivanović N, Büche D, Fringer A. Voluntary stopping of eating and drinking at the end of life—a 'systematic search and review' giving insight into an option of hastening death in capacitated adults at the end of life. *BMC Palliat Care*. 2014;13(1):1.
6669. Symington BE. Ethics and the legalization of physician-assisted suicide. *Ann Intern Med*. 2018;168(11):833–4.
6670. Blanke C, Ellis L, Meyskens F. Oregon's death with dignity act—reply. *JAMA Oncol*. 2018;4(5):748.
6671. Pope TM. Voluntarily stopping eating and drinking. *Narrat Inq Bioeth*. 2016;6(2):75–7.
6672. Corbett M. VSED: death with dignity or without? *Narrat Inq Bioeth*. 2016;6(2):109–13.
6673. Schwarz JK. Hospice care for patients who choose to hasten death by voluntarily stopping eating and drinking. *J Hosp Palliat Nurs*. 2014;16(3):126–31.

6674. Stängle S, Schnepp W, Büche D, Häuptle C, Fringer A. Family physicians' perspective on voluntary stopping of eating and drinking: a cross-sectional study. *J Int Med Res*. 2020;48(8):300060520936069.
6675. Ivanović N, Büche D, Fringer A. Voluntary stopping of eating and drinking at the end of life—a 'systematic search and review' giving insight into an option of hastening death in capacitated adults at the end of life. *BMC Palliat Care*. 2014;13(1):1.
6676. Schwarz JK. Hospice care for patients who choose to hasten death by voluntarily stopping eating and drinking. *J Hosp Palliat Nurs*. 2014;16(3):126–31.
6677. Lachman VD. Voluntary stopping of eating and drinking: an ethical alternative to physician-assisted suicide. *Medsurg Nurs*. 2015;24(1):56–9.
6678. Ferrand E, Dreyfus JF, Chastrusse M, Ellien F, Lemaire F, Fischler M. Evolution of requests to hasten death among patients managed by palliative care teams in France: a multicentre cross-sectional survey (DemandE). *Eur J Cancer*. 2012;48(3):368–76.
6679. Pope TM, Anderson LE. Voluntarily stopping eating and drinking: a legal treatment option at the end of life. *Weidner Law Review*. 2011;17:363–427.
6680. Bolt EE, Hagens M, Willems D, Onwuteaka-Philipsen BD. Primary care patients hastening death by voluntarily stopping eating and drinking. *Ann Fam Med*. 2015;13(5):421–8.
6681. Gruenewald DA, Vandekieft G. Options of last resort: palliative sedation, physician aid in dying, and voluntary cessation of eating and drinking. *Med Clin North Am*. 2020;104(3):539–60.
6682. Printz LA. Terminal dehydration, a compassionate treatment. *Arch Intern Med*. 1992;152(4):697–700.
6683. Volicer L, Stets K. Acceptability of an advance directive that limits food and liquids in advanced dementia. *Am J Hosp Palliat Care*. 2016;33(1):55–63.
6684. Ivanović N, Büche D, Fringer A. Voluntary stopping of eating and drinking at the end of life—a 'systematic search and review' giving insight into an option of hastening death in capacitated adults at the end of life. *BMC Palliat Care*. 2014;13(1):1.

6685. Eddy DM. A piece of my mind. A conversation with my mother. *JAMA*. 1994;272(3):179–81.
6686. Jackonen S. Dehydration and hydration in the terminally ill: care considerations. *Nurs Forum*. 1997;32(3):5–13.
6687. Rakatansky H. Complexities to consider when patients choose VSED (voluntarily stopping eating and drinking). *R I Med (2013).* 2017;100(2):12–3.
6688. Menzel PT. Justifying a surrogate's request to forego oral feeding. *Am J Bioeth*. 2019;19(1):92–4.

IV. Dr. Greger's Anti-Aging Eight

6689. Perls TT. Anti-aging quackery: human growth hormone and tricks of the trade—more dangerous than ever. *J Gerontol A Biol Sci Med Sci*. 2004;59(7):682–91.

6690. Pillitteri JL, Shiffman S, Rohay JM, Harkins AM, Burton SL, Wadden TA. Use of dietary supplements for weight loss in the United States: results of a national survey. *Obesity (Silver Spring)*. 2008;16(4):790–6.

6691. Sissung TM, Cordes LM, Figg WD. The Dietary Supplement Health and Education Act: are we healthier and better informed after 27 years? *Lancet Oncol*. 2021;22(7):915–6.

6692. MacFarlane D, Hurlstone MJ, Ecker UKH. Protecting consumers from fraudulent health claims: a taxonomy of psychological drivers, interventions, barriers, and treatments. *Soc Sci Med*. 2020;259:112790.

6693. Sissung TM, Cordes LM, Figg WD. The Dietary Supplement Health and Education Act: are we healthier and better informed after 27 years? *Lancet Oncol*. 2021;22(7):915–6.

6694. Newmaster SG, Grguric M, Shanmughanandhan D, Ramalingam S, Ragupathy S. DNA barcoding detects contamination and substitution in North American herbal products. *BMC Med*. 2013;11:222.

6695. Long J. FDA GMP inspectors cite 70% of dietary supplement firms. *Natural Products INSIDER*. https://www.naturalproductsinsider.com/fda-gmp-inspectors-cite-70-dietary-supplement-firms. Published May 20, 2013. Accessed September 29, 2022.

6696. O'Connor A. New York attorney general targets supplements at major retailers. *The New York Times*. https://well.blogs.nytimes.com/2015/02/03/new-york-attorney-general-targets-supplements-at-major-retailers. Published February 3, 2015. Accessed September 29, 2022.

6697. Cohen PA, Maller G, Desouza R, Neal-Kababick J. Presence of banned drugs in dietary supplements following FDA recalls. *JAMA*. 2014;312(16):1691–3.
6698. Marcus DM. Dietary supplements: what's in a name? What's in the bottle? *Drug Test Anal*. 2016;8(3–4):410–2.
6699. Gahche JJ, Bailey RL, Potischman N, Dwyer JT. Dietary supplement use was very high among older adults in the United States in 2011–2014. *J Nutr*. 2017;147(10):1968–76.
6700. Institute of Medicine. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline. National Academy Press;1998.
6701. O'Connor EA, Evans CV, Ivlev I, et al. Vitamin and mineral supplements for the primary prevention of cardiovascular disease and cancer: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2022;327(23):2334–47.
6702. Guallar E, Stranges S, Mulrow C, Appel LJ, Miller ER. Enough is enough: stop wasting money on vitamin and mineral supplements. *Ann Intern Med*. 2013;159(12):850–1.
6703. Jenkins DJA, Spence JD, Giovannucci EL, et al. Supplemental vitamins and minerals for cardiovascular disease prevention and treatment. *J Am Coll Cardiol*. 2021;77(4):423–36.
6704. Biesalski HK, Tinz J. Multivitamin/mineral supplements: rationale and safety—a systematic review. *Nutrition*. 2017;33:76–82.
6705. Mursu J, Robien K, Harnack LJ, Park K, Jacobs DR. Dietary supplements and mortality rate in older women: the Iowa Women's Health Study. *Arch Intern Med.* 2011;171(18):1625–33.
6706. Schwingshackl L, Boeing H, Stelmach-Mardas M, et al. Dietary supplements and risk of cause-specific death, cardiovascular disease, and cancer: a systematic review and meta-analysis of primary prevention trials. *Adv Nutr*. 2017;8(1):27–39.
6707. Biesalski HK, Tinz J. Multivitamin/mineral supplements: rationale and safety—a systematic review. *Nutrition*. 2017;33:76–82.
6708. Chang YY, Chiou WB. The liberating effect of weight loss supplements on dietary control: a field experiment. *Nutrition*. 2014;30(9):1007–10.

6709. Chiou WB, Wan CS, Wu WH, Lee KT. A randomized experiment to examine unintended consequences of dietary supplement use among daily smokers: taking supplements reduces self-regulation of smoking. *Addiction*. 2011;106(12):2221–8.
6710. Chang YY, Chiou WB. Taking weight-loss supplements may elicit liberation from dietary control. A laboratory experiment. *Appetite*. 2014;72:8–12.
6711. Spindler SR, Mote PL, Flegal JM. Lifespan effects of simple and complex nutraceutical combinations fed isocalorically to mice. *Age (Dordr)*. 2014;36(2):705–18.
6712. Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst Rev*. 2014;(1):CD007470.
6713. Pludowski P, Holick MF, Pilz S, et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality—a review of recent evidence. *Autoimmun Rev*. 2013;12(10):976–89.
6714. Autier P, Mullie P, Macacu A, et al. Effect of vitamin D supplementation on non-skeletal disorders: a systematic review of meta-analyses and randomised trials. *Lancet Diabetes Endocrinol*. 2017;5(12):986–1004.
6715. Barbarawi M, Kheiri B, Zayed Y, et al. Vitamin D supplementation and cardiovascular disease risks in more than 83 000 individuals in 21 randomized clinical trials: a meta-analysis. *JAMA Cardiol*. 2019;4(8):765–76.
6716. Seida JC, Mitri J, Colmers IN, et al. Clinical review: effect of vitamin D3 supplementation on improving glucose homeostasis and preventing diabetes: a systematic review and meta-analysis [published correction appears in *J Clin Endocrinol Metab.* 2015;100(8):3219]. *J Clin Endocrinol Metab*. 2014;99(10):3551–60.
6717. Jagannath VA, Filippini G, Di Pietrantonj C, et al. Vitamin D for the management of multiple sclerosis. *Cochrane Database Syst Rev*. 2018;9:CD008422.
6718. Duan L, Han L, Liu Q, Zhao Y, Wang L, Wang Y. Effects of vitamin D supplementation on general and central obesity: results from 20

randomized controlled trials involving apparently healthy populations. *Ann Nutr Metab*. 2020;76(3):153–64.

6719. Shahvazi S, Soltani S, Ahmadi SM, de Souza RJ, Salehi-Abargouei A. The effect of vitamin D supplementation on prostate cancer: a systematic review and meta-analysis of clinical trials. *Horm Metab Res*. 2019;51(1):11–21.

6720. Beveridge LA, Struthers AD, Khan F, et al. Effect of vitamin D supplementation on blood pressure: a systematic review and meta-analysis incorporating individual patient data. *JAMA Intern Med*. 2015;175(5):745–54.

6721. Giustina A, Adler RA, Binkley N, et al. Consensus statement from 2nd International Conference on Controversies in Vitamin D. *Rev Endocr Metab Disord*. 2020;21(1):89–116.

6722. Jolliffe DA, Greenberg L, Hooper RL, et al. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. *Lancet Respir Med*. 2017;5(11):881–90.

6723. Jolliffe DA, Greenberg L, Hooper RL, et al. Vitamin D to prevent exacerbations of COPD: systematic review and meta-analysis of individual participant data from randomised controlled trials. *Thorax*. 2019;74(4):337–45.

6724. Okereke OI, Reynolds CF, Mischoulon D, et al. Effect of long-term vitamin D_3 supplementation vs placebo on risk of depression or clinically relevant depressive symptoms and on change in mood scores: a randomized clinical trial. *JAMA*. 2020;324(5):471–80.

6725. Cheng YC, Huang YC, Huang WL. The effect of vitamin D supplement on negative emotions: a systematic review and meta-analysis. *Depress Anxiety*. 2020;37(6):549–64.

6726. Martineau AR, Jolliffe DA, Greenberg L, et al. Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis. *Health Technol Assess*. 2019;23(2):1–44.

6727. Maretzke F, Bechthold A, Egert S, et al. Role of vitamin D in preventing and treating selected extraskeletal diseases—an umbrella review. *Nutrients*. 2020;12(4):E969.

6728. Heath AK, Kim IY, Hodge AM, English DR, Muller DC. Vitamin D status and mortality: a systematic review of observational studies. *Int J Environ Res Public Health*. 2019;16(3):E383.
6729. Ferri E, Casati M, Cesari M, Vitale G, Arosio B. Vitamin D in physiological and pathological aging: lesson from centenarians. *Rev Endocr Metab Disord*. 2019;20(3):273–82.
6730. Passeri G, Pini G, Troiano L, et al. Low vitamin D status, high bone turnover, and bone fractures in centenarians. *J Clin Endocrinol Metab*. 2003;88(11):5109–15.
6731. Heath AK, Kim IY, Hodge AM, English DR, Muller DC. Vitamin D status and mortality: a systematic review of observational studies. *Int J Environ Res Public Health*. 2019;16(3):E383.
6732. Rodríguez AJ, Scott D, Srikanth V, Ebeling P. Effect of vitamin D supplementation on measures of arterial stiffness: a systematic review and meta-analysis of randomized controlled trials. *Clin Endocrinol (Oxf)*. 2016;84(5):645–57.
6733. Hussin AM, Ashor AW, Schoenmakers I, Hill T, Mathers JC, Siervo M. Effects of vitamin D supplementation on endothelial function: a systematic review and meta-analysis of randomised clinical trials. *Eur J Nutr*. 2017;56(3):1095–104.
6734. Biesalski HK, Tinz J. Multivitamin/mineral supplements: rationale and safety—a systematic review. *Nutrition*. 2017;33:76–82.
6735. Zhang Y, Fang F, Tang J, et al. Association between vitamin D supplementation and mortality: systematic review and meta-analysis. *BMJ*. 2019;366:l4673.
6736. Manson JE, Cook NR, Lee IM, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med*. 2019;380(1):33–44.
6737. Manson JE, Cook NR, Lee IM, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med*. 2019;380(1):23–32.
6738. Giustina A, Bouillon R, Binkley N, et al. Controversies in vitamin D: a statement from the Third International Conference. *JBMR Plus*. 2020;4(12):e10417.
6739. Frame LA, Fischer JP, Geller G, Cheskin LJ. Use of placebo in supplementation studies—vitamin D research illustrates an ethical

quandary. *Nutrients*. 2018;10(3):347.
6740. Manson JE, Cook NR, Lee IM, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med*. 2019;380(1):33–44.
6741. Zhang Y, Fang F, Tang J, et al. Association between vitamin D supplementation and mortality: systematic review and meta-analysis. *BMJ*. 2019;366:l4673.
6742. LeClair BM, Si C, Solomon J. Vitamin D supplementation and all-cause mortality. *Am Fam Physician*. 2020;102(1):online.
6743. Autier P, Mullie P, Macacu A, et al. Effect of vitamin D supplementation on non-skeletal disorders: a systematic review of meta-analyses and randomised trials. *Lancet Diabetes Endocrinol*. 2017;5(12):986–1004.
6744. Biesalski HK, Tinz J. Multivitamin/mineral supplements: rationale and safety—a systematic review. *Nutrition*. 2017;33:76–82.
6745. Healthy diet. World Health Organization. https://cdn.who.int/media/docs/default-source/healthy-diet/healthy-diet-fact-sheet-394.pdf?sfvrsn=69f1f9a1_2&download=true. Updated August 2018. Accessed October 7, 2022.
6746. Schwingshackl L, Schwedhelm C, Hoffmann G, et al. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr*. 2017;105(6):1462–73.
6747. Pribis P, Shukitt-Hale B. Cognition: the new frontier for nuts and berries. *Am J Clin Nutr*. 2014;100 Suppl 1:347S-52S.
6748. Aune D, Keum N, Giovannucci E, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. *BMC Med*. 2016;14(1):207.
6749. Fadelu T, Zhang S, Niedzwiecki D, et al. Nut consumption and survival in patients with stage III colon cancer: results from CALGB 89803 (Alliance). *J Clin Oncol*. 2018;36(11):1112–20.
6750. Fraser GE, Shavlik DJ. Risk factors for all-cause and coronary heart disease mortality in the oldest-old. The Adventist Health Study. *Arch Intern Med*. 1997;157(19):2249–58.
6751. Ros E. Eat nuts, live longer. *J Am Coll Cardiol*. 2017;70(20):2533–5.

6752. Fraser GE, Shavlik DJ. Ten years of life: is it a matter of choice? *Arch Intern Med*. 2001;161(13):1645–52.
6753. Chen GC, Zhang R, Martínez-González MA, et al. Nut consumption in relation to all-cause and cause-specific mortality: a meta-analysis 18 prospective studies. *Food Funct*. 2017;8(11):3893–905.
6754. Aune D, Keum NN, Giovannucci E, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. *BMC Med*. 2016;14(1):207.
6755. Fernández-Montero A, Bes-Rastrollo M, Barrio-López MT, et al. Nut consumption and 5-y all-cause mortality in a Mediterranean cohort: the SUN project. *Nutrition*. 2014;30(9):1022–7.
6756. Baer HJ, Glynn RJ, Hu FB, et al. Risk factors for mortality in the Nurses' Health Study: a competing risks analysis. *Am J Epidemiol*. 2011;173(3):319–29.
6757. Fernández-Montero A, Martínez-González MA, Moreno-Galarraga L. Re. "Nut consumption and 5-y all-cause mortality in a Mediterranean cohort: the SUN project": Authors' response. *Nutrition*. 2015;31(10):1299–300.
6758. Aune D, Keum N, Giovannucci E, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. *BMC Med*. 2016;14(1):207.
6759. Kim Y, Keogh JB, Clifton PM. Does nut consumption reduce mortality and/or risk of cardiometabolic disease? An updated review based on meta-analyses. *Int J Environ Res Public Health*. 2019;16(24):4957.
6760. Mohammadi-Sartang M, Bellissimo N, Totosy de Zepetnek JO, Bazyar H, Mahmoodi M, Mazloom Z. Effects of walnuts consumption on vascular endothelial function in humans: a systematic review and meta-analysis of randomized controlled trials. *Clin Nutr ESPEN*. 2018;28:52–8.
6761. Schwingshackl L, Hoffmann G, Iqbal K, Schwedhelm C, Boeing H. Food groups and intermediate disease markers: a systematic review and network meta-analysis of randomized trials. *Am J Clin Nutr*. 2018;108(3):576–86.

6762. Bitok E, Jaceldo-Siegl K, Rajaram S, et al. Favourable nutrient intake and displacement with long-term walnut supplementation among elderly: results of a randomised trial. *Br J Nutr*. 2017;118(3):201–9.
6763. Sun Y, Liu B, Snetselaar LG, et al. Association of major dietary protein sources with all-cause and cause-specific mortality: prospective cohort study. *J Am Heart Assoc*. 2021;10(5):e015553.
6764. Sabaté J. Nut consumption, vegetarian diets, ischemic heart disease risk, and all-cause mortality: evidence from epidemiologic studies. *Am J Clin Nutr*. 1999;70(3 Suppl):500S-3S.
6765. Chen GC, Zhang R, Martínez-González MA, et al. Nut consumption in relation to all-cause and cause-specific mortality: a meta-analysis 18 prospective studies. *Food Funct*. 2017;8(11):3893–905.
6766. Aune D, Keum NN, Giovannucci E, et al. Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. *BMC Med*. 2016;14(1):207.
6767. Dreher ML, Maher CV, Kearney P. The traditional and emerging role of nuts in healthful diets. *Nutr Rev*. 2009;54(8):241–5.
6768. Guarneiri LL, Cooper JA. Intake of nuts or nut products does not lead to weight gain, independent of dietary substitution instructions: a systematic review and meta-analysis of randomized trials. *Adv Nutr*. 2021;12(2):384–401.
6769. Barman AK, Goel R, Sharma M, Mahanta PJ. Acute kidney injury associated with ingestion of star fruit: acute oxalate nephropathy. *Indian J Nephrol*. 2016;26(6):446–8.
6770. Albersmeyer M, Hilge R, Schröttle A, Weiss M, Sitter T, Vielhauer V. Acute kidney injury after ingestion of rhubarb: secondary oxalate nephropathy in a patient with type 1 diabetes. *BMC Nephrol*. 2012;13:141.
6771. Kikuchi Y, Seta K, Ogawa Y, et al. Chaga mushroom-induced oxalate nephropathy. *Clin Nephrol*. 2014;81(6):440–4.
6772. Gandhi A, Nasser S, Kassis Akl N, Kotadia S. Quiz page June 2016: rapidly progressive kidney failure. *Am J Kidney Dis*. 2016;67(6):A15–7.
6773. Syed F, Mena-Gutierrez A, Ghaffar U. A case of iced-tea nephropathy. *N Engl J Med*. 2015;372(14):1377–8.

6774. Bernardino M, Parmar MS. Oxalate nephropathy from cashew nut intake. *CMAJ*. 2017;189(10):E405–8.
6775. Haaskjold YL, Drotningsvik A, Leh S, Marti HP, Svarstad E. Renal failure due to excessive intake of almonds in the absence of *Oxalobacter formigenes*. *Am J Med*. 2015;128(12):e29–30.
6776. Garland V, Herlitz L, Regunathan-Shenk R. Diet-induced oxalate nephropathy from excessive nut and seed consumption. *BMJ Case Rep*. 2020;13(11):e237212.
6777. Carlsen MH, Halvorsen BL, Holte K, et al. The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. *Nutr J*. 2010;9(1):3.
6778. Ros E, Mataix J. Fatty acid composition of nuts—implications for cardiovascular health. *Br J Nutr.* 2006;96 Suppl 2:S29–35.
6779. Xiao Y, Huang W, Peng C, et al. Effect of nut consumption on vascular endothelial function: a systematic review and meta-analysis of randomized controlled trials. *Clin Nutr*. 2018;37(3):831–9.
6780. Yang J, Liu RH, Halim L. Antioxidant and antiproliferative activities of common edible nut seeds. *Food Sci Tech.* 2009;42(1):1–8.
6781. Arias-Fernández L, Machado-Fragua MD, Graciani A, et al. Prospective association between nut consumption and physical function in older men and women. *J Gerontol A Biol Sci Med Sci*. 2019;74(7):1091–7.
6782. Freitas-Simoes TM, Wagner M, Samieri C, Sala-Vila A, Grodstein F. Consumption of nuts at midlife and healthy aging in women. *J Aging Res*. 2020;2020:5651737.
6783. Guasch-Ferré M, Bulló M, Martínez-González MÁ, et al. Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial. *BMC Med.* 2013;11:164.
6784. Toner CD. Communicating clinical research to reduce cancer risk through diet: walnuts as a case example. *Nutr Res Pract.* 2014;8(4):347–51.
6785. Kwok CS, Gulati M, Michos ED, et al. Dietary components and risk of cardiovascular disease and all-cause mortality: a review of evidence from meta-analyses. *Eur J Prev Cardiol*. 2019;26(13):1415–29.

6786. Li N, Wu X, Zhuang W, et al. Green leafy vegetable and lutein intake and multiple health outcomes. *Food Chem*. 2021;360:130145.
6787. Helander HF, Fändriks L. Surface area of the digestive tract—revisited. *Scand J Gastroenterol.* 2014;49(6):681–9.
6788. Sheridan BS, Lefranan BSL. Intraepithelial lymphocytes: to serve and protect. *Curr Gastroenterol Rep*. 2010;12(6):513–21.
6789. Hooper LV. You AhR what you eat: linking diet and immunity. *Cell* 2011;147(3):489–91.
6790. Serna E, Cespedes C, Vina J. Anti-aging physiological roles of aryl hydrocarbon receptor and its dietary regulators. *Int J Mol Sci*. 2020;22(1):E374.
6791. Esser C. Biology and function of the aryl hydrocarbon receptor: report of an international and interdisciplinary conference. *Arch Toxicol*. 2012;86(8):1323–9.
6792. Ashida H, Fukuda I, Yamashita T, Kanazawa K. Flavones and flavonols at dietary levels inhibit a transformation of aryl hydrocarbon receptor induced by dioxin. *FEBS Lett*. 2000;476(3):213–7.
6793. Healthy eating saves lives. Institute for Health Metrics and Evaluation. https://www.healthdata.org/infographic/healthy-eating-saves-lives. Published April 3, 2019. Accessed October 10, 2022.
6794. Cohen AJ, Brauer M, Burnett R, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet*. 2017;389(10082):1907–18.
6795. Lee BJ, Kim B, Lee K. Air pollution exposure and cardiovascular disease. *Toxicol Res*. 2014;30(2):71–5.
6796. He G, Pan Y, Tanaka T. COVID-19, city lockdowns, and air pollution: evidence from China. https://www.medrxiv.org/content/10.1101/2020.03.29.20046649v2. Published April 21, 2020. Accessed October 9, 2022.
6797. Air pollution data portal. World Health Organization. https://www.who.int/data/gho/data/themes/air-pollution. Accessed October 7. 2022.
6798. Lee K, Greenstone M. Air Quality Life Index: annual update. https://aqli.epic.uchicago.edu/wp-

content/uploads/2021/08/AQLI_2021-Report.EnglishGlobal.pdf. Published September 2021. Accessed October 8, 2022.
6799. Schikowski T, Hüls A. Air pollution and skin aging. *Curr Environ Health Rep*. 2020;7(1):58–64.
6800. Peters R, Ee N, Peters J, Booth A, Mudway I, Anstey KJ. Air pollution and dementia: a systematic review. *J Alzheimers Dis*. 2019;70(s1):S145–63.
6801. Lee K, Greenstone M. Air Quality Life Index: annual update. https://aqli.epic.uchicago.edu/wp-content/uploads/2021/08/AQLI_2021-Report.EnglishGlobal.pdf. Published September 2021. Accessed October 8, 2022.
6802. Olmo NRS, do Nascimento Saldiva PH, Braga ALF, Lin CA, de Paula Santos U, Pereira LAA. A review of low-level air pollution and adverse effects on human health: implications for epidemiological studies and public policy. *Clinics (Sao Paulo)*. 2011;66(4):681–90.
6803. Carlsten C, Salvi S, Wong GWK, Chung KF. Personal strategies to minimise effects of air pollution on respiratory health: advice for providers, patients and the public. *Eur Respir J*. 2020;55(6):1902056.
6804. Sinharay R, Gong J, Barratt B, et al. Respiratory and cardiovascular responses to walking down a traffic-polluted road compared with walking in a traffic-free area in participants aged 60 years and older with chronic lung or heart disease and age-matched healthy controls: a randomised, crossover study. *Lancet*. 2018;391(10118):339–49.
6805. Carlsten C, Salvi S, Wong GWK, Chung KF. Personal strategies to minimise effects of air pollution on respiratory health: advice for providers, patients and the public. *Eur Respir J*. 2020;55(6):1902056.
6806. Allen RW, Barn P. Individual- and household-level interventions to reduce air pollution exposures and health risks: a review of the recent literature. *Curr Environ Health Rep*. 2020;7(4):424–40.
6807. Barn PK, Elliott CT, Allen RW, Kosatsky T, Rideout K, Henderson SB. Portable air cleaners should be at the forefront of the public health response to landscape fire smoke. *Environ Health*. 2016;15(1):116.
6808. Allen RW, Barn P. Individual- and household-level interventions to reduce air pollution exposures and health risks: a review of the recent literature. *Curr Environ Health Rep*. 2020;7(4):424–40.

6809. Dong W, Liu S, Chu M, et al. Different cardiorespiratory effects of indoor air pollution intervention with ionization air purifier: findings from a randomized, double-blind crossover study among school children in Beijing. *Environ Pollut*. 2019;254(Pt B):113054.
6810. Liu W, Huang J, Lin Y, et al. Negative ions offset cardiorespiratory benefits of $PM_{2.5}$ reduction from residential use of negative ion air purifiers. *Indoor Air*. 2021;31(1):220–8.
6811. Healthy eating saves lives. Institute for Health Metrics and Evaluation. https://www.healthdata.org/infographic/healthy-eating-saves-lives. Published April 3, 2019. Accessed October 10, 2022.
6812. Eagles SK, Gross AS, McLachlan AJ. The effects of cruciferous vegetable-enriched diets on drug metabolism: a systematic review and meta-analysis of dietary intervention trials in humans. *Clin Pharmacol Ther*. 2020;108(2):212–27.
6813. Gilliland FD, Li YF, Saxon A, Diaz-Sanchez D. Effect of glutathione-S-transferase M1 and P1 genotypes on xenobiotic enhancement of allergic responses: randomised, placebo-controlled crossover study. *Lancet.* 2004;363(9403):119–25.
6814. Ritz SA, Wan J, Diaz-Sanchez D. Sulforaphane-stimulated phase II enzyme induction inhibits cytokine production by airway epithelial cells stimulated with diesel extract. *Am J Physiol Lung Cell Mol Physiol*. 2007;292(1):L33–9.
6815. Heber D, Li Z, Garcia-Lloret M, et al. Sulforaphane-rich broccoli sprout extract attenuates nasal allergic response to diesel exhaust particles. *Food Funct*. 2014;5(1):35–41.
6816. Müller L, Meyer M, Bauer RN, et al. Effect of broccoli sprouts and live attenuated influenza virus on peripheral blood natural killer cells: a randomized, double-blind study. *PLoS One*. 2016;11(1):e0147742.
6817. Riso P, Vendrame S, Del Bo' C, et al. Effect of 10-day broccoli consumption on inflammatory status of young healthy smokers. *Int J Food Sci Nutr*. 2014;65(1):106–11.
6818. Egner PA, Chen JG, Zarth AT, et al. Rapid and sustainable detoxication of airborne pollutants by broccoli sprout beverage: results of a randomized clinical trial in China. *Cancer Prev Res (Phila)*. 2014;7(8):813–23.

6819. Clarke JD, Hsu A, Riedl K, et al. Bioavailability and inter-conversion of sulforaphane and erucin in human subjects consuming broccoli sprouts or broccoli supplement in a cross-over study design. *Pharmacol Res.* 2011;64(5):456–63.
6820. Atwell LL, Hsu A, Wong CP, et al. Absorption and chemopreventive targets of sulforaphane in humans following consumption of broccoli sprouts or a myrosinase-treated broccoli sprout extract. *Mol Nutr Food Res*. 2015;59(3):424–33.
6821. Larsen FJ, Schiffer TA, Ekblom B, et al. Dietary nitrate reduces resting metabolic rate: a randomized, crossover study in humans. *Am J Clin Nutr.* 2014;99(4):843–50.
6822. Larsen FJ, Schiffer TA, Borniquel S, et al. Dietary inorganic nitrate improves mitochondrial efficiency in humans. *Cell Metabolism*. 2011;13(2):149–59.
6823. Engan HK, Jones AM, Ehrenberg F, Schagatay E. Acute dietary nitrate supplementation improves dry static apnea performance. *Respir Physiol Neurobiol*. 2012;182(2–3):53–9.
6824. Bailey SJ, Winyard P, Vanhatalo A, et al. Dietary nitrate supplementation reduces the O_2 cost of low-intensity exercise and enhances tolerance to high-intensity exercise in humans. *J Appl Physiol*. 2009;107(4):1144–55.
6825. European Food Safety Authority. Nitrate in vegetables: Scientific Opinion of the Panel on Contaminants in the Food chain. *EFSA J*. 2008;689:1–79.
6826. Rocha BS, Laranjinha J. Nitrate from diet might fuel gut microbiota metabolism: minding the gap between redox signaling and inter-kingdom communication. *Free Radic Biol Med*. 2020;149:37–43.
6827. Larsen FJ, Schiffer TA, Ekblom B, et al. Dietary nitrate reduces resting metabolic rate: a randomized, crossover study in humans. *Am J Clin Nutr.* 2014;99(4):843–50.
6828. *What we eat in America, NHANES 2017–March 2020 prepandemic*. Agricultural Research Service, United States Department of Agriculture. https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/1720/Table_1_NIN_GEN_1720.pdf. Published 2022. Accessed January 13, 2023.

6829. Larsen FJ, Schiffer TA, Ekblom B, et al. Dietary nitrate reduces resting metabolic rate: a randomized, crossover study in humans. *Am J Clin Nutr*. 2014;99(4):843–50.
6830. Kwok CS, Gulati M, Michos ED, et al. Dietary components and risk of cardiovascular disease and all-cause mortality: a review of evidence from meta-analyses. *Eur J Prev Cardiol*. 2019;26(13):1415–29.
6831. Van De Walle GP, Vukovich MD. The effect of nitrate supplementation on exercise tolerance and performance: a systematic review and meta-analysis. *J Strength Cond Res*. 2018;32(6):1796–808.
6832. Campos HO, Drummond LR, Rodrigues QT, et al. Nitrate supplementation improves physical performance specifically in non-athletes during prolonged open-ended tests: a systematic review and meta-analysis. *Br J Nutr*. 2018;119(6):636–57.
6833. Bailey SJ, Winyard P, Vanhatalo A, et al. Dietary nitrate supplementation reduces the O_2 cost of low-intensity exercise and enhances tolerance to high-intensity exercise in humans. *J Appl Physiol (1985)*. 2009;107(4):1144–55.
6834. Lara J, Ashor AW, Oggioni C, Ahluwalia A, Mathers JC, Siervo M. Effects of inorganic nitrate and beetroot supplementation on endothelial function: a systematic review and meta-analysis. *Eur J Nutr*. 2016;55(2):451–9.
6835. Carter SJ, Gruber AH, Raglin JS, Baranauskas MN, Coggan AR. Potential health effects of dietary nitrate supplementation in aging and chronic degenerative disease. *Med Hypotheses*. 2020;141:109732.
6836. Sim M, Lewis JR, Blekkenhorst LC, et al. Dietary nitrate intake is associated with muscle function in older women. *J Cachexia Sarcopenia Muscle.* 2019;10(3):601–10.
6837. Coggan AR, Hoffman RL, Gray DA, et al. A single dose of dietary nitrate increases maximal knee extensor angular velocity and power in healthy older men and women. *J Gerontol A Biol Sci Med Sci*. 2020;75(6):1154–60.

6838. de Oliveira GV, Morgado M, Conte-Junior CA, Alvares TS. Acute effect of dietary nitrate on forearm muscle oxygenation, blood volume and strength in older adults: a randomized clinical trial. *PLoS One*. 2017;12(11):e0188893.
6839. Borlaug BA. Cardiac aging and the fountain of youth. *Eur J Heart Fail*. 2016;18(6):611–2.
6840. Rammos C, Hendgen-Cotta UB, Totzeck M, et al. Impact of dietary nitrate on age-related diastolic dysfunction. *Eur J Heart Fail*. 2016;18(6):599–610.
6841. Lara J, Ashor AW, Oggioni C, Ahluwalia A, Mathers JC, Siervo M. Effects of inorganic nitrate and beetroot supplementation on endothelial function: a systematic review and meta-analysis. *Eur J Nutr*. 2016;55(2):451–9.
6842. Walker MA, Bailey TG, McIlvenna L, Allen JD, Green DJ, Askew CD. Acute dietary nitrate supplementation improves flow mediated dilatation of the superficial femoral artery in healthy older males. *Nutrients*. 2019;11(5):E954.
6843. Kenjale AA, Ham KL, Stabler T, et al. Dietary nitrate supplementation enhances exercise performance in peripheral arterial disease. *J Appl Physiol (1985)*. 2011;110(6):1582–91.
6844. McDonagh ST, Wylie LJ, Morgan PT, Vanhatalo A, Jones AM. A randomised controlled trial exploring the effects of different beverages consumed alongside a nitrate-rich meal on systemic blood pressure. *Nutr Health*. 2018;24(3):183–92.
6845. Murphy M, Eliot K, Heuertz RM, Weiss E. Whole beetroot consumption acutely improves running performance. *J Acad Nutr Diet*. 2012;112(4):548–52.
6846. Clements WT, Lee SR, Bloomer RJ. Nitrate ingestion: a review of the health and physical performance effects. *Nutrients*. 2014;6(11):5224–64.
6847. Hord NG, Tang Y, Bryan NS. Food sources of nitrates and nitrites: the physiologic context for potential health benefits. *Am J Clin Nutr*. 2009;90(1):1–10.
6848. Siervo M, Lara J, Ogbonmwan I, Mathers JC. Inorganic nitrate and beetroot juice supplementation reduces blood pressure in adults: a systematic review and meta-analysis. *J Nutr*. 2013;143(6):818–26.

6849. Blekkenhorst LC, Lewis JR, Prince RL, et al. Nitrate-rich vegetables do not lower blood pressure in individuals with mildly elevated blood pressure: a 4-wk randomized controlled crossover trial. *Am J Clin Nutr*. 2018;107(6):894–908.
6850. Rosier BT, Buetas E, Moya-Gonzalvez EM, Artacho A, Mira A. Nitrate as a potential prebiotic for the oral microbiome. *Sci Rep*. 2020;10(1):12895.
6851. Bondonno CP, Liu AH, Croft KD, et al. Antibacterial mouthwash blunts oral nitrate reduction and increases blood pressure in treated hypertensive men and women. *Am J Hypertens*. 2015;28(5):572–5.
6852. Tribble GD, Angelov N, Weltman R, et al. Frequency of tongue cleaning impacts the human tongue microbiome composition and enterosalivary circulation of nitrate. *Front Cell Infect Microbiol*. 2019;9:39.
6853. Redmond AM, Meiklejohn C, Kidd TJ, Horvath R, Coulter C. Endocarditis after use of tongue scraper. *Emerg Infect Dis*. 2007;13(9):1440–1.
6854. Capurso A, Capurso C. The Mediterranean way. Should elderly people eat leafy vegetables and beetroot to lower high blood pressure? *Aging Clin Exp Res*. 2021;33(9):2613–21.
6855. Strazzullo P, Ferro-Luzzi A, Siani A, et al. Changing the Mediterranean diet: effects on blood pressure. *J Hypertens*. 1986;4(4):407–12.
6856. Dellavalle CT, Daniel CR, Aschebrook-Kilfoy B, et al. Dietary intake of nitrate and nitrite and risk of renal cell carcinoma in the NIH-AARP Diet and Health Study. *Br J Cancer*. 2013;108(1):205–12.
6857. Sebranek JG, Jackson-Davis AL, Myers KL, Lavieri NA. Beyond celery and starter culture: advances in natural/organic curing processes in the United States. *Meat Sci*. 2012 Nov;92(3):267–73.
6858. Rohrmann S, Overvad K, Bueno-de-Mesquita HB, et al. Meat consumption and mortality—results from the European Prospective Investigation into Cancer and Nutrition. *BMC Med*. 2013;11:63.
6859. Sinha R, Cross AJ, Graubard BI, Leitzmann MF, Schatzkin A. Meat intake and mortality: a prospective study of over half a million people. *Arch Intern Med*. 2009;169(6):562–71.

6860. American Institute for Cancer Research. Recommendations for Cancer Prevention. http://www.aicr.org/reduce-your-cancer-risk/recommendations-for-cancer-prevention/recommendations_05_red_meat.html. April 17, 2011. Accessed October 7, 2022.
6861. Vermeer ITM, Pachen DMFA, Dallinga JW, Kleinjans JCS, van Maanen JMS. Volatile *N*-nitrosamine formation after intake of nitrate at the ADI level in combination with an amine-rich diet. *Environ Health Perspect*. 1998;106(8):459–63.
6862. van Breda SG, Mathijs K, Sági-Kiss V, et al. Impact of high drinking water nitrate levels on the endogenous formation of apparent *N*-nitroso compounds in combination with meat intake in healthy volunteers. *Environ Health*. 2019;18(1):87.
6863. Berends JE, van den Berg LMM, Guggeis MA, et al. Consumption of nitrate-rich beetroot juice with or without vitamin C supplementation increases the excretion of urinary nitrate, nitrite, and *N*-nitroso compounds in humans. *Int J Mol Sci*. 2019;20(9):E2277.
6864. Bartsch H, Ohshima H, Pignatelli B. Inhibitors of endogenous nitrosation. Mechanisms and implications in human cancer prevention. *Mutat Res*. 1988;202(2):307–24.
6865. Dellavalle CT, Daniel CR, Aschebrook-kilfoy B, et al. Dietary intake of nitrate and nitrite and risk of renal cell carcinoma in the NIH-AARP Diet and Health Study. *Br J Cancer*. 2013;108(1):205–12.
6866. Vermeer ITM, Pachen DMFA, Dallinga JW, Kleinjans JCS, van Maanen JMS. Volatile *N*-nitrosamine formation after intake of nitrate at the ADI level in combination with an amine-rich diet. *Environ Health Perspect*. 1998;106(8):459–63.
6867. Grivetti LE, Corlett JL, Gordon BM, Lockett GT. Food in American history: Part 10. Greens: Part 1. Vegetable greens in a historical context. *Nutr Today.* 2008;42(2):88–94.
6868. Krebs-Smith SM, Guenther PM, Subar AF, Kirkpatrick SI, Dodd KW. Americans do not meet federal dietary recommendations. *J Nutr.* 2010;140(10):1832–8.
6869. Sobko T, Marcus C, Govoni M, Kamiya S. Dietary nitrate in Japanese traditional foods lowers diastolic blood pressure in healthy volunteers. *Nitric Oxide*. 2010;22(2):136–40.

6870. Tamakoshi A, Tamakoshi K, Lin Y, Yagyu K, et al. Healthy lifestyle and preventable death: findings from the Japan Collaborative Cohort (JACC) Study. *Prev Med*. 2009;48(5):486–92.
6871. Hung HC, Joshipura KJ, Jiang R, et al. Fruit and vegetable intake and risk of major chronic disease. *J Natl Cancer Inst.* 2004;96(21):1577–84.
6872. Joshipura KJ, Hu FB, Manson JE, et al. The effect of fruit and vegetable intake on risk for coronary heart disease. *Ann Intern Med.* 2001;134(12):1106–14.
6873. Joshipura KJ, Ascherio A, Manson JE, et al. Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA.* 1999;282(13):1233–9.
6874. Kwok CS, Gulati M, Michos ED, et al. Dietary components and risk of cardiovascular disease and all-cause mortality: a review of evidence from meta-analyses. *Eur J Prev Cardiol*. 2019;26(13):1415–29.
6875. Walker FB. Myocardial infarction after diet-induced warfarin resistance. *Arch Intern Med.* 1984;144(10):2089–90.
6876. Herforth A, Arimond M, Álvarez-Sánchez C, Coates J, Christianson K, Muehlhoff E. A global review of food-based dietary guidelines. *Adv Nutr*. 2019;10(4):590–605.
6877. Aune D, Giovannucci E, Boffetta P, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality—a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol*. 2017;46(3):1029–56.
6878. Hjartåker A, Knudsen MD, Tretli S, Weiderpass E. Consumption of berries, fruits and vegetables and mortality among 10,000 Norwegian men followed for four decades. *Eur J Nutr*. 2015;54(4):599–608.
6879. Aune D, Giovannucci E, Boffetta P, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality—a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol*. 2017;46(3):1029–56.
6880. Aune D, Giovannucci E, Boffetta P, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality—a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol*. 2017;46(3):1029–56.

6881. Hernandez-Marin E, Galano A, Martínez A. *Cis* carotenoids: colorful molecules and free radical quenchers. *J Phys Chem B.* 2013;117(15):4050–61.
6882. Carlsen MH, Halvorsen BL, Holte K, et al. The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. *Nutr J.* 2010;9:3.
6883. Souza-Monteiro JR, Arrifano GPF, Queiroz AIDG, et al. Antidepressant and antiaging effects of açaí (*Euterpe oleracea* Mart.) in mice. *Oxid Med Cell Longev*. 2019;2019:3614960.
6884. Peixoto HS, Roxo M, Krstin S, Röhrig T, Richling E, Wink M. An anthocyanin-rich extract of acai (*Euterpe precatoria* Mart.) increases stress resistance and retards aging-related markers in *Caenorhabditis elegans*. *J Agric Food Chem*. 2016;64(6):1283–90.
6885. Sun X, Seeberger J, Alberico T, et al. Açai palm fruit (*Euterpe oleracea* Mart.) pulp improves survival of flies on a high fat diet. *Exp Gerontol*. 2010;45(3):243–51.
6886. Mertens-Talcott SU, Rios J, Jilma-Stohlawetz P, et al. Pharmacokinetics of anthocyanins and antioxidant effects after the consumption of anthocyanin-rich acai juice and pulp (*Euterpe oleracea* Mart.) in human healthy volunteers. *J Agric Food Chem*. 2008;56(17):7796–802.
6887. Kanner J, Lapidot T. The stomach as a bioreactor: dietary lipid peroxidation in the gastric fluid and the effects of plant-derived antioxidants. *Free Radic Biol Med*. 2001;31(11):1388–95.
6888. Macho-González A, Garcimartín A, López-Oliva ME, et al. Can meat and meat-products induce oxidative stress? *Antioxidants (Basel)*. 2020;9(7):638.
6889. Gorelik S, Kanner J, Schurr D, Kohen R. A rational approach to prevent postprandial modification of LDL by dietary polyphenols. *J Funct Foods*. 2013;5(1):163–9.
6890. Ayala A, Muñoz MF, Argüelles S. Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. *Oxid Med Cell Longev*. 2014;2014:360438.
6891. Haddad E, Jambazian P, Karunia M, Tanzman J, Sabaté J. A pecan-enriched diet increases γ-tocopherol/cholesterol and decreases

thiobarbituric acid reactive substances in plasma of adults. *Nutr Res*. 2006;26(8):397–402.

6892. Carlsen MH, Halvorsen BL, Holte K, et al. The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. *Nutr J*. 2010 Jan 22;9:3.

6893. Li Z, Henning SM, Zhang Y, et al. Antioxidant-rich spice added to hamburger meat during cooking results in reduced meat, plasma, and urine malondialdehyde concentrations. *Am J Clin Nutr*. 2010;91(5):1180–4.

6894. Gobert M, Rémond D, Loonis M, Buffière C, Santé-Lhoutellier V, Dufour C. Fruits, vegetables and their polyphenols protect dietary lipids from oxidation during gastric digestion. *Food Funct*. 2014;5(9):2166–74.

6895. Di Renzo L, Carraro A, Valente R, Iacopino L, Colica C, De Lorenzo A. Intake of red wine in different meals modulates oxidized LDL level, oxidative and inflammatory gene expression in healthy people: a randomized crossover trial. *Oxid Med Cell Longev*. 2014;2014:681318.

6896. Natella F, Macone A, Ramberti A, et al. Red wine prevents the postprandial increase in plasma cholesterol oxidation products: a pilot study. *Br J Nutr*. 2011;105(12):1718–23.

6897. Mellor DD, Hamer H, Smyth S, Atkin SL, Courts FL. Antioxidant-rich spice added to hamburger meat during cooking results in reduced meat, plasma, and urine malondialdehyde concentrations. *Am J Clin Nutr*. 2010;92(4):996–7; author reply 997.

6898. Li Z, Henning SM, Zhang Y, et al. Antioxidant-rich spice added to hamburger meat during cooking results in reduced meat, plasma, and urine malondialdehyde concentrations. *Am J Clin Nutr*. 2010;91(5):1180–4.

6899. Zhang Y, Henning SM, Lee RP, et al. Turmeric and black pepper spices decrease lipid peroxidation in meat patties during cooking. *Int J Food Sci Nutr*. 2015;66(3):260–5.

6900. Gorelik S, Kanner J, Schurr D, Kohen R. A rational approach to prevent postprandial modification of LDL by dietary polyphenols. *J Funct Foods*. 2013;5(1):163–9.

6901. Kanner J, Gorelik S, Roman S, Kohen R. Protection by polyphenols of postprandial human plasma and low-density lipoprotein modification: the stomach as a bioreactor. *J Agric Food Chem*. 2012;60(36):8790–6.
6902. Urquiaga I, Ávila F, Echeverria G, Perez D, Trejo S, Leighton F. A Chilean berry concentrate protects against postprandial oxidative stress and increases plasma antioxidant activity in healthy humans. *Oxid Med Cell Longev*. 2017;2017:8361493.
6903. Martini S, Conte A, Bottazzi S, Tagliazucchi D. Mediterranean diet vegetable foods protect meat lipids from oxidation during *in vitro* gastro-intestinal digestion. *Int J Food Sci Nutr*. 2020;71(4):424–39.
6904. Tirosh O, Shpaizer A, Kanner J. Lipid peroxidation in a stomach medium is affected by dietary oils (olive/fish) and antioxidants: the Mediterranean versus Western diet. *J Agric Food Chem*. 2015;63(31):7016–23.
6905. Martini S, Cavalchi M, Conte A, Tagliazucchi D. The paradoxical effect of extra-virgin olive oil on oxidative phenomena during in vitro co-digestion with meat. *Food Res Int*. 2018;109:82–90.
6906. Sebastian RS, Enns CW, Goldman JD, Hoy MK, Moshfegh AJ. Salad consumption in the U.S.: what we eat in America, NHANES 2011–2014. Food Surveys Research Group, Dietary Data Brief No. 19. https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/DBrief/19_Salad_consumption_2011_2014.pdf. Published February 2018. Accessed October 12, 2022.
6907. Eastman P. New research on antioxidants shows surprising role for coffee. *Oncology Times*. 2005;27(20):39–40.
6908. Kanner J, Selhub J, Shpaizer A, Rabkin B, Shacham I, Tirosh O. Redox homeostasis in stomach medium by foods: The Postprandial Oxidative Stress Index (POSI) for balancing nutrition and human health. *Redox Biol*. 2017;12:929–36.
6909. Kanner J, Selhub J, Shpaizer A, Rabkin B, Shacham I, Tirosh O. Redox homeostasis in stomach medium by foods: The Postprandial Oxidative Stress Index (POSI) for balancing nutrition and human health. *Redox Biol*. 2017;12:929–36.
6910. Kanner J, Selhub J, Shpaizer A, Rabkin B, Shacham I, Tirosh O. Redox homeostasis in stomach medium by foods: The Postprandial

Oxidative Stress Index (POSI) for balancing nutrition and human health. *Redox Biol*. 2017;12:929–36.

6911. Timoshnikov VA, Kobzeva TV, Polyakov NE, Kontoghiorghes GJ. Redox interactions of vitamin C and iron: inhibition of the pro-oxidant activity by deferiprone. *Int J Mol Sci*. 2020;21(11):3967.

6912. Van Hecke T, Wouters A, Rombouts C, et al. Reducing compounds equivocally influence oxidation during digestion of a high-fat beef product, which promotes cytotoxicity in colorectal carcinoma cell lines. *J Agric Food Chem*. 2016;64(7):1600–9.

6913. Baliga MS, Dsouza JJ. Amla (*Emblica officinalis* Gaertn), a wonder berry in the treatment and prevention of cancer. *Eur J Cancer Prev*. 2011;20(3):225–39.

6914. Carlsen MH, Halvorsen BL, Holte K, et al. The total antioxidant content of more than 3100 foods, beverages, spices, herbs and supplements used worldwide. Nutr J. 2010;9:3.

6915. Pathak P, Prasad BRG, Murthy NA, Hegde SN. The effect of *Emblica officinalis* diet on lifespan, sexual behavior, and fitness characters in *Drosophila melanogaster*. *Ayu*. 2011;32(2):279–84.

6916. Variya BC, Bakrania AK, Patel SS. *Emblica officinalis* (amla): a review for its phytochemistry, ethnomedicinal uses and medicinal potentials with respect to molecular mechanisms. *Pharmacol Res*. 2016;111:180–200.

6917. Akhtar MS, Ramzan A, Ali A, Ahmad M. Effect of Amla fruit (*Emblica officinalis* Gaertn.) on blood glucose and lipid profile of normal subjects and type 2 diabetic patients. *Int J Food Sci Nutr*. 2011;62(6):609–16.

6918. Akhtar MS, Ramzan A, Ali A, Ahmad M. Effect of Amla fruit (*Emblica officinalis* Gaertn.) on blood glucose and lipid profile of normal subjects and type 2 diabetic patients. *Int J Food Sci Nutr*. 2011;62(6):609–16.

6919. Kapoor MP, Suzuki K, Derek T, Ozeki M, Okubo T. Clinical evaluation of *Emblica officinalis* Gatertn (amla) in healthy human subjects: health benefits and safety results from a randomized, double-blind, crossover placebo-controlled study. *Contemp Clin Trials Commun*. 2020;17:100499.

6920. Usharani P, Merugu PL, Nutalapati C. Evaluation of the effects of a standardized aqueous extract of *Phyllanthus emblica* fruits on endothelial dysfunction, oxidative stress, systemic inflammation and lipid profile in subjects with metabolic syndrome: a randomised, double blind, placebo controlled clinical study. *BMC Complement Altern Med*. 2019;19:97.
6921. Akhtar MS, Ramzan A, Ali A, Ahmad M. Effect of Amla fruit (*Emblica officinalis* Gaertn.) on blood glucose and lipid profile of normal subjects and type 2 diabetic patients. *Int J Food Sci Nutr*. 2011;62(6):609–16.
6922. Fatima N, Pingali U, Pilli R. Evaluation of *Phyllanthus emblica* extract on cold pressor induced cardiovascular changes in healthy human subjects. *Pharmacognosy Res*. 2014;6(1):29–35.
6923. Karkon Varnosfaderani S, Hashem-Dabaghian F, Amin G, et al. Efficacy and safety of amla (*Phyllanthus emblica* L.) in non-erosive reflux disease: a double-blind, randomized, placebo-controlled clinical trial. *J Integr Med*. 2018;16(2):126–31.
6924. Minich DM. A review of the science of colorful, plant-based food and practical strategies for "eating the rainbow." *J Nutr Metab*. 2019;2019:2125070.
6925. America's phytonutrient report: quantifying the gap. Nutrilite Health Institute. https://www.pwrnewmedia.com/2009/nutrilite90921nmr/downloads/AmerciasPhytonutrientReport.pdf. Published September 11, 2009. Updated January 13, 2010. Accessed October 12, 2022.
6926. Wood E, Hein S, Heiss C, Williams C, Rodriguez-Mateos A. Blueberries and cardiovascular disease prevention. *Food Funct*. 2019;10(12):7621–33.
6927. Tena N, Asuero AG. Antioxidant capacity of anthocyanins and other vegetal pigments. *Antioxidants (Basel)*. 2020;9(8):665.
6928. Hair R, Sakaki JR, Chun OK. Anthocyanins, microbiome and health benefits in aging. *Molecules*. 2021;26(3):537.
6929. Bonyadi N, Dolatkhah N, Salekzamani Y, Hashemian M. Effect of berry-based supplements and foods on cognitive function: a systematic review. *Sci Rep*. 2022;12(1):3239.

6930. Lee J, Lee HK, Kim CY, et al. Purified high-dose anthocyanoside oligomer administration improves nocturnal vision and clinical symptoms in myopia subjects. *Br J Nutr*. 2005;93(6):895–9.
6931. Camire ME. Bilberries and blueberries as functional foods and nutraceuticals. In: Mazza G, Oomah BD, eds. *Herbs, Botanicals & Teas*. Technomic Publishing Co Inc; 2000:289–319.
6932. Nakaishi H, Matsumoto H, Tominaga S, Hirayama M. Effects of black current anthocyanoside intake on dark adaptation and VDT work-induced transient refractive alteration in healthy humans. *Altern Med Rev*. 2000;5(6):553–62. Erratum in: *Altern Med Rev*. 2001;6(1):60.
6933. Camire ME. Bilberries and blueberries as functional foods and nutraceuticals. In: Mazza G, Oomah BD, eds. *Herbs, Botanicals & Teas*. Technomic Publishing Co Inc; 2000:289–319.
6934. Xu L, Tian Z, Chen H, Zhao Y, Yang Y. Anthocyanins, anthocyanin-rich berries, and cardiovascular risks: systematic review and meta-analysis of 44 randomized controlled trials and 15 prospective cohort studies. *Front Nutr*. 2021;8:747884.
6935. Biedermann L, Mwinyi J, Scharl M, et al. Bilberry ingestion improves disease activity in mild to moderate ulcerative colitis—an open pilot study. *J Crohns Colitis*. 2013;7(4):271–9.
6936. Hair R, Sakaki JR, Chun OK. Anthocyanins, microbiome and health benefits in aging. *Molecules*. 2021;26(3):537.
6937. Vendrame S, Guglielmetti S, Riso P, Arioli S, Klimis-Zacas D, Porrini M. Six-week consumption of a wild blueberry powder drink increases bifidobacteria in the human gut. *J Agric Food Chem*. 2011;59(24):12815–20.
6938. Molan AL, Liu Z, Plimmer G. Evaluation of the effect of blackcurrant products on gut microbiota and on markers of risk for colon cancer in humans. *Phytother Res*. 2014;28(3):416–22.
6939. Mayta-Apaza AC, Pottgen E, De Bodt J, et al. Impact of tart cherries polyphenols on the human gut microbiota and phenolic metabolites *in vitro* and *in vivo*. *J Nutr Biochem*. 2018;59:160–72.
6940. Fallah AA, Sarmast E, Jafari T. Effect of dietary anthocyanins on biomarkers of glycemic control and glucose metabolism: a systematic

review and meta-analysis of randomized clinical trials. *Food Res Int*. 2020;137:109379.

6941. Stull AJ, Cash KC, Johnson WD, Champagne CM, Cefalu WT. Bioactives in blueberries improve insulin sensitivity in obese, insulin-resistant men and women. *J Nutr*. 2010;140(10):1764–8.

6942. Kimble R, Keane KM, Lodge JK, Howatson G. Dietary intake of anthocyanins and risk of cardiovascular disease: a systematic review and meta-analysis of prospective cohort studies. *Crit Rev Food Sci Nutr*. 2019;59(18):3032–43.

6943. Wedick NM, Pan A, Cassidy A, et al. Dietary flavonoid intakes and risk of type 2 diabetes in US men and women. *Am J Clin Nutr*. 2012;95(4):925–33.

6944. Ahles S, Joris PJ, Plat J. Effects of berry anthocyanins on cognitive performance, vascular function and cardiometabolic risk markers: a systematic review of randomized placebo-controlled intervention studies in humans. *Int J Mol Sci*. 2021;22(12):6482.

6945. Xu L, Tian Z, Chen H, Zhao Y, Yang Y. Anthocyanins, anthocyanin-rich berries, and cardiovascular risks: systematic review and meta-analysis of 44 randomized controlled trials and 15 prospective cohort studies. *Front Nutr*. 2021;8:747884.

6946. Aune D, Giovannucci E, Boffetta P, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality—a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol*. 2017;46(3):1029–56.

6947. Del Bo' C, Porrini M, Fracassetti D, Campolo J, Klimis-Zacas D, Riso P. A single serving of blueberry (*V. corymbosum*) modulates peripheral arterial dysfunction induced by acute cigarette smoking in young volunteers: a randomized-controlled trial. *Food Funct*. 2014;5(12):3107–16.

6948. Zhu Y, Xia M, Yang Y, et al. Purified anthocyanin supplementation improves endothelial function via NO-cGMP activation in hypercholesterolemic individuals. *Clin Chem*. 2011;57(11):1524–33.

6949. Rodriguez-Mateos A, Istas G, Boschek L, et al. Circulating anthocyanin metabolites mediate vascular benefits of blueberries: insights from randomized controlled trials, metabolomics, and nutrigenomics. *J Gerontol A Biol Sci Med Sci*. 2019;74(7):967–76.

6950. Daneshzad E, Shab-Bidar S, Mohammadpour Z, Djafarian K. Effect of anthocyanin supplementation on cardio-metabolic biomarkers: a systematic review and meta-analysis of randomized controlled trials. *Clin Nutr*. 2019;38(3):1153–65.
6951. Horbowicz M, Kosson R, Grzesiuk A, Dębski H. Anthocyanins of fruits and vegetables—their occurrence, analysis and role in human nutrition. *J Fruit Ornam Plant Res*. 2008;68(1):5–22.
6952. Ucar SK, Sözmen E, Yıldırım HK, Coker M. Effect of blueberry tea on lipid and antioxidant status in children with heterozygous familial hypercholesterolemia: pilot study. *Clin Lipidol*. 2014;9(3):295–304.
6953. Pojer E, Mattivi F, Johnson D, Stockley CS. The case for anthocyanin consumption to promote human health: a review. *Compr Rev Food Sci Food Saf*. 2013;12(5):483–508.
6954. Mattioli R, Francioso A, Mosca L, Silva P. Anthocyanins: a comprehensive review of their chemical properties and health effects on cardiovascular and neurodegenerative diseases. *Molecules*. 2020;25(17):E3809.
6955. Lu X, Zhou Y, Wu T, Hao L. Ameliorative effect of black rice anthocyanin on senescent mice induced by D-galactose. *Food Funct*. 2014;5(11):2892–7.
6956. Chen W, Müller D, Richling E, Wink M. Anthocyanin-rich purple wheat prolongs the life span *of Caenorhabditis elegans* probably by activating the DAF-16/FOXO transcription factor. *J Agric Food Chem*. 2013;61(12):3047–53.
6957. Blau LW. Cherry diet control for gout and arthritis. *Tex Rep Biol Med.* 1950;8(3):309–11.
6958. Kelley DS, Rasooly R, Jacob RA, Kader AA, Mackey BE. Consumption of Bing sweet cherries lowers circulating concentrations of inflammation markers in healthy men and women. *J Nutr.* 2006;136(4):981–6.
6959. Kelley DS, Adkins Y, Laugero KD. A review of the health benefits of cherries. *Nutrients*. 2018;10(3):368.
6960. Sun Y, Yolitz J, Alberico T, Sun X, Zou S. Lifespan extension by cranberry supplementation partially requires SOD2 and is life stage independent. *Exp Gerontol*. 2014;50:57–63.

6961. Guha S, Cao M, Kane RM, Savino AM, Zou S, Dong Y. The longevity effect of cranberry extract in *Caenorhabditis elegans* is modulated by *daf-16* and *osr-1*. *Age (Dordr)*. 2013;35(5):1559–74.
6962. Zhu M, Hu J, Perez E, et al. Effects of long-term cranberry supplementation on endocrine pancreas in aging rats. *J Gerontol A Biol Sci Med Sci*. 2011;66(11):1139–51.
6963. Gao Y, Wei Y, Wang Y, Gao F, Chen Z. *Lycium barbarum*: a traditional Chinese herb and a promising anti-aging agent. *Aging and Disease*. 2017;8(6):778.
6964. Neelam K, Dey S, Sim R, Lee J, Au Eong KG. *Fructus lycii*: a natural dietary supplement for amelioration of retinal diseases. *Nutrients*. 2021;13(1):246.
6965. Jeszka-Skowron M, Zgoła-Grześkowiak A, Stanisz E, Waśkiewicz A. Potential health benefits and quality of dried fruits: goji fruits, cranberries and raisins. *Food Chem*. 2017;221:228–36.
6966. Wu WB, Hung DK, Chang FW, Ong ET, Chen BH. Anti-inflammatory and anti-angiogenic effects of flavonoids isolated from *Lycium barbarum* Linnaeus on human umbilical vein endothelial cells. *Food Funct*. 2012;3(10):1068–81.
6967. Lee YJ, Ahn Y, Kwon O, et al. Dietary wolfberry extract modifies oxidative stress by controlling the expression of inflammatory mRNAs in overweight and hypercholesterolemic subjects: a randomized, double-blind, placebo-controlled trial. *J Agric Food Chem*. 2017;65(2):309–16.
6968. Grassi F, Arroyo-Garcia R. Editorial: origins and domestication of the grape. *Front Plant Sci*. 2020;11:1176.
6969. Yang J, Xiao YY. Grape phytochemicals and associated health benefits. *Crit Rev Food Sci Nutr*. 2013;53(11):1202–25.
6970. Ghaedi E, Moradi S, Aslani Z, Kord-Varkaneh H, Miraghajani M, Mohammadi H. Effects of grape products on blood lipids: a systematic review and dose-response meta-analysis of randomized controlled trials. *Food Funct*. 2019;10(10):6399–416.
6971. Rahbar AR, Mahmoudabadi MMS, Islam MS. Comparative effects of red and white grapes on oxidative markers and lipidemic parameters in adult hypercholesterolemic humans. *Food Funct*. 2015;6(6):1992–8.

6972. Kanellos PT, Kaliora AC, Protogerou AD, Tentolouris N, Perrea DN, Karathanos VT. The effect of raisins on biomarkers of endothelial function and oxidant damage; an open-label and randomized controlled intervention. *Food Res Int*. 2017;102:674–80.
6973. Chaves AA, Joshi MS, Coyle CM, et al. Vasoprotective endothelial effects of a standardized grape product in humans. Vascul Pharmacol. 2009;50(1-2):20-6.
6974. Vaisman N, Niv E. Daily consumption of red grape cell powder in a dietary dose improves cardiovascular parameters: a double blind, placebo-controlled, randomized study. *Int J Food Sci Nutr*. 2015;66(3):342–9.
6975. Yang J, Xiao YY. Grape phytochemicals and associated health benefits. *Crit Rev Food Sci Nutr*. 2013;53(11):1202–25.
6976. Li X, Yang T, Sun Z. Hormesis in health and chronic diseases. *Trends Endocrinol Metab*. 2019;30(12):944–58.
6977. Epel ES. The geroscience agenda: toxic stress, hormetic stress, and the rate of aging. *Ageing ResRev*. 2020;63:101167.
6978. Collier R. Intermittent fasting: the science of going without. *CMAJ*. 2013;185(9):E363–4.
6979. Bárcena C, Mayoral P, Quirós PM. Mitohormesis, an antiaging paradigm. *Int Rev Cell Mol Biol*. 2018;340:35–77.
6980. Calabrese EJ, Dhawan G, Kapoor R, Iavicoli I, Calabrese V. What is hormesis and its relevance to healthy aging and longevity? *Biogerontology.* 2015;16(6):693–707.
6981. Li X, Yang T, Sun Z. Hormesis in health and chronic diseases. *Trends Endocrinol Metab*. 2019;30(12):944–58.
6982. Mao L, Franke J. Hormesis in aging and neurodegeneration—a prodigy awaiting dissection. *Int J Mol Sci*. 2013;14(7):13109–28.
6983. Kaiser J. Hormesis. Sipping from a poisoned chalice. *Science*. 2003;302(5644):376–9.
6984. Calabrese EJ. Toxicology rewrites its history and rethinks its future: giving equal focus to both harmful and beneficial effects. *Environ Toxicol Chem*. 2011;30(12):2658–73.
6985. Calabrese EJ, Dhawan G, Kapoor R, Iavicoli I, Calabrese V. What is hormesis and its relevance to healthy aging and longevity? *Biogerontology.* 2015;16(6):693–707.

6986. Web of Science search results for ‘hormesis’ or ‘hormetic’. https://www.webofscience.com. Accessed December 20, 2022.
6987. Calabrese EJ, Dhawan G, Kapoor R, Iavicoli I, Calabrese V. What is hormesis and its relevance to healthy aging and longevity? *Biogerontology.* 2015;16(6):693–707.
6988. Davey WP. Prolongation of life of *Tribolium confusum* apparently due to small doses of x-rays. *J Exp Zool*. 1919;28(3):447–58.
6989. Calabrese EJ. Low doses of radiation can enhance insect lifespans. *Biogerontology*. 2013;14(4):365–81.
6990. Sutou S. Low-dose radiation from A-bombs elongated lifespan and reduced cancer mortality relative to un-irradiated individuals. *Genes Environ*. 2018;40:26.
6991. Thome C, Tharmalingam S, Pirkkanen J, Zarnke A, Laframboise T, Boreham DR. The REPAIR Project: examining the biological impacts of sub-background radiation exposure within SNOLAB, a deep underground laboratory. *Radiat Res*. 2017;188(4.2):470–4.
6992. MacLeod RD, Van den Block L, eds. *Textbook of Palliative Care*. Springer International Publishing; 2019.
6993. Marie Curie. NobelPrize.org. https://www.nobelprize.org/womenwhochangedscience/stories/marie-curie. Accessed December 26, 2022.
6994. Butler D. X-rays, not radium, may have killed Curie. *Nature*. 1995;377(6545):96.
6995. Gradari S, Pallé A, McGreevy KR, Fontán-Lozano Á, Trejo JL. Can exercise make you smarter, happier, and have more neurons? A hormetic perspective. *Front Neurosci*. 2016;10:93.
6996. Mastaloudis A, Yu TW, O’Donnell RP, Frei B, Dashwood RH, Traber MG. Endurance exercise results in DNA damage as detected by the comet assay. *Free Radic Biol Med*. 2004;36(8):966–75.
6997. Mastaloudis A, Yu TW, O’Donnell RP, Frei B, Dashwood RH, Traber MG. Endurance exercise results in DNA damage as detected by the comet assay. *Free Radic Biol Med*. 2004;36(8):966–75.
6998. Sharma A, Kaur T, Singh H, Kaur G. Intermittent fasting—dietary restriction as a biological hormetin for health benefits. In: *The Science of Hormesis in Health and Longevity*. Elsevier; 2019:99–104.

6999. Masoro EJ. The role of hormesis in life extension by dietary restriction. *Interdiscip Top Gerontol*. 2007;35:1–17.
7000. Masoro EJ. The role of hormesis in life extension by dietary restriction. *Interdiscip Top Gerontol*. 2007;35:1–17.
7001. Franco R, Navarro G, Martínez-Pinilla E. Hormetic and mitochondria-related mechanisms of antioxidant action of phytochemicals. *Antioxidants (Basel)*. 2019;8(9):373.
7002. Masoro EJ. The role of hormesis in life extension by dietary restriction. *Interdiscip Top Gerontol*. 2007;35:1–17.
7003. Schultz JC. Shared signals and the potential for phylogenetic espionage between plants and animals. *Integr Comp Biol*. 2002;42(3):454–62.
7004. Kennedy DO. Polyphenols and the human brain: plant "secondary metabolite" ecologic roles and endogenous signaling functions drive benefits. *Adv Nutr*. 2014;5(5):515–33.
7005. Franco, Navarro, Martínez-Pinilla. Hormetic and mitochondria-related mechanisms of antioxidant action of phytochemicals. *Antioxidants*. 2019;8(9):373.
7006. Glover N. The banana conjecture. Dessimoz Lab. https://lab.dessimoz.org/blog/2020/12/08/human-banana-orthologs. Published December 8, 2020. Accessed October 17, 2022.
7007. Wang DY, Kumar S, Hedges SB. Divergence time estimates for the early history of animal phyla and the origin of plants, animals and fungi. *Proc Biol Sci*. 1999;266(1415):163–71.
7008. Kushiro T, Nambara E, McCourt P. Hormone evolution: the key to signalling. *Nature.* 2003;422(6928):122.
7009. Kennedy DO. Polyphenols and the human brain: plant "secondary metabolite" ecologic roles and endogenous signaling functions drive benefits. *Adv Nutr*. 2014;5(5):515–33.
7010. Schultz JC. Shared signals and the potential for phylogenetic espionage between plants and animals. *Integr Comp Biol*. 2002;42(3):454–62.
7011. Mattson MP. Hormesis defined. *Ageing Res Rev*. 2008;7(1):1–7.
7012. Langhans W. Food components in health promotion and disease prevention. *J Agric Food Chem*. 2018;66(10):2287–94.

7013. Eid HM, Wright ML, Anil Kumar NV, et al. Significance of microbiota in obesity and metabolic diseases and the modulatory potential by medicinal plant and food ingredients. *Front Pharmacol*. 2017;8:387.
7014. Hooper PL, Hooper PL, Tytell M, Vígh L. Xenohormesis: health benefits from an eon of plant stress response evolution. *Cell Stress Chaperones*. 2010;15(6):761–70.
7015. Schultz JC. Shared signals and the potential for phylogenetic espionage between plants and animals. *Integr Comp Biol*. 2002;42(3):454–62.
7016. Franco R, Navarro G, Martínez-Pinilla E. Hormetic and mitochondria-related mechanisms of antioxidant action of phytochemicals. *Antioxidants (Basel)*. 2019;8(9):373.
7017. Martel J, Ojcius DM, Ko YF, et al. Hormetic effects of phytochemicals on health and longevity. *Trends Endocrinol Metab*. 2019;30(6):335–46.
7018. Dani C, Oliboni LS, Vanderlinde R, et al. Phenolic content and antioxidant activities of white and purple juices manufactured with organically- or conventionally-produced grapes. Food Chem Toxicol. 2007;45(12):2574-80.
7019. Baxter GJ, Graham AB, Lawrence JR, et al. Salicylic acid in soups prepared from organically and non-organically grown vegetables. Eur J Nutr. 2001;40(6):289-92.
7020. Choi SW, Yeung VTF, Collins AR, Benzie IFF. Redox-linked effects of green tea on DNA damage and repair, and influence of microsatellite polymorphism in *HMOX-1*: results of a human intervention trial. *Mutagenesis*. 2015;30(1):129–37.
7021. Niu Y, Na L, Feng R, et al. The phytochemical, EGCG, extends lifespan by reducing liver and kidney function damage and improving age-associated inflammation and oxidative stress in healthy rats. *Aging Cell*. 2013;12(6):1041–9.
7022. Yi M, Wu X, Zhuang W, et al. Tea consumption and health outcomes: umbrella review of meta-analyses of observational studies in humans. *Mol Nutr Food Res*. 2019;63(16):e1900389.
7023. Spiegelhalter D. Using speed of ageing and “microlives” to communicate the effects of lifetime habits and environment. *BMJ*.

2012 Dec 14;345:e8223.
7024. Zhang DD, Chapman E. The role of natural products in revealing NRF2 function. *Nat Prod Rep*. 2020;37(6):797–826.
7025. Botonis PG, Miliotis PG, Kounalakis SN, Koskolou MD, Geladas ND. Effects of capsaicin application on the skin during resting exposure to temperate and warm conditions. *Scand J Med Sci Sports*. 2019;29(2):171–9.
7026. Scharfenberg K, Wagner R, Wagner KG. The cytotoxic effect of ajoene, a natural product from garlic, investigated with different cell lines. *Cancer Lett*. 1990;53(2–3):103–8.
7027. Friedman T, Shalom A, Westreich M. Self-inflicted garlic burns: our experience and literature review. *Int J Dermatol*. 2006;45(10):1161–3.
7028. Mattson MP. Dietary factors, hormesis and health. *Ageing Res Rev*. 2008;7(1):43–8.
7029. Murakami A. Modulation of protein quality control systems by food phytochemicals. *J Clin Biochem Nutr*. 2013;52(3):215–27.
7030. Liu RH. Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. *Am J Clin Nutr.* 2003;78(3 Suppl):517S-20S.
7031. Holst B, Williamson G. Nutrients and phytochemicals: from bioavailability to bioefficacy beyond antioxidants. *Curr Opin Biotechnol.* 2008;19(2):73–82.
7032. Aune D, Giovannucci E, Boffetta P, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality—a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol*. 2017;46(3):1029–56.
7033. Aune D, Giovannucci E, Boffetta P, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality—a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol*. 2017;46(3):1029–56.
7034. Long T, Zhang K, Chen Y, Wu C. Trends in diet quality among older US adults from 2001 to 2018. *JAMA Netw Open*. 2022;5(3):e221880.
7035. Huang Q, Braffett BH, Simmens SJ, Young HA, Ogden CL. Dietary polyphenol intake in US adults and 10-year trends: 2007–2016. *J Acad Nutr Diet*. 2020;120(11):1821–33.

7036. Long T, Zhang K, Chen Y, Wu C. Trends in diet quality among older US adults from 2001 to 2018. *JAMA Netw Open*. 2022;5(3):e221880.
7037. Rathaur P, S R JK. Metabolism and pharmacokinetics of phytochemicals in the human body. *Curr Drug Metab*. 2019;20(14):1085–102.
7038. Zhang F, Luo W, Shi Y, Fan Z, Ji G. Should we standardize the 1,700-year-old fecal microbiota transplantation? *Am J Gastroenterol*. 2012;107(11):1755.
7039. Kong LY, Tan RX. Artemisinin, a miracle of traditional Chinese medicine. *Nat Prod Rep*. 2015;32(12):1617–21.
7040. Sharma R, Padwad Y. Perspectives of the potential implications of polyphenols in influencing the interrelationship between oxi-inflammatory stress, cellular senescence and immunosenescence during aging. *Trends Food Sci Technol*. 2020;98:41–52.
7041. Del Bo' C, Bernardi S, Marino M, et al. Systematic review on polyphenol intake and health outcomes: is there sufficient evidence to define a health-promoting polyphenol-rich dietary pattern? *Nutrients*. 2019;11(6):E1355.
7042. Williamson G, Holst B. Dietary reference intake (DRI) value for dietary polyphenols: are we heading in the right direction? *Br J Nutr*. 2008;99 Suppl 3:S55–8.
7043. Ivey KL, Jensen MK, Hodgson JM, Eliassen AH, Cassidy A, Rimm EB. Association of flavonoid-rich foods and flavonoids with risk of all-cause mortality. *Br J Nutr*. 2017;117(10):1470–7.
7044. Aliper A, Belikov AV, Garazha A, et al. In search for geroprotectors: in silico screening and in vitro validation of signalome-level mimetics of young healthy state. *Aging (Albany NY)*. 2016;8(9):2127–52.
7045. Lutchman V, Medkour Y, Samson E, et al. Discovery of plant extracts that greatly delay yeast chronological aging and have different effects on longevity-defining cellular processes. *Oncotarget*. 2016;7(13):16542–66.
7046. Navrotskaya VV, Oxenkrug G, Vorobyova LI, Summergrad P. Berberine prolongs life span and stimulates locomotor activity of *Drosophila melanogaster*. *Am J Plant Sci*. 2012;3(7A):1037–40.
7047. Chattopadhyay D, Thirumurugan K. Longevity promoting efficacies of different plant extracts in lower model organisms. *Mech Ageing*

Dev. 2018;171:47–57.

7048. Vayndorf EM, Lee SS, Liu RH. Whole apple extracts increase lifespan, healthspan and resistance to stress in *Caenorhabditis elegans*. *J Funct Foods*. 2013;5(3):1236–43.

7049. Chattopadhyay D, Thirumurugan K. Longevity promoting efficacies of different plant extracts in lower model organisms. *Mech Ageing Dev*. 2018;171:47–57.

7050. Dakik P, Rodriguez MEL, Junio JAB, et al. Discovery of fifteen new geroprotective plant extracts and identification of cellular processes they affect to prolong the chronological lifespan of budding yeast. *Oncotarget*. 2020;11(23):2182–203.

7051. Chattopadhyay D, Thirumurugan K. Longevity promoting efficacies of different plant extracts in lower model organisms. *Mech Ageing Dev*. 2018;171:47–57.

7052. Shimizu C, Wakita Y, Inoue T, et al. Effects of lifelong intake of lemon polyphenols on aging and intestinal microbiome in the senescence-accelerated mouse prone 1 (SAMP1). *Sci Rep*. 2019;9(1):3671.

7053. Spindler SR, Mote PL, Flegal JM, Teter B. Influence on longevity of blueberry, cinnamon, green and black tea, pomegranate, sesame, curcumin, morin, pycnogenol, quercetin, and taxifolin fed iso-calorically to long-lived, F1 hybrid mice. *Rejuvenation Res*. 2013;16(2):143–51.

7054. Kitani K, Osawa T, Yokozawa T. The effects of tetrahydrocurcumin and green tea polyphenol on the survival of male C57BL/6 mice. *Biogerontology*. 2007;8(5):567–73.

7055. Spindler SR, Mote PL, Flegal JM, Teter B. Influence on longevity of blueberry, cinnamon, green and black tea, pomegranate, sesame, curcumin, morin, pycnogenol, quercetin, and taxifolin fed iso-calorically to long-lived, F1 hybrid mice. *Rejuvenation Res*. 2013;16(2):143–51.

7056. Harris SB, Weindruch R, Smith GS, Mickey MR, and Walford RL. Dietary restriction alone and in combination with oral ethoxyquine/2-mercaptoethylamine in mice. *J Gerontol.* 1990;45(5):B141–7.

7057. Aires DJ, Rockwell G, Wang T, et al. Potentiation of dietary restriction-induced lifespan extension by polyphenols. *Biochim*

Biophys Acta. 2012;1822(4):522–6.
7058. Brykman MC, Streusand Goldman V, Sarma N, Oketch-Rabah HA, Biswas D, Giancaspro GI. What should clinicians know about dietary supplement quality? *AMA J Ethics*. 2022;24(5):E382–9.
7059. Marginã D, Ilie M, Grădinaru D, Androutsopoulos VP, Kouretas D, Tsatsakis AM. Natural products—friends or foes? *Toxicol Lett.* 2015;236(3):154–67.
7060. Ames BN. Prolonging healthy aging: longevity vitamins and proteins. *Proc Natl Acad Sci U S A*. 2018;115(43):10836–44.
7061. Uysal U, Seremet S, Lamping JW, et al. Consumption of polyphenol plants may slow aging and associated diseases. *Curr Pharm Des*. 2013;19(34):6094–111.
7062. Nakatani Y, Yaguchi Y, Komura T, et al. Sesamin extends lifespan through pathways related to dietary restriction in *Caenorhabditis elegans*. *Eur J Nutr.* 2018;57(3):1137–46.
7063. Zuo Y, Peng C, Liang Y, et al. Sesamin extends the mean lifespan of fruit flies. *Biogerontology*. 2013;14(2):107–19.
7064. Wichitsranoi J, Weerapreeyakul N, Boonsiri P, et al. Antihypertensive and antioxidant effects of dietary black sesame meal in pre-hypertensive humans. *Nutr J*. 2011;10:82.
7065. Zhou L, Lin X, Abbasi AM, Zheng B. Phytochemical contents and antioxidant and antiproliferative activities of selected black and white sesame seeds. *Biomed Res Int*. 2016;2016:8495630.
7066. Kim KS, Park SH. Anthrasesamone F from the seeds of black *Sesamum indicum*. *Biosci Biotechnol Biochem*. 2008;72(6):1626–7.
7067. Lansky EP, Jiang W, Mo H, et al. Possible synergistic prostate cancer suppression by anatomically discrete pomegranate fractions. *Invest New Drugs*. 2005;23(1):11–20.
7068. Seeram NP, Adams LS, Hardy ML, Heber D. Total cranberry extract versus its phytochemical constituents: antiproliferative and synergistic effects against human tumor cell lines. *J Agric Food Chem*. 2004;52(9):2512–7.
7069. Brahmbhatt M, Gundala SR, Asif G, Shamsi SA, Aneja R. Ginger phytochemicals exhibit synergy to inhibit prostate cancer cell proliferation. *Nutr Cancer*. 2013;65(2):263–72.

7070. Radhakrishnan S, Reddivari L, Sclafani R, Das UN, Vanamala J. Resveratrol potentiates grape seed extract induced human colon cancer cell apoptosis. *Front Biosci (Elite Ed).* 2011;3(4):1509–23.
7071. Pérez-Sánchez A, Barrajón-Catalán E, Ruiz-Torres V, et al. Rosemary (*Rosmarinus officinalis*) extract causes ROS-induced necrotic cell death and inhibits tumor growth *in vivo*. *Sci Rep*. 2019;9(1):808.
7072. Sporn MB, Liby KT. Is lycopene an effective agent for preventing prostate cancer? *Cancer Prev Res (Phila).* 2013;6(5):384–6.
7073. Kumar NB, Besterman-Dahan K, Kang L, et al. Results of a randomized clinical trial of the action of several doses of lycopene in localized prostate cancer: administration prior to radical prostatectomy. *Clin Med Urol*. 2008;1:1–14.
7074. Bowen P, Chen L, Stacewicz-Sapuntzakis M, et al. Tomato sauce supplementation and prostate cancer: lycopene accumulation and modulation of biomarkers of carcinogenesis. *Exp Biol Med (Maywood)*. 2002;227(10):886–93.
7075. Linnewiel-Hermoni K, Khanin M, Danilenko M, et al. The anti-cancer effects of carotenoids and other phytonutrients resides in their combined activity. *Arch Biochem Biophys*. 2015;572:28–35.
7076. Talvas J, Caris-Veyrat C, Guy L, et al. Differential effects of lycopene consumed in tomato paste and lycopene in the form of a purified extract on target genes of cancer prostatic cells. *Am J Clin Nutr*. 2010;91(6):1716–24.
7077. Warner M. *Pandora's Lunchbox: How Processed Food Took Over the American Meal*. Simon & Schuster; 2014.
7078. Liu RH. Potential synergy of phytochemicals in cancer prevention: mechanism of action. *J Nutr*. 2004;134(12 Suppl):3479S-85S.
7079. Wang S, Meckling KA, Marcone MF, Kakuda Y, Tsao R. Synergistic, additive, and antagonistic effects of food mixtures on total antioxidant capacities. *J Agric Food Chem*. 2011;59(3):960–8.
7080. Wang S, Meckling KA, Marcone MF, Kakuda Y, Tsao R. Synergistic, additive, and antagonistic effects of food mixtures on total antioxidant capacities. *J Agric Food Chem*. 2011;59(3):960–8.
7081. Zhou JR, Yu L, Zhong Y, Blackburn GL. Soy phytochemicals and tea bioactive components synergistically inhibit androgen-sensitive human prostate tumors in mice. *J Nutr*. 2003;133(2):516–21.

7082. Morré DJ, Morré DM. Synergistic *Capsicum*-tea mixtures with anticancer activity. *J Pharm Pharmacol*. 2003;55(7):987–94.
7083. Ouhtit A, Gaur RL, Abdraboh M, et al. Simultaneous inhibition of cell-cycle, proliferation, survival, metastatic pathways and induction of apoptosis in breast cancer cells by a phytochemical super-cocktail: genes that underpin its mode of action. *J Cancer*. 2013;4(9):703–15.
7084. Canene-Adams K, Lindshield BL, Wang S, Jeffery EH, Clinton SK, Erdman JW. Combinations of tomato and broccoli enhance antitumor activity in Dunning R3327-H prostate adenocarcinomas. *Cancer Res*. 2007;67(2):836–43.
7085. Simon HB. On Call: two points of view on pizza. *Harvard Men's Health Watch*. 2003;(6):8.
7086. Boivin D, Lamy S, Lord-Dufour S, et al. Antiproliferative and antioxidant activities of common vegetables: a comparative study. *Food Chem*. 2009;112(2):374–80.
7087. Yong LC, Petersen MR, Sigurdson AJ, Sampson LA, Ward EM. High dietary antioxidant intakes are associated with decreased chromosome translocation frequency in airline pilots. *Am J Clin Nutr*. 2009;90(5):1402–10.
7088. Thompson HJ, Heimendinger J, Gillette C, et al. *In vivo* investigation of changes in biomarkers of oxidative stress induced by plant food rich diets. *J Agric Food Chem*. 2005;53(15):6126–32.
7089. Thompson HJ, Heimendinger J, Diker A, et al. Dietary botanical diversity affects the reduction of oxidative biomarkers in women due to high vegetable and fruit intake. *J Nutr*. 2006;136(8):2207–12.
7090. Bhupathiraju SN, Tucker KL. Greater variety in fruit and vegetable intake is associated with lower inflammation in Puerto Rican adults. *Am J Clin Nutr*. 2011;93(1):37–46.
7091. Ye X, Bhupathiraju SN, Tucker KL. Variety in fruit and vegetable intake and cognitive function in middle-aged and older Puerto Rican adults. *Br J Nutr*. 2013;109(3):503–10.
7092. Thomas R, Williams M, Sharma H, Chaudry A, Bellamy P. A double-blind, placebo-controlled randomised trial evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer—the U.K. NCRN Pomi-T study. *Prostate Cancer Prostatic Dis*. 2014;17(2):180–6.

7093. World Cancer Research Fund International. Diet, Nutrition, Physical Activity and Cancer: A Global Perspective: A Summary of the Third Expert Report. World Cancer Research Fund International; 2018.
7094. Ornish D, Weidner G, Fair WR, et al. Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol*. 2005;174(3):1065–70.
7095. Robinson VL. Rethinking the central dogma: noncoding RNAs are biologically relevant. *Urol Oncol*. 2009;27(3):304–6.
7096. Robinson VL. Rethinking the central dogma: noncoding RNAs are biologically relevant. *Urol Oncol*. 2009;27(3):304–6.
7097. McNeill EM, Hirschi KD. Roles of regulatory RNAs in nutritional control. *Annu Rev Nutr*. 2020;40:77–104.
7098. Robinson VL. Rethinking the central dogma: noncoding RNAs are biologically relevant. *Urol Oncol*. 2009;27(3):304–6.
7099. Ruvkun G. Glimpses of a tiny RNA world. *Science*. 2001;294(5543):797–9.
7100. Roberts BM, Blewitt G, Dailey C, et al. Search for domain wall dark matter with atomic clocks on board global positioning system satellites. *Nat Commun*. 2017;8(1):1195.
7101. Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T. Identification of novel genes coding for small expressed RNAs. *Science*. 2001;294(5543):853–8.
7102. Kalarikkal SP, Sundaram GM. Inter-kingdom regulation of human transcriptome by dietary microRNAs: emerging bioactives from edible plants to treat human diseases? *Trends Food Sci Technol*. 2021;118:723–34.
7103. Robinson VL. Rethinking the central dogma: noncoding RNAs are biologically relevant. *Urol Oncol*. 2009;27(3):304–6.
7104. Piovesan A, Caracausi M, Antonaros F, Pelleri MC, Vitale L. GeneBase 1.1: a tool to summarize data from NCBI gene datasets and its application to an update of human gene statistics. *Database (Oxford)*. 2016;2016:baw153.
7105. Lee RC, Feinbaum RL, Ambros V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell*. 1993;75(5):843–54.

7106. Díez-Sainz E, Lorente-Cebrián S, Aranaz P, Riezu-Boj JI, Martínez JA, Milagro FI. Potential mechanisms linking food-derived microRNAs, gut microbiota and intestinal barrier functions in the context of nutrition and human health. *Front Nutr*. 2021;8:586564.
7107. Tarallo S, Pardini B, Mancuso G, et al. MicroRNA expression in relation to different dietary habits: a comparison in stool and plasma samples. *Mutagenesis*. 2014;29(5):385–91.
7108. Majidinia M, Karimian A, Alemi F, Yousefi B, Safa A. Targeting miRNAs by polyphenols: novel therapeutic strategy for aging. *Biochem Pharmacol*. 2020;173:113688.
7109. McNeill EM, Hirschi KD. Roles of regulatory RNAs in nutritional control. *Annu Rev Nutr*. 2020;40:77–104.
7110. Cong L, Zhao Y, Pogue AI, Lukiw WJ. Role of microRNA (miRNA) and viroids in lethal diseases of plants and animals. Potential contribution to human neurodegenerative disorders. *Biochemistry Moscow*. 2018;83(9):1018–29.
7111. McNeill EM, Hirschi KD. Roles of regulatory RNAs in nutritional control. *Annu Rev Nutr*. 2020;40:77–104.
7112. Weber JA, Baxter DH, Zhang S, et al. The microRNA spectrum in 12 body fluids. *Clin Chem*. 2010;56(11):1733–41.
7113. Alshehri B. Plant-derived xenomiRs and cancer: cross-kingdom gene regulation. *Saudi J Biol Sci*. 2021;28(4):2408–22.
7114. Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol*. 2007;9(6):654–9.
7115. Cammarata G, Duro G, Chiara TD, Curto AL, Taverna S, Candore G. Circulating miRNAs in successful and unsuccessful aging. A mini-review. *Curr Pharm Des*. 2019;25(39):4150–3.
7116. Wang L, Sadri M, Giraud D, Zempleni J. RNase H2-dependent polymerase chain reaction and elimination of confounders in sample collection, storage, and analysis strengthen evidence that microRNAs in bovine milk are bioavailable in humans. *J Nutr*. 2018;148(1):153–9.
7117. Bernstein E, Kim SY, Carmell MA, et al. Dicer is essential for mouse development. *Nat Genet*. 2003;35(3):215–7.

7118. Kalarikkal SP, Sundaram GM. Inter-kingdom regulation of human transcriptome by dietary microRNAs: emerging bioactives from edible plants to treat human diseases? *Trends Food Sci Technol*. 2021;118:723–34.
7119. Cammarata G, Duro G, Chiara TD, Curto AL, Taverna S, Candore G. Circulating miRNAs in successful and unsuccessful aging. A mini-review. *Curr Pharm Des*. 2019;25(39):4150–3.
7120. Majidinia M, Mir SM, Mirza-Aghazadeh-Attari M, et al. MicroRNAs, DNA damage response and ageing. *Biogerontology*. 2020;21(3):275–91.
7121. Lee RC, Feinbaum RL, Ambros V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell*. 1993;75(5):843–54.
7122. Boehm M, Slack F. A developmental timing microRNA and its target regulate life span in *C. elegans*. *Science*. 2005;310(5756):1954–7.
7123. Morris BJ, Willcox DC, Donlon TA, Willcox BJ. B>FOXO$_3$: a major gene for human longevity—a mini-review. *Gerontology*. 2015;61(6):515–25.
7124. Calissi G, Lam EWF, Link W. Therapeutic strategies targeting FOXO transcription factors. *Nat Rev Drug Discov*. 2021;20(1):21–38.
7125. Pincus Z, Smith-Vikos T, Slack FJ. MicroRNA predictors of longevity in *Caenorhabditis elegans*. *PLoS Genet*. 2011;7(9):e1002306.
7126. Green CD, Huang Y, Dou X, Yang L, Liu Y, Han JDJ. Impact of dietary interventions on noncoding RNA networks and mRNAs encoding chromatin-related factors. *Cell Rep*. 2017;18(12):2957–68.
7127. Du WW, Yang W, Fang L, et al. miR-17 extends mouse lifespan by inhibiting senescence signaling mediated by MKP7. *Cell Death Dis*. 2014;5(7):e1355.
7128. Cammarata G, Duro G, Chiara TD, Curto AL, Taverna S, Candore G. Circulating miRNAs in successful and unsuccessful aging. A mini-review. *Curr Pharm Des*. 2019;25(39):4150–3.
7129. Smith-Vikos T, Liu Z, Parsons C, et al. A serum miRNA profile of human longevity: findings from the Baltimore Longitudinal Study of Aging (BLSA). *Aging (Albany NY)*. 2016;8(11):2971–87.

7130. Kumar P, Dezso Z, MacKenzie C, et al. Circulating miRNA biomarkers for Alzheimer's disease. *PLoS One.* 2013;8(7):e69807.
7131. Wu S, Kim TK, Wu X, et al. Circulating microRNAs and life expectancy among identical twins. *Ann Hum Genet*. 2016;80(5):247–56.
7132. Kalarikkal SP, Sundaram GM. Inter-kingdom regulation of human transcriptome by dietary microRNAs: emerging bioactives from edible plants to treat human diseases? *Trends Food Sci Technol*. 2021;118:723–34.
7133. Dávalos A, Pinilla L, López de Las Hazas MC, et al. Dietary microRNAs and cancer: a new therapeutic approach? *Semin Cancer Biol*. 2021;73:19–29.
7134. Gkotzamanis V, Magriplis E, Panagiotakos D. The effect of physical activity interventions on cognitive function of older adults: a systematic review of clinical trials. *Psychiatriki*. Published online February 21, 2022.
7135. Pisani S, Mueller C, Huntley J, Aarsland D, Kempton MJ. A meta-analysis of randomised controlled trials of physical activity in people with Alzheimer's disease and mild cognitive impairment with a comparison to donepezil. *Int J Geriatr Psychiatry*. 2021;36(10):1471–87.
7136. Wang Y, Veremeyko T, Wong AHK, et al. Downregulation of miR-132/212 impairs S-nitrosylation balance and induces tau phosphorylation in Alzheimer's disease. *Neurobiol Aging*. 2017;51:156–66.
7137. Lugli G, Cohen AM, Bennett DA, et al. Plasma exosomal miRNAs in persons with and without Alzheimer disease: altered expression and prospects for biomarkers. *PloS One*. 2015;10(10):e0139233.
7138. Radom-Aizik S, Zaldivar F, Leu S, Adams GR, Oliver S, Cooper DM. Effects of exercise on microRNA expression in young males peripheral blood mononuclear cells. *Clin Transl Sci*. 2012;5(1):32–8.
7139. Nielsen S, Åkerström T, Rinnov A, et al. The miRNA plasma signature in response to acute aerobic exercise and endurance training. *PLoS One*. 2014;9(2):e87308.
7140. Fernández-de Frutos M, Galán-Chilet I, Goedeke L, et al. MicroRNA 7 impairs insulin signaling and regulates aβ levels through

posttranscriptional regulation of the insulin receptor substrate 2, insulin receptor, insulin-degrading enzyme, and liver X receptor pathway. *Mol Cell Biol*. 2019;39(22):e00170–19.

7141. Denk J, Boelmans K, Siegismund C, Lassner D, Arlt S, Jahn H. MicroRNA profiling of CSF reveals potential biomarkers to detect Alzheimer's disease. *PloS One*. 2015;10(5):e0126423.

7142. Nielsen S, Åkerström T, Rinnov A, et al. The miRNA plasma signature in response to acute aerobic exercise and endurance training. *PloS One*. 2014;9(2):e87308.

7143. Barber JL, Zellars KN, Barringhaus KG, Bouchard C, Spinale FG, Sarzynski MA. The effects of regular exercise on circulating cardiovascular-related microRNAs. *Sci Rep*. 2019;9(1):7527.

7144. Wu Y, Xu J, Xu J, et al. Lower serum levels of miR-29c-3p and miR-19b-3p as biomarkers for Alzheimer's disease. *Tohoku J Exp Med*. 2017;242(2):129–36.

7145. Arena A, Iyer AM, Milenkovic I, et al. Developmental expression and dysregulation of miR-146a and miR-155 in Down's syndrome and mouse models of Down's syndrome and Alzheimer's disease. *Curr Alzheimer Res*. 2017;14(12):1305–17.

7146. Alexandrov PN, Dua P, Hill JM, Bhattacharjee S, Zhao Y, Lukiw WJ. MicroRNA (miRNA) speciation in Alzheimer's disease (AD) cerebrospinal fluid (CSF) and extracellular fluid (ECF). *Int J Biochem Mol Biol.* 2012;3(4):365–73.

7147. Sawada S, Kon M, Wada S, Ushida T, Suzuki K, Akimoto T. Profiling of circulating microRNAs after a bout of acute resistance exercise in humans. *PLoS One*. 2013;8(7):e70823.

7148. Li Y, Yao M, Zhou Q, et al. Dynamic regulation of circulating microRNAs during acute exercise and long-term exercise training in basketball athletes. *Front Physiol*. 2018;9:282.

7149. Baggish AL, Hale A, Weiner RB, et al. Dynamic regulation of circulating microRNA during acute exhaustive exercise and sustained aerobic exercise training. *J Physiol*. 2011;589(Pt 16):3983–94.

7150. Baggish AL, Park J, Min PK, et al. Rapid upregulation and clearance of distinct circulating microRNAs after prolonged aerobic exercise. *J Appl Physiol (1985).* 2014;116(5):522–31.

7151. Improta-Caria AC, Nonaka CKV, Cavalcante BRR, De Sousa RAL, Aras Júnior R, Souza BS de F. Modulation of microRNAs as a potential molecular mechanism involved in the beneficial actions of physical exercise in Alzheimer disease. *Int J Mol Sci*. 2020;21(14):E4977.
7152. Majidinia M, Karimian A, Alemi F, Yousefi B, Safa A. Targeting miRNAs by polyphenols: novel therapeutic strategy for aging. *Biochem Pharmacol*. 2020;173:113688.
7153. García-Segura L, Pérez-Andrade M, Miranda-Ríos J. The emerging role of microRNAs in the regulation of gene expression by nutrients. *J Nutrigenet Nutrigenomics*. 2013;6(1):16–31.
7154. Daimiel L, Micó V, Valls RM, et al. Impact of phenol-enriched virgin olive oils on the postprandial levels of circulating microRNAs related to cardiovascular disease. *Mol Nutr Food Res*. 2020;64(15):2000049.
7155. López de Las Hazas MC, Gil-Zamorano J, Cofán M, et al. One-year dietary supplementation with walnuts modifies exosomal miRNA in elderly subjects. *Eur J Nutr*. 2021;60(4):1999–2011.
7156. Ortega FJ, Cardona-Alvarado MI, Mercader JM, et al. Circulating profiling reveals the effect of a polyunsaturated fatty acid–enriched diet on common microRNAs. *J Nutr Biochem*. 2015;26(10):1095–101.
7157. Shao D, Lian Z, Di Y, et al. Dietary compounds have potential in controlling atherosclerosis by modulating macrophage cholesterol metabolism and inflammation via miRNA. *NPJ Sci Food*. 2018;2:13.
7158. Koolivand M, Ansari M, Piroozian F, Moein S, MalekZadeh K. Alleviating the progression of acute myeloid leukemia (AML) by sulforaphane through controlling miR-155 levels. *Mol Biol Rep*. 2018;45(6):2491–9.
7159. Singh S, Raza W, Parveen S, Meena A, Luqman S. Flavonoid display ability to target microRNAs in cancer pathogenesis. *Biochem Pharmacol*. 2021;189:114409.
7160. Guo X, Cai Q, Bao P, et al. Long-term soy consumption and tumor tissue microRNA and gene expression in triple negative breast cancer. *Cancer*. 2016;122(16):2544–51.
7161. Boutas I, Kontogeorgi A, Dimitrakakis C, Kalantaridou SN. Soy isoflavones and breast cancer risk: a meta-analysis. *In Vivo*.

2022;36(2):556–62.
7162. Qiu S, Jiang C. Soy and isoflavones consumption and breast cancer survival and recurrence: a systematic review and meta-analysis. *Eur J Nutr*. 2019;58(8):3079–90.
7163. Tarallo S, Ferrero G, De Filippis F, et al. Stool microRNA profiles reflect different dietary and gut microbiome patterns in healthy individuals. *Gut*. 2022;71(7):1302–14.
7164. Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple health outcomes: a systematic review with meta-analysis of observational studies. *Crit Rev Food Sci Nutr*. 2017;57(17):3640–9.
7165. Humphreys KJ, Conlon MA, Young GP, et al. Dietary manipulation of oncogenic microRNA expression in human rectal mucosa: a randomized trial. *Cancer Prev Res (Phila)*. 2014;7(8):786–95.
7166. Papaioannou MD, Koufaris C, Gooderham NJ. The cooked meat-derived mammary carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) elicits estrogenic-like microRNA responses in breast cancer cells. *Toxicol Lett*. 2014;229(1):9–16.
7167. Yang WM, Jeong HJ, Park SY, Lee W. Induction of miR-29a by saturated fatty acids impairs insulin signaling and glucose uptake through translational repression of IRS-1 in myocytes. *FEBS Lett*. 2014;588(13):2170–6.
7168. Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, vegan diets and multiple health outcomes: a systematic review with meta-analysis of observational studies. *Crit Rev Food Sci Nutr*. 2017;57(17):3640–9.
7169. Sinha R, Rothman N, Brown ED, et al. High concentrations of the carcinogen 2-amino-1-methyl-6-phynylimidazo-[4,5-b]pyridine (PhIP) occur in chicken but are dependent on the cooking method. *Cancer Res*. 1995;55(20):4516–9.
7170. Liu T, Gatto NM, Chen Z, et al. Vegetarian diets, circulating miRNA expression and healthspan in subjects living in the Blue Zone. *Precis Clin Med*. 2020;3(4):245–59.
7171. Von Linné, C. Salvius L. *Caroli Linnæi ... systema naturæ per regna tria naturæ, secundum classes, ordines, genera, species, cum*

characteribus differentiis, synonymis, locis. Impensis Direct. Laurentii Salvii; 1758.
7172. Haeckel E. *Generelle morphologie der organismen. Allgemeine grundzüge der organischen formen-wissenschaft, mechanisch begründet durch die von Charles Darwin reformirte descendenztheorie.* G. Reimer; 1866.
7173. Ruggiero MA, Gordon DP, Orrell TM, et al. A higher level classification of all living organisms. *PLoS One*. 2015;10(4):e0119248.
7174. Dalmasso G, Nguyen HTT, Yan Y, et al. Microbiota modulate host gene expression via microRNAs. *PLoS One*. 2011;6(4):e19293.
7175. Choi JW, Kim SC, Hong SH, Lee HJ. Secretable small RNAs via outer membrane vesicles in periodontal pathogens. *J Dent Res*. 2017;96(4):458–66.
7176. Liu S, da Cunha AP, Rezende RM, et al. The host shapes the gut microbiota via fecal microRNA. *Cell Host Microbe*. 2016;19(1):32–43.
7177. Munroe R. Family reunion. xkcd. https://xkcd.com/2608/. Accessed October 17, 2022.
7178. Wang DY, Kumar S, Hedges SB. Divergence time estimates for the early history of animal phyla and the origin of plants, animals and fungi. *Proc Biol Sci*. 1999;266(1415):163–71.
7179. Zhao Y, Cong L, Lukiw WJ. Plant and animal microRNAs (miRNAs) and their potential for inter-kingdom communication. *Cell Mol Neurobiol*. 2018;38(1):133–40.
7180. Zhang T, Jin Y, Zhao JH, et al. Host-induced gene silencing of the target gene in fungal cells confers effective resistance to the cotton wilt disease pathogen *Verticillium dahliae*. *Mol Plant*. 2016;9(6):939–42.
7181. Cong L, Zhao Y, Pogue AI, Lukiw WJ. Role of microRNA (miRNA) and viroids in lethal diseases of plants and animals. Potential contribution to human neurodegenerative disorders. *Biochemistry Moscow*. 2018;83(9):1018–29.
7182. McNeill EM, Hirschi KD. Roles of regulatory RNAs in nutritional control. *Annu Rev Nutr*. 2020;40:77–104.

7183. Jia M, He J, Bai W, et al. Cross-kingdom regulation by dietary plant miRNAs: an evidence-based review with recent updates. *Food Funct*. 2021;12(20):9549–62.
7184. Li Z, Xu R, Li N. MicroRNAs from plants to animals, do they define a new messenger for communication? *Nutr Metab (Lond)*. 2018;15:68.
7185. Cong L, Zhao Y, Pogue AI, Lukiw WJ. Role of microRNA (miRNA) and viroids in lethal diseases of plants and animals. Potential contribution to human neurodegenerative disorders. *Biochemistry Moscow*. 2018;83(9):1018–29.
7186. Díez-Sainz E, Lorente-Cebrián S, Aranaz P, Riezu-Boj JI, Martínez JA, Milagro FI. Potential mechanisms linking food-derived microRNAs, gut microbiota and intestinal barrier functions in the context of nutrition and human health. *Front Nutr*. 2021;8:586564.
7187. Zhao JH, Zhang T, Liu QY, Guo HS. Trans-kingdom RNAs and their fates in recipient cells: advances, utilization, and perspectives. *Plant Commun*. 2021;2(2):100167.
7188. García-Segura L, Pérez-Andrade M, Miranda-Ríos J. The emerging role of microRNAs in the regulation of gene expression by nutrients. *J Nutrigenet Nutrigenomics*. 2013;6(1):16–31.
7189. Campbell K. The doubts about dietary RNA. *Nature*. 2020;582:s10–1.
7190. Zhu WJ, Liu Y, Cao YN, Peng LX, Yan ZY, Zhao G. Insights into health-promoting effects of plant microRNAs: a review. *J Agric Food Chem*. 2021;69(48):14372–86.
7191. Li M, Chen T, He JJ, et al. Plant MIR167e-5p inhibits enterocyte proliferation by targeting β-catenin. *Cells*. 2019;8(11):1385.
7192. del Pozo-Acebo L, López de las Hazas M, Margollés A, Dávalos A, García-Ruiz A. Eating microRNAs: pharmacological opportunities for cross-kingdom regulation and implications in host gene and gut microbiota modulation. *British J Pharmacology*. 2021;178(11):2218–45.
7193. Dávalos A, Pinilla L, López de Las Hazas MC, et al. Dietary microRNAs and cancer: a new therapeutic approach? *Semin Cancer Biol*. 2021;73:19–29.

7194. Chin AR, Fong MY, Somlo G, et al. Cross-kingdom inhibition of breast cancer growth by plant miR159. *Cell Res*. 2016;26(2):217–28.
7195. Cavallini A, Minervini F, Garbetta A, et al. High degradation and no bioavailability of artichoke miRNAs assessed using an in vitro digestion/Caco-2 cell model. *Nutr Res*. 2018;60:68–76.
7196. Philip A, Ferro VA, Tate RJ. Determination of the potential bioavailability of plant microRNAs using a simulated human digestion process. *Mol Nutr Food Res*. 2015;59(10):1962–72.
7197. Link J, Thon C, Schanze D, et al. Food-derived xeno-microRNAs: influence of diet and detectability in gastrointestinal tract–proof-of-principle study. *Mol Nutr Food Res*. 2019;63(2):e1800076.
7198. Snow JW, Hale AE, Isaacs SK, Baggish AL, Chan SY. Ineffective delivery of diet-derived microRNAs to recipient animal organisms. *RNA Biol*. 2013;10(7):1107–16.
7199. Link J, Thon C, Schanze D, et al. Food-derived xeno-microRNAs: influence of diet and detectability in gastrointestinal tract–proof-of-principle study. *Mol Nutr Food Res*. 2019;63(2):e1800076.
7200. Kalarikkal SP, Sundaram GM. Inter-kingdom regulation of human transcriptome by dietary microRNAs: emerging bioactives from edible plants to treat human diseases? *Trends Food Sci Technol*. 2021;118:723–34.
7201. Zhang L, Hou D, Chen X, et al. Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA. *Cell Res*. 2012;22(1):107–26.
7202. Chen Q, Zhang F, Dong L, et al. SIDT1-dependent absorption in the stomach mediates host uptake of dietary and orally administered microRNAs. *Cell Res*. 2021;31(3):247–58.
7203. Kalarikkal SP, Sundaram GM. Inter-kingdom regulation of human transcriptome by dietary microRNAs: emerging bioactives from edible plants to treat human diseases? *Trends Food Sci Technol*. 2021;118:723–34.
7204. Wang Q, Zhuang X, Mu J, et al. Delivery of therapeutic agents by nanoparticles made of grapefruit-derived lipids. *Nat Commun*. 2013;4:1867.
7205. Kalarikkal SP, Sundaram GM. Inter-kingdom regulation of human transcriptome by dietary microRNAs: emerging bioactives from

edible plants to treat human diseases? *Trends Food Sci Technol*. 2021;118:723–34.
7206. Zhu WJ, Liu Y, Cao YN, Peng LX, Yan ZY, Zhao G. Insights into health-promoting effects of plant microRNAs: a review. *J Agric Food Chem*. 2021;69(48):14372–86.
7207. Yu B, Yang Z, Li J, et al. Methylation as a crucial step in plant microRNA biogenesis. *Science*. 2005;307(5711):932–5.
7208. Link J, Thon C, Schanze D, et al. Food-derived xeno-microRNAs: influence of diet and detectability in gastrointestinal tract–proof-of-principle study. *Mol Nutr Food Res*. 2019;63(2):e1800076.
7209. Liang G, Zhu Y, Sun B, et al. Assessing the survival of exogenous plant microRNA in mice. *Food Sci Nutr*. 2014;2(4):380–8.
7210. Luo Y, Wang P, Wang X, et al. Detection of dietetically absorbed maize-derived microRNAs in pigs. *Sci Rep*. 2017;7(1):645.
7211. Chen Q, Zhang F, Dong L, et al. SIDT1-dependent absorption in the stomach mediates host uptake of dietary and orally administered microRNAs. *Cell Res*. 2021;31(3):247–58.
7212. Alvarez-Erviti L, Seow Y, Yin H, Betts C, Lakhal S, Wood MJA. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. *Nat Biotechnol*. 2011;29(4):341–5.
7213. Liang G, Zhu Y, Sun B, et al. Assessing the survival of exogenous plant microRNA in mice. *Food Sci Nutr*. 2014;2(4):380–8.
7214. Zhang L, Hou D, Chen X, et al. Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA. *Cell Res*. 2012;22(1):107–26.
7215. Chen X, Liu L, Chu Q, et al. Large-scale identification of extracellular plant miRNAs in mammals implicates their dietary intake. *PLoS One*. 2021;16(9):e0257878.
7216. Li J, Zhang Y, Li D, et al. Small non-coding RNAs transfer through mammalian placenta and directly regulate fetal gene expression. *Protein Cell*. 2015;6(6):391–6.
7217. Xiao J, Feng S, Wang X, et al. Identification of exosome-like nanoparticle-derived microRNAs from 11 edible fruits and vegetables. *PeerJ*. 2018;6:e5186.
7218. Ju S, Mu J, Dokland T, et al. Grape exosome-like nanoparticles induce intestinal stem cells and protect mice from DSS-induced

colitis. *Mol Ther*. 2013;21(7):1345–57.
7219. Mu J, Zhuang X, Wang Q, et al. Interspecies communication between plant and mouse gut host cells through edible plant derived exosome-like nanoparticles. *Mol Nutr Food Res*. 2014;58(7):1561–73.
7220. Cavalieri D, Rizzetto L, Tocci N, et al. Plant microRNAs as novel immunomodulatory agents. *Sci Rep*. 2016;6:25761.
7221. Hou D, He F, Ma L, et al. The potential atheroprotective role of plant MIR156a as a repressor of monocyte recruitment on inflamed human endothelial cells. *J Nutr Biochem*. 2018;57:197–205.
7222. Ojagbemi A, Okekunle AP, Owolabi M, et al. Dietary intakes of green leafy vegetables and incidence of cardiovascular diseases. *Cardiovasc J Afr*. 2021;32(4):215–23.
7223. Kalarikkal SP, Sundaram GM. Inter-kingdom regulation of human transcriptome by dietary microRNAs: emerging bioactives from edible plants to treat human diseases? *Trends Food Sci Technol*. 2021;118:723–34.
7224. Ngo SNT, Williams DB. Protective effect of isothiocyanates from cruciferous vegetables on breast cancer: epidemiological and preclinical perspectives. *Anticancer Agents Med Chem*. 2021;21(11):1413–30.
7225. Li D, Yang J, Yang Y, et al. A timely review of cross-kingdom regulation of plant-derived microRNAs. *Front Genet*. 2021;12:613197.
7226. Xiang J, Huang JC, Xu C, et al. [Effect of miRNA from *Glycyrrhiza uralensis* decoction on gene expression of human immune cells]. *Zhongguo Zhong Yao Za Zhi*. 2017;42(9):1752–6.
7227. Qin Y, Zheng B, Yang G shan, et al. *Salvia miltiorrhiza*-derived Sal-miR-58 induces autophagy and attenuates inflammation in vascular smooth muscle cells. *Mol Ther Nucleic Acids*. 2020;21:492–511.
7228. Yang GS, Zheng B, Qin Y, et al. *Salvia miltiorrhiza*-derived miRNAs suppress vascular remodeling through regulating OTUD7B/KLF4/NMHC IIA axis. *Theranostics*. 2020;10(17):7787–811.
7229. Zhou LK, Zhou Z, Jiang XM, et al. Absorbed plant MIR2911 in honeysuckle decoction inhibits SARS-CoV-2 replication and

accelerates the negative conversion of infected patients. *Cell Discov*. 2020;6(1):1–4.

7230. Avsar B, Zhao Y, Li W, Lukiw WJ. *Atropa belladonna* expresses a microRNA (*aba-miRNA-9497*) highly homologous to *Homo sapiens* miRNA-378 (*hsa-miRNA-378*); both miRNAs target the 3'-untranslated region (3'-UTR) of the mRNA encoding the neurologically relevant, zinc-finger transcription factor ZNF-691. *Cell Mol Neurobiol*. 2020;40(1):179–88.

7231. McNeill EM, Hirschi KD. Roles of regulatory RNAs in nutritional control. *Annu Rev Nutr*. 2020;40:77–104.

7232. Wang L, Sadri M, Giraud D, Zempleni J. RNase H2-dependent polymerase chain reaction and elimination of confounders in sample collection, storage, and analysis strengthen evidence that microRNAs in bovine milk are bioavailable in humans. *J Nutr*. 2018;148(1):153–9.

7233. Chen X, Liu L, Chu Q, et al. Large-scale identification of extracellular plant miRNAs in mammals implicates their dietary intake. *PLoS One*. 2021;16(9):e0257878.

7234. Igaz I, Igaz P. Hypothetic interindividual and interspecies relevance of microRNAs released in body fluids. *Exp Suppl*. 2015;106:281–8.

7235. Witwer KW, Zhang CY. Diet-derived microRNAs: unicorn or silver bullet? *Genes Nutr*. 2017;12:15.

7236. Sundaram GM. Dietary non-coding RNAs from plants: fairy tale or treasure? *Noncoding RNA Res*. 2019;4(2):63–8.

7237. McNeill EM, Hirschi KD. Roles of regulatory RNAs in nutritional control. *Annu Rev Nutr*. 2020;40:77–104.

7238. Link J, Thon C, Schanze D, et al. Food-derived xeno-microRNAs: influence of diet and detectability in gastrointestinal tract–proof-of-principle study. *Mol Nutr Food Res*. 2019;63(2):e1800076.

7239. Quintanilha B, Reis B, Duarte G, Cozzolino S, Rogero M. Nutrimiromics: role of microRNAs and nutrition in modulating inflammation and chronic diseases. *Nutrients*. 2017;9(11):1168.

7240. Mar-Aguilar F, Arreola-Triana A, Mata-Cardona D, Gonzalez-Villasana V, Rodríguez-Padilla C, Reséndez-Pérez D. Evidence of transfer of miRNAs from the diet to the blood still inconclusive. *PeerJ*. 2020;8:e9567

7241. Wang W, Hang C, Zhang Y, et al. Dietary miR-451 protects erythroid cells from oxidative stress via increasing the activity of Foxo3 pathway. *Oncotarget*. 2017;8(63):107109–24.
7242. Teodori L, Petrignani I, Giuliani A, et al. Inflamm-aging microRNAs may integrate signals from food and gut microbiota by modulating common signalling pathways. *Mech Ageing Dev*. 2019;182:111127.
7243. Mar-Aguilar F, Arreola-Triana A, Mata-Cardona D, Gonzalez-Villasana V, Rodríguez-Padilla C, Reséndez-Pérez D. Evidence of transfer of miRNAs from the diet to the blood still inconclusive. *PeerJ.* 2020;8:e9567.
7244. Humphreys KJ, Conlon MA, Young GP, et al. Dietary manipulation of oncogenic microRNA expression in human rectal mucosa: a randomized trial. *Cancer Prev Res (Phila).* 2014;7(8):786–95.
7245. Baier S, Howard K, Cui J, Shu J, Zempleni J. MicroRNAs in chicken eggs are bioavailable in healthy adults and can modulate mRNA expression in peripheral blood mononuclear cells. *FASEB J.* 2015;29(S1):LB322.
7246. Igaz I, Igaz P. Hypothetic interindividual and interspecies relevance of microRNAs released in body fluids. *Exp Suppl*. 2015;106:281–8.
7247. Melnik BC, Schmitz G. MicroRNAs: milk's epigenetic regulators. *Best Pract Res Clin Endocrinol Metab*. 2017;31(4):427–42.
7248. Benmoussa A, Provost P. Milk microRNAs in health and disease. *Compr Rev Food Sci Food Saf*. 2019;18(3):703–22.
7249. Tooley KL, El-Merhibi A, Cummins AG, et al. Maternal milk, but not formula, regulates the immune response to β-lactoglobulin in allergy-prone rat pups. *J Nutr*. 2009;139(11):2145–51.
7250. Melnik BC, Stremmel W, Weiskirchen R, John SM, Schmitz G. Exosome-derived microRNAs of human milk and their effects on infant health and development. *Biomolecules*. 2021;11(6):851.
7251. Melnik BC, Stremmel W, Weiskirchen R, John SM, Schmitz G. Exosome-derived microRNAs of human milk and their effects on infant health and development. *Biomolecules*. 2021;11(6):851.
7252. Melnik BC, Schmitz G. MicroRNAs: milk's epigenetic regulators. *Best Pract Res Clin Endocrinol Metab*. 2017;31(4):427–42.
7253. Melnik BC. Lifetime impact of cow's milk on overactivation of mTORC1: from fetal to childhood overgrowth, acne, diabetes,

cancers, and neurodegeneration. *Biomolecules*. 2021;11(3):404.
7254. Melnik BC, Schmitz G. Exosomes of pasteurized milk: potential pathogens of Western diseases. *J Transl Med*. 2019;17(1):3.
7255. Victora CG, Bahl R, Barros AJD, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet*. 2016;387(10017):475–90.
7256. Chen Z, Xie Y, Luo J, et al. Milk exosome-derived miRNAs from water buffalo are implicated in immune response and metabolism process. *BMC Vet Res*. 2020;16(1):123.
7257. Baier SR, Nguyen C, Xie F, Wood JR, Zempleni J. MicroRNAs are absorbed in biologically meaningful amounts from nutritionally relevant doses of cow milk and affect gene expression in peripheral blood mononuclear cells, HEK-293 kidney cell cultures, and mouse livers. *J Nutr*. 2014;144(10):1495–500.
7258. McNeill EM, Hirschi KD. Roles of regulatory RNAs in nutritional control. *Annu Rev Nutr*. 2020;40:77–104.
7259. Melnik BC, Schmitz G. Exosomes of pasteurized milk: potential pathogens of Western diseases. *J Transl Med*. 2019;17(1):3.
7260. Benmoussa A, Lee CHC, Laffont B, et al. Commercial dairy cow milk microRNAs resist digestion under simulated gastrointestinal tract conditions. *J Nutr*. 2016;146(11):2206–15.
7261. López de Las Hazas MC, Del Pozo-Acebo L, Hansen MS, et al. Dietary bovine milk miRNAs transported in extracellular vesicles are partially stable during GI digestion, are bioavailable and reach target tissues but need a minimum dose to impact on gene expression. *Eur J Nutr*. 2022;61(2):1043–56.
7262. Baier SR, Nguyen C, Xie F, Wood JR, Zempleni J. MicroRNAs are absorbed in biologically meaningful amounts from nutritionally relevant doses of cow milk and affect gene expression in peripheral blood mononuclear cells, HEK-293 kidney cell cultures, and mouse livers. *J Nutr*. 2014;144(10):1495–500.
7263. Wang L, Sadri M, Giraud D, Zempleni J. RNase H2-dependent polymerase chain reaction and elimination of confounders in sample collection, storage, and analysis strengthen evidence that microRNAs in bovine milk are bioavailable in humans. *J Nutr*. 2018;148(1):153–9.

7264. Melnik BC, Schmitz G. Exosomes of pasteurized milk: potential pathogens of Western diseases. *J Transl Med*. 2019;17(1):3.
7265. Melnik BC. Milk exosomal miRNAs: potential drivers of AMPK-to-mTORC1 switching in β-cell de-differentiation of type 2 diabetes mellitus. *Nutr Metab (Lond)*. 2019;16:85.
7266. Melnik BC. Synergistic effects of milk-derived exosomes and galactose on α-synuclein pathology in Parkinson's disease and type 2 diabetes mellitus. *Int J Mol Sci*. 2021;22(3):1059.
7267. Melnik BC, Schmitz G. MicroRNAs: milk's epigenetic regulators. *Best Pract Res Clin Endocrinol Metab*. 2017;31(4):427–42.
7268. Melnik BC, Schmitz G. Exosomes of pasteurized milk: potential pathogens of Western diseases. *J Transl Med*. 2019;17(1):3.
7269. Murata T, Takayama K, Katayama S, et al. miR-148a is an androgen-responsive microRNA that promotes LNCaP prostate cell growth by repressing its target CAND1 expression. *Prostate Cancer Prostatic Dis*. 2010;13(4):356–61.
7270. Tate PL, Bibb R, Larcom LL. Milk stimulates growth of prostate cancer cells in culture. *Nutr Cancer*. 2011;63(8):1361–6.
7271. Sargsyan A, Dubasi HB. Milk consumption and prostate cancer: a systematic review. *World J Mens Health*. 2021;39(3):419–28.
7272. Melnik BC, Schmitz G. Milk's role as an epigenetic regulator in health and disease. *Diseases*. 2017;5(1):12.
7273. Melnik BC, Schmitz G. Exosomes of pasteurized milk: potential pathogens of Western diseases. *J Transl Med*. 2019;17(1):3.
7274. Michaëlsson K, Wolk A, Langenskiöld S, et al. Milk intake and risk of mortality and fractures in women and men: cohort studies. *BMJ*. 2014;349:g6015.
7275. Yu S, Zhao Z, Sun LM, Li P. Fermentation results in quantitative changes in milk-derived exosomes and different effects on cell growth and survival. *J Agric Food Chem*. 2017;65(6):1220–8.
7276. Savaiano DA, Hutkins RW. Yogurt, cultured fermented milk, and health: a systematic review. *Nutr Rev*. 2021;79(5):599–614.
7277. Wehbe Z, Kreydiyyeh S. Cow's milk may be delivering potentially harmful undetected cargoes to humans. Is it time to reconsider dairy recommendations? *Nutr Rev*. 2022;80(4):874–88.

7278. Melnik BC, Schmitz G. Exosomes of pasteurized milk: potential pathogens of Western diseases. *J Transl Med*. 2019;17(1):3.
7279. Teodori L, Petrignani I, Giuliani A, et al. Inflamm-aging microRNAs may integrate signals from food and gut microbiota by modulating common signalling pathways. *Mech Ageing Dev*. 2019;182:111127.
7280. Tsai F, Coyle WJ. The microbiome and obesity: is obesity linked to our gut flora? *Curr Gastroenterol Rep*. 2009;11(4):307–13.
7281. Stephen AM, Cummings JH. The microbial contribution to human faecal mass. *J Med Microbiol*. 1980;13(1):45–56.
7282. Singh RK, Chang HW, Yan D, et al. Influence of diet on the gut microbiome and implications for human health. *J Transl Med*. 2017;15(1):73.
7283. Kim A. Dysbiosis: a review highlighting obesity and inflammatory bowel disease. *J Clin Gastroenterol*. 2015;49 Suppl 1:S20–4.
7284. Patterson E, Ryan PM, Cryan JF, et al. Gut microbiota, obesity and diabetes. *Postgrad Med J*. 2016;92(1087):286–300.
7285. Tsai F, Coyle WJ. The microbiome and obesity: is obesity linked to our gut flora? *Curr Gastroenterol Rep*. 2009;11(4):307–13.
7286. Wikoff W, Anfora A, Liu J, et al. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *Proc Natl Acad Sci U S A*. 2009;106(10):3698–703.
7287. Sanmiguel C, Gupta A, Mayer EA. Gut microbiome and obesity: a plausible explanation for obesity. *Curr Obes Rep*. 2015;4(2):250–61.
7288. Aydin S. Can peptides and gut microbiota be involved in the etiopathology of obesity? *Obes Surg*. 2017;27(1):202–4.
7289. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol*. 2016;14(8):e1002533.
7290. Goodacre R. Metabolomics of a superorganism. *J Nutr*. 2007;137(1 Suppl):259S-66S.
7291. Simões CD, Maukonen J, Kaprio J, Rissanen A, Pietiläinen KH, Saarela M. Habitual dietary intake is associated with stool microbiota composition in monozygotic twins. *J Nutr*. 2013;143(4):417–23.
7292. Biagi E, Nylund L, Candela M, et al. Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. *PLoS One*. 2010;5(5):e10667.

7293. Bana B, Cabreiro F. The microbiome and aging. *Annu Rev Genet*. 2019;53:239–61.
7294. Bischoff SC. Microbiota and aging. *Curr Opin Clin Nutr Metab Care*. 2016;19(1):26–30.
7295. Venkatakrishnan A, Holzknecht ZE, Holzknecht R, et al. Evolution of bacteria in the human gut in response to changing environments: an invisible player in the game of health. *Comput Struct Biotechnol J*. 2021;19:752–8.
7296. Vermorken AJM, Cui Y, Kleerebezem R, Andrès E. Bowel movement frequency and cardiovascular mortality, a matter of fibers and oxidative stress? *Atherosclerosis*. 2016;253:278–80.
7297. Lichtenstein GR. Letter from the editor. *Gastroenterol Hepatol (N Y)*. 2013;9(9):552.
7298. Allison DB, Roberts MS. On constructing the disorder of hysteria. *J Med Philos*. 1994;19(3):239–59.
7299. Walter J, Armet AM, Finlay BB, Shanahan F. Establishing or exaggerating causality for the gut microbiome: lessons from human microbiota-associated rodents. *Cell*. 2020;180(2):221–32.
7300. Copeland CE, Stahlfeld K. Two tall poppies and the discovery of *Helicobacter pylori*. *J Am Coll Surg*. 2012;214(2):237–41.
7301. Walter J, Armet AM, Finlay BB, Shanahan F. Establishing or exaggerating causality for the gut microbiome: lessons from human microbiota-associated rodents. *Cell*. 2020;180(2):221–32.
7302. Ragonnaud E, Biragyn A. Gut microbiota as the key controllers of "healthy" aging of elderly people. *Immun Ageing*. 2021;18(1):2.
7303. Metchnikoff É. *The Prolongation of Life: Optimistic Studies*. G.P. Putnam's Sons; 1908.
7304. Mackowiak PA. Recycling Metchnikoff: probiotics, the intestinal microbiome and the quest for long life. *Front Public Health*. 2013;1.
7305. Vikhanski L. Elie Metchnikoff rediscovered: comeback of a founding father of gerontology. *Gerontologist*. 2016;56(Suppl_3):181.
7306. Gasbarrini G, Bonvicini F, Gramenzi A. Probiotics history. *J Clin Gastroenterol*. 2016;50(Supplement 2):S116–9.
7307. Mackowiak PA. Recycling Metchnikoff: probiotics, the intestinal microbiome and the quest for long life. *Front Public Health*. 2013;1.

7308. Mowat AM. Historical perspective: Metchnikoff and the intestinal microbiome. *J Leukoc Biol*. 2021;109(3):513–7.
7309. Salazar N, Valdés-Varela L, González S, Gueimonde M, de Los Reyes-Gavilán CG. Nutrition and the gut microbiome in the elderly. *Gut Microbes*. 2017;8(2):82–97.
7310. Narasimhan H, Ren CC, Deshpande S, Sylvia KE. Young at gut—turning back the clock with the gut microbiome. *Microorganisms*. 2021;9(3):555.
7311. Madison AA, Kiecolt-Glaser JK. The gut microbiota and nervous system: age-defined and age-defying. *Semin Cell Dev Biol*. 2021;116:98–107.
7312. Xu C, Zhu H, Qiu P. Aging progression of human gut microbiota. *BMC Microbiol*. 2019;19(1):236.
7313. Galkin F, Mamoshina P, Aliper A, et al. Human gut microbiome aging clock based on taxonomic profiling and deep learning. *iScience*. 2020;23(6):101199.
7314. Ling Z, Liu X, Cheng Y, Yan X, Wu S. Gut microbiota and aging. *Crit Rev Food Sci Nutr*. 2022;62(13):3509–34.
7315. Vaiserman AM, Koliada AK, Marotta F. Gut microbiota: a player in aging and a target for anti-aging intervention. *Ageing Res Rev*. 2017;35:36–45.
7316. An R, Wilms E, Masclee AAM, Smidt H, Zoetendal EG, Jonkers D. Age-dependent changes in GI physiology and microbiota: time to reconsider? *Gut*. 2018;67(12):2213–22.
7317. Vemuri R, Gundamaraju R, Shastri MD, et al. Gut microbial changes, interactions, and their implications on human lifecycle: an ageing perspective. *BioMed Res Int*. 2018;2018:4178607.
7318. Ragonnaud E, Biragyn A. Gut microbiota as the key controllers of "healthy" aging of elderly people. *Immun Ageing*. 2021;18(1):2.
7319. Biagi E, Nylund L, Candela M, et al. Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. *PLoS One*. 2010;5(5):e10667.
7320. Badal VD, Vaccariello ED, Murray ER, et al. The gut microbiome, aging, and longevity: a systematic review. *Nutrients*. 2020;12(12):E3759.

7321. Cai D, Zhao S, Li D, et al. Nutrient intake is associated with longevity characterization by metabolites and element profiles of healthy centenarians. *Nutrients*. 2016;8(9):E564.
7322. Zhang S, Zeng B, Chen Y, et al. Gut microbiota in healthy and unhealthy long-living people. *Gene*. 2021;779:145510.
7323. DeJong EN, Surette MG, Bowdish DME. The gut microbiota and unhealthy aging: disentangling cause from consequence. *Cell Host Microbe*. 2020;28(2):180–9.
7324. Biagi E, Nylund L, Candela M, et al. Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. *PLoS One*. 2010;5(5):e10667.
7325. Biagi E, Franceschi C, Rampelli S, et al. Gut microbiota and extreme longevity. *Curr Biol*. 2016;26(11):1480–5.
7326. Ling Z, Liu X, Cheng Y, Yan X, Wu S. Gut microbiota and aging. *Crit Rev Food Sci Nutr*. 2022;62(13):3509–34.
7327. Yang HY, Liu SL, Ibrahim SA, et al. Oral administration of live *Bifidobacterium* substrains isolated from healthy centenarians enhanced immune function in BALB/c mice. *Nutr Res*. 2009;29(4):281–9.
7328. Exopolysaccharides produced by lactic acid bacteria and *Bifidobacteria*: structures, physiochemical functions and applications in the food industry. *Food Hydrocoll*. 2019;94:475–99.
7329. Koo H, Falsetta ML, Klein MI. The exopolysaccharide matrix: a virulence determinant of cariogenic biofilm. *J Dent Res*. 2013;92(12):1065–73.
7330. Xu R, Shang N, Li P. *In vitro* and *in vivo* antioxidant activity of exopolysaccharide fractions from *Bifidobacterium animalis* RH. *Anaerobe*. 2011;17(5):226–31.
7331. O'Toole PW, Jeffery IB. Microbiome-health interactions in older people. *Cell Mol Life Sci*. 2018;75(1):119–28.
7332. Everard A, Belzer C, Geurts L, et al. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *Proc Natl Acad Sci U S A*. 2013;110(22):9066–71.
7333. Shintouo CM, Mets T, Beckwee D, et al. Is inflammageing influenced by the microbiota in the aged gut? A systematic review. *Exp Gerontol*. 2020;141:111079.

7334. Greathouse KL, Faucher MA, Hastings-Tolsma M. The gut microbiome, obesity, and weight control in women's reproductive health. *West J Nurs Res*. 2017;39(8):1094–119.
7335. Zmora N, Suez J, Elinav E. You are what you eat: diet, health and the gut microbiota. *Nat Rev Gastroenterol Hepatol*. 2019;16(1):35–56.
7336. Desai MS, Seekatz AM, Koropatkin NM, et al. A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell*. 2016;167(5):1339–53.e21.
7337. Roberts CL, Keita AV, Duncan SH, et al. Translocation of Crohn's disease *Escherichia coli* across M-cells: contrasting effects of soluble plant fibres and emulsifiers. *Gut*. 2010;59(10):1331–9.
7338. Biragyn A, Ferrucci L. Gut dysbiosis: a potential link between increased cancer risk in ageing and inflammaging. *Lancet Oncol*. 2018;19(6):e295–304.
7339. Biagi E, Franceschi C, Rampelli S, et al. Gut microbiota and extreme longevity. *Curr Biol*. 2016;26(11):1480–5.
7340. Ragonnaud E, Biragyn A. Gut microbiota as the key controllers of "healthy" aging of elderly people. *Immun Ageing*. 2021;18(1):2.
7341. Biragyn A, Ferrucci L. Gut dysbiosis: a potential link between increased cancer risk in ageing and inflammaging. *Lancet Oncol*. 2018;19(6):e295–304.
7342. Luan Z, Sun G, Huang Y, et al. Metagenomics study reveals changes in gut microbiota in centenarians: a cohort study of Hainan centenarians. *Front Microbiol*. 2020;11:1474.
7343. Bárcena C, Valdés-Mas R, Mayoral P, et al. Healthspan and lifespan extension by fecal microbiota transplantation into progeroid mice. *Nat Med*. 2019;25(8):1234–42.
7344. Vemuri R, Gundamaraju R, Shastri MD, et al. Gut microbial changes, interactions, and their implications on human lifecycle: an ageing perspective. *BioMed Res Int*. 2018;2018:4178607.
7345. Wang F, Yu T, Huang G, et al. Gut microbiota community and its assembly associated with age and diet in Chinese centenarians. *J Microbiol Biotechnol*. 2015;25(8):1195–204.
7346. Cătoi AF, Corina A, Katsiki N, et al. Gut microbiota and aging—a focus on centenarians. *Biochim Biophys Acta Mol Basis Dis*. 2020;1866(7):165765.

7347. DeJong EN, Surette MG, Bowdish DME. The gut microbiota and unhealthy aging: disentangling cause from consequence. *Cell Host Microbe*. 2020;28(2):180–9.
7348. Nagpal R, Mainali R, Ahmadi S, et al. Gut microbiome and aging: physiological and mechanistic insights. *Nutr Healthy Aging*. 2018;4(4):267–85.
7349. O'Toole PW, Jeffery IB. Microbiome-health interactions in older people. *Cell Mol Life Sci*. 2018;75(1):119–28.
7350. Biagi E, Rampelli S, Turroni S, Quercia S, Candela M, Brigidi P. The gut microbiota of centenarians: signatures of longevity in the gut microbiota profile. *Mech Ageing Dev*. 2017;165(Pt B):180–4.
7351. O'Toole PW, Jeffery IB. Microbiome-health interactions in older people. *Cell Mol Life Sci*. 2018;75(1):119–28.
7352. Buford TW. (Dis)Trust your gut: the gut microbiome in age-related inflammation, health, and disease. *Microbiome*. 2017;5(1):80.
7353. Maier L, Pruteanu M, Kuhn M, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature*. 2018;555(7698):623–8.
7354. Tiihonen K, Ouwehand AC, Rautonen N. Human intestinal microbiota and healthy ageing. *Ageing Res Rev*. 2010;9(2):107–16.
7355. DeJong EN, Surette MG, Bowdish DME. The gut microbiota and unhealthy aging: disentangling cause from consequence. *Cell Host Microbe*. 2020;28(2):180–9.
7356. Claesson MJ, Jeffery IB, Conde S, et al. Gut microbiota composition correlates with diet and health in the elderly. *Nature*. 2012;488(7410):178–84.
7357. Biagi E, Rampelli S, Turroni S, Quercia S, Candela M, Brigidi P. The gut microbiota of centenarians: signatures of longevity in the gut microbiota profile. *Mech Ageing Dev*. 2017;165(Pt B):180–4.
7358. Rampelli S, Schnorr SL, Consolandi C, et al. Metagenome sequencing of the Hadza hunter-gatherer gut microbiota. *Curr Biol*. 2015;25(13):1682–93.
7359. Rampelli S, Soverini M, D'Amico F, et al. Shotgun metagenomics of gut microbiota in humans with up to extreme longevity and the increasing role of xenobiotic degradation. *mSystems*. 2020;5(2):e00124–20.

7360. Rampelli S, Soverini M, D'Amico F, et al. Shotgun metagenomics of gut microbiota in humans with up to extreme longevity and the increasing role of xenobiotic degradation. *mSystems*. 2020;5(2):e00124–20.
7361. Cai D, Zhao S, Li D, et al. Nutrient intake is associated with longevity characterization by metabolites and element profiles of healthy centenarians. *Nutrients*. 2016;8(9):E564.
7362. Smith P, Willemsen D, Popkes M, et al. Regulation of life span by the gut microbiota in the short-lived African turquoise killifish. *eLife*. 2017;6:e27014.
7363. Chen Y, Zhang S, Zeng B, et al. Transplant of microbiota from long-living people to mice reduces aging-related indices and transfers beneficial bacteria. *Aging (Albany NY)*. 2020;12(6):4778–93.
7364. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;505(7484):559–63.
7365. Chen Y, Zhang S, Zeng B, et al. Transplant of microbiota from long-living people to mice reduces aging-related indices and transfers beneficial bacteria. *Aging (Albany NY)*. 2020;12(6):4778–93.
7366. Kim M, Benayoun BA. The microbiome: an emerging key player in aging and longevity. *Transl Med Aging*. 2020;4:103–16.
7367. Riccio P, Rossano R. Undigested food and gut microbiota may cooperate in the pathogenesis of neuroinflammatory diseases: a matter of barriers and a proposal on the origin of organ specificity. *Nutrients*. 2019;11(11):E2714.
7368. Riccio P, Rossano R. Undigested food and gut microbiota may cooperate in the pathogenesis of neuroinflammatory diseases: a matter of barriers and a proposal on the origin of organ specificity. *Nutrients*. 2019;11(11):E2714.
7369. Patel KP, Luo FJ, Plummer NS, Hostetter TH, Meyer TW. The production of p-cresol sulfate and indoxyl sulfate in vegetarians versus omnivores. *Clin J Am Soc Nephrol*. 2012;7(6):982–8.
7370. Riccio P, Rossano R. Undigested food and gut microbiota may cooperate in the pathogenesis of neuroinflammatory diseases: a matter of barriers and a proposal on the origin of organ specificity. *Nutrients*. 2019;11(11):E2714.

7371. Russo F, Linsalata M, Clemente C, et al. Inulin-enriched pasta improves intestinal permeability and modifies the circulating levels of zonulin and glucagon-like peptide 2 in healthy young volunteers. *Nutr Res*. 2012;32(12):940–6.
7372. Donnadieu-Rigole H, Pansu N, Mura T, et al. Beneficial effect of alcohol withdrawal on gut permeability and microbial translocation in patients with alcohol use disorder. *Alcohol Clin Exp Res*. 2018;42(1):32–40.
7373. Lambert GP, Schmidt A, Schwarzkopf K, Lanspa S. Effect of aspirin dose on gastrointestinal permeability. *Int J Sports Med*. 2012;33(6):421–5.
7374. Ivey KJ, Baskin WN, Krause WJ, Terry B. Effect of aspirin and acid on human jejunal mucosa. An ultrastructural study. *Gastroenterology*. 1979;76(1):50–6.
7375. Tran CD, Hawkes J, Graham RD, et al. Zinc-fortified oral rehydration solution improved intestinal permeability and small intestinal mucosal recovery. *Clin Pediatr (Phila)*. 2015;54(7):676–82.
7376. Ling Z, Liu X, Cheng Y, Yan X, Wu S. Gut microbiota and aging. *Crit Rev Food Sci Nutr*. 2022;62(13):3509–34.
7377. Giovannini S, Onder G, Liperoti R, et al. Interleukin-6, C-reactive protein, and tumor necrosis factor-alpha as predictors of mortality in frail, community-living elderly individuals. *J Am Geriatr Soc*. 2011;59(9):1679–85.
7378. de Gonzalo-Calvo D, de Luxán-Delgado B, Martínez-Camblor P, et al. Chronic inflammation as predictor of 1-year hospitalization and mortality in elderly population. *Eur J Clin Invest*. 2012;42(10):1037–46.
7379. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. *Ageing Res Rev*. 2016;31:1–8.
7380. de Gonzalo-Calvo D, de Luxán-Delgado B, Rodríguez-González S, et al. Interleukin 6, soluble tumor necrosis factor receptor I and red blood cell distribution width as biological markers of functional dependence in an elderly population: a translational approach. *Cytokine*. 2012;58(2):193–8.

7381. Thevaranjan N, Puchta A, Schulz C, et al. Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. *Cell Host Microbe*. 2017;21(4):455–66.e4.
7382. Lustgarten MS. Classifying aging as a disease: the role of microbes. *Front Genet*. 2016;7:212.
7383. Evans CJ, Ho Y, Daveson BA, et al. Place and cause of death in centenarians: a population-based observational study in England, 2001 to 2010. *PLoS Med*. 2014;11(6):e1001653.
7384. Yende S, Tuomanen EI, Wunderink R, et al. Preinfection systemic inflammatory markers and risk of hospitalization due to pneumonia. *Am J Respir Crit Care Med*. 2005;172(11):1440–6.
7385. Antunes G, Evans SA, Lordan JL, Frew AJ. Systemic cytokine levels in community-acquired pneumonia and their association with disease severity. *Eur Respir J*. 2002;20(4):990–5.
7386. Reade MC, Yende S, D'Angelo G, et al. Differences in immune response may explain lower survival among older men with pneumonia. *Crit Care Med*. 2009;37(5):1655–62.
7387. Hearps AC, Martin GE, Angelovich TA, et al. Aging is associated with chronic innate immune activation and dysregulation of monocyte phenotype and function. *Aging Cell*. 2012;11(5):867–75.
7388. Thevaranjan N, Puchta A, Schulz C, et al. Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. *Cell Host Microbe*. 2017;21(4):455–66.
7389. Biragyn A, Ferrucci L. Gut dysbiosis: a potential link between increased cancer risk in ageing and inflammaging. *Lancet Oncol*. 2018;19(6):e295–304.
7390. Venkatakrishnan A, Holzknecht ZE, Holzknecht R, et al. Evolution of bacteria in the human gut in response to changing environments: an invisible player in the game of health. *Comput Struct Biotechnol J*. 2021;19:752–8.
7391. Kilkkinen A, Rissanen H, Klaukka T, et al. Antibiotic use predicts an increased risk of cancer. *Int J Cancer*. 2008;123(9):2152–5.
7392. Wise R, Hart T, Cars O, et al. Antimicrobial resistance. *BMJ*. 1998;317(7159):609–10.

7393. Vemuri R, Gundamaraju R, Shastri MD, et al. Gut microbial changes, interactions, and their implications on human lifecycle: an ageing perspective. *BioMed Res Int*. 2018;2018:4178607.
7394. Collignon PJ, Conly JM, Andremont A, et al. World Health Organization ranking of antimicrobials according to their importance in human medicine: a critical step for developing risk management strategies to control antimicrobial resistance from food animal production. *Clin Infect Dis*. 2016;63(8):1087–93.
7395. Office of Technology Assessment. *Drugs in Livestock Feed*. Congress of the United States, Office of Technology Assessment; 1979.
7396. Galloway-Peña JR, Jenq RR. The only thing that stops a bad microbiome, is a good microbiome. *Haematologica*. 2019;104(8):1511–3.
7397. Subirats J, Domingues A, Topp E. Does dietary consumption of antibiotics by humans promote antibiotic resistance in the gut microbiome? *J Food Prot*. 2019;82(10):1636–42.
7398. Angulo FJ, Baker NL, Olsen SJ, Anderson A, Barrett TJ. Antimicrobial use in agriculture: controlling the transfer of antimicrobial resistance to humans. *Semin Pediatr Infect Dis*. 2004;15(2):78–85.
7399. Milanović V, Osimani A, Aquilanti L, et al. Occurrence of antibiotic resistance genes in the fecal DNA of healthy omnivores, ovo-lacto vegetarians and vegans. *Mol Nutr Food Res*. 2017;61(9).
7400. Cabral DJ, Wurster JI, Korry BJ, Penumutchu S, Belenky P. Consumption of a Western-style diet modulates the response of the murine gut microbiome to ciprofloxacin. *mSystems*. 2020;5(4):e00317–20.
7401. Schnizlein MK, Vendrov KC, Edwards SJ, Martens EC, Young VB. Dietary xanthan gum alters antibiotic efficacy against the murine gut microbiota and attenuates *Clostridioides difficile* colonization. *mSphere*. 2020;5(1):e00708–19.
7402. Bassis CM. Live and diet by your gut microbiota. *mBio*. 2019;10(5):e02335–19.
7403. Martínez Steele E, Baraldi LG, Louzada ML da C, Moubarac JC, Mozaffarian D, Monteiro CA. Ultra-processed foods and added

sugars in the US diet: evidence from a nationally representative cross-sectional study. *BMJ Open*. 2016;6(3):e009892.

7404. Wilck N, Matus MG, Kearney SM, et al. Salt-responsive gut commensal modulates T_H17 axis and disease. *Nature*. 2017;551(7682):585–9.

7405. Bisoendial R, Lubberts E. A mechanistic insight into the pathogenic role of interleukin 17A in systemic autoimmune diseases. *Mediators Inflamm*. 2022;2022:6600264.

7406. Wilck N, Matus MG, Kearney SM, et al. Salt-responsive gut commensal modulates T_H17 axis and disease. *Nature*. 2017;551(7682):585–9.

7407. Suez J, Korem T, Zilberman-Schapira G, Segal E, Elinav E. Non-caloric artificial sweeteners and the microbiome: findings and challenges. *Gut Microbes*. 2015;6(2):149–55.

7408. Laster J, Bonnes SL, Rocha J. Increased use of emulsifiers in processed foods and the links to obesity. *Curr Gastroenterol Rep*. 2019;21(11):61.

7409. Naimi S, Viennois E, Gewirtz AT, Chassaing B. Direct impact of commonly used dietary emulsifiers on human gut microbiota. *Microbiome*. 2021;9(1):66.

7410. Birkett A, Muir J, Phillips J, Jones G, O'Dea K. Resistant starch lowers fecal concentrations of ammonia and phenols in humans. *Am J Clin Nutr*. 1996;63(5):766–72.

7411. Windey K, De Preter V, Verbeke K. Relevance of protein fermentation to gut health. *Mol Nutr Food Res*. 2012;56(1):184–96.

7412. Magee E. A nutritional component to inflammatory bowel disease: the contribution of meat to fecal sulfide excretion. *Nutrition*. 1999;15(3):244–6.

7413. Ge J, Han TJ, Liu J, et al. Meat intake and risk of inflammatory bowel disease: a meta-analysis. *Turk J Gastroenterol*. 2015;26(6):492–7.

7414. Parra-Soto S, Ahumada D, Petermann-Rocha F, et al. Association of meat, vegetarian, pescatarian and fish-poultry diets with risk of 19 cancer sites and all cancer: findings from the UK Biobank

prospective cohort study and meta-analysis. *BMC Med*. 2022;20(1):79.
7415. Florin THJ, Neale G, Goretski S, Cummings JH. The sulfate content of foods and beverages. *J Food Comp Anal*. 1993;6(2):140–51.
7416. Ananthakrishnan AN, Khalili H, Konijeti GG, et al. A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis. *Gastroenterology*. 2013;145(5):970–7.
7417. Yao CK, Muir JG, Gibson PR. Review article: insights into colonic protein fermentation, its modulation and potential health implications. *Aliment Pharmacol Ther*. 2016;43(2):181–96.
7418. Bosch S, Lemmen JPM, Menezes R, et al. The influence of lifestyle factors on fecal volatile organic compound composition as measured by an electronic nose. *J Breath Res*. 2019;13(4):046001.
7419. How you can limit your gas production. 12 tips for dealing with flatulence. *Harv Health Lett.* 2007;32(12):3.
7420. do Rosario VA, Fernandes R, Trindade EBS de M. Vegetarian diets and gut microbiota: important shifts in markers of metabolism and cardiovascular disease. *Nutr Rev*. 2016;74(7):444–54.
7421. Magee EA, Richardson CJ, Hughes R, Cummings JH. Contribution of dietary protein to sulfide production in the large intestine: an in vitro and a controlled feeding study in humans. *Am J Clin Nutr.* 2000;72(6):1488–94.
7422. Falony G, Vieira-Silva S, Raes J. Microbiology meets big data: the case of gut microbiota-derived trimethylamine. *Annu Rev Microbiol*. 2015;69:305–21.
7423. Rak K, Rader DJ. Cardiovascular disease: the diet-microbe morbid union. *Nature*. 2011;472(7341):40–1.
7424. Tang WHW, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med*. 2013;368(17):1575–84.
7425. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*. 2013;19(5):576–85.
7426. Farhangi MA, Vajdi M, Asghari-Jafarabadi M. Gut microbiota-associated metabolite trimethylamine *N*-oxide and the risk of stroke:

a systematic review and dose-response meta-analysis. *Nutr J*. 2020;19(1):76.
7427. Zhai Q, Wang X, Chen C, et al. Prognostic value of plasma trimethylamine n-oxide levels in patients with acute ischemic stroke. *Cell Mol Neurobiol*. 2019;39(8):1201–6.
7428. Zhu W, Wang Z, Tang WHW, Hazen SL. Gut microbe-generated trimethylamine *N*-oxide from dietary choline is prothrombotic in subjects. *Circulation*. 2017;135(17):1671–3.
7429. Brunt VE, Gioscia-Ryan RA, Casso AG, et al. Trimethylamine-N-oxide promotes age-related vascular oxidative stress and endothelial dysfunction in mice and healthy humans. *Hypertension*. 2020;76(1):101–12.
7430. He Z, Chen ZY. What are missing parts in the research story of trimethylamine-n-oxide (TMAO)? *J Agric Food Chem*. 2017;65(26):5227–8.
7431. Coras R, Kavanaugh A, Boyd T, et al. Choline metabolite, trimethylamine *N*-oxide (TMAO), is associated with inflammation in psoriatic arthritis. *Clin Exp Rheumatol*. 2019;37(3):481–4.
7432. Eyupoglu ND, Caliskan Guzelce E, Acikgoz A, et al. Circulating gut microbiota metabolite trimethylamine N-oxide and oral contraceptive use in polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 2019;91(6):810–5.
7433. Zeng ST, Guo L, Liu SK, et al. Egg consumption is associated with increased risk of ovarian cancer: evidence from a meta-analysis of observational studies. *Clin Nutr.* 2015;34(4):635–41.
7434. Tse G, Eslick GD. Egg consumption and risk of GI neoplasms: dose-response meta-analysis and systematic review. *Eur J Nutr*. 2014;53(7):1581–90.
7435. Chan CWH, Law BMH, Waye MMY, Chan JYW, So WKW, Chow KM. Trimethylamine-N-oxide as one hypothetical link for the relationship between intestinal microbiota and cancer—where we are and where shall we go? *J Cancer*. 2019;10(23):5874–82.
7436. Heron M. Deaths: leading causes for 2017. *Natl Vital Stat Rep*. 2019;68(6):1–77.
7437. Vogt NM, Romano KA, Darst BF, et al. The gut microbiota-derived metabolite trimethylamine *N*-oxide is elevated in Alzheimer's

disease. *Alzheimers Res Ther*. 2018;10(1):124.
7438. Heron M. Deaths: leading causes for 2017. *Natl Vital Stat Rep*. 2019;68(6):1–77.
7439. Ottiger M, Nickler M, Steuer C, et al. Trimethylamine-N-oxide (TMAO) predicts fatal outcomes in community-acquired pneumonia patients without evident coronary artery disease. *Eur J Intern Med*. 2016;36:67–73.
7440. Rhee EP, Clish CB, Ghorbani A, et al. A combined epidemiologic and metabolomic approach improves CKD prediction. *J Am Soc Nephrol*. 2013;24(8):1330–8.
7441. Farhangi MA. Gut microbiota–dependent trimethylamine N-oxide and all-cause mortality: findings from an updated systematic review and meta-analysis. *Nutrition*. 2020;78:110856.
7442. Tang WH, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med*. 2013;368(17):1575–84.
7443. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*. 2013;19(5):576–85.
7444. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*. 2013;19(5):576–85.
7445. Demarquoy J, Georges, B, Rigault C, et al. Radioisotopic determination of L-carnitine content in foods commonly eaten in Western countries. *Food Chem*. 2004;86(1):137–42.
7446. Stefan M, Sharp M, Gheith R, et al. L-carnitine tartrate supplementation for 5 weeks improves exercise recovery in men and women: a randomized, double-blind, placebo-controlled trial. *Nutrients*. 2021;13(10):3432.
7447. Koeth RA, Lam-Galvez BR, Kirsop J, et al. $_{L}$-Carnitine in omnivorous diets induces an atherogenic gut microbial pathway in humans. *J Clin Invest*. 2019;129(1):373–87.
7448. Hernández-Alonso P, Cañueto D, Giardina S, et al. Effect of pistachio consumption on the modulation of urinary gut microbiota-related metabolites in prediabetic subjects. *J Nutr Biochem*. 2017;45:48–53.

7449. Cashman JR, Xiong Y, Lin J, et al. *In vitro* and *in vivo* inhibition of human flavin-containing monooxygenase form 3 (FMO3) in the presence of dietary indoles. *Biochem Pharmacol*. 1999;58(6):1047–55.
7450. Winther SA, Rossing P. TMAO: trimethylamine-N-oxide or time to minimize intake of animal products? *J Clin Endocrinol Metab*. 2020;105(12):e4958–60.
7451. Galloway-Peña JR, Jenq RR. The only thing that stops a bad microbiome, is a good microbiome. *Haematologica*. 2019;104(8):1511–3.
7452. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. *Nat Med*. 2019;25(5):716–29.
7453. Neunez M, Goldman M, Ghezzi P. Online information on probiotics: does it match scientific evidence? *Front Med*. 2020;6:296.
7454. Hutchinson AN, Bergh C, Kruger K, et al. The effect of probiotics on health outcomes in the elderly: a systematic review of randomized, placebo-controlled studies. *Microorganisms*. 2021;9(6):1344.
7455. Bafeta A, Koh M, Riveros C, Ravaud P. Harms reporting in randomized controlled trials of interventions aimed at modifying microbiota: a systematic review. *Ann Intern Med*. 2018;169(4):240–7.
7456. Turjeman S, Koren O. ARGuing the case for (or against) probiotics. *Trends Microbiol*. 2021;29(11):959–60.
7457. Montassier E, Valdés-Mas R, Batard E, et al. Probiotics impact the antibiotic resistance gene reservoir along the human GI tract in a person-specific and antibiotic-dependent manner. *Nat Microbiol*. 2021;6(8):1043–54.
7458. Suez J, Zmora N, Zilberman-Schapira G, et al. Post-antibiotic gut mucosal microbiome reconstitution is impaired by probiotics and improved by autologous FMT. *Cell*. 2018;174(6):1406–23.e16.
7459. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. *Nat Med*. 2019;25(5):716–29.
7460. Swain Ewald HA, Ewald PW. Natural selection, the microbiome, and public health. *Yale J Biol Med*. 2018;91(4):445–55.
7461. Peng Z, Mao X, Zhang J, Du G, Chen J. Effective biodegradation of chicken feather waste by co-cultivation of keratinase producing strains. *Microb Cell Fact*. 2019;18(1):84.

7462. Lewis ZT, Shani G, Masarweh CF, et al. Validating bifidobacterial species and subspecies identity in commercial probiotic products. *Pediatr Res*. 2016;79(3):445–52.
7463. Drago L, Rodighiero V, Celeste T, Rovetto L, De Vecchi E. Microbiological evaluation of commercial probiotic products available in the USA in 2009. *J Chemother*. 2010;22(6):373–7.
7464. Mazzantini D, Calvigioni M, Celandroni F, Lupetti A, Ghelardi E. Spotlight on the compositional quality of probiotic formulations marketed worldwide. *Front Microbiol*. 2021;12:693973.
7465. Temmerman R, Pot B, Huys G, Swings J. Identification and antibiotic susceptibility of bacterial isolates from probiotic products. *Int J Food Microbiol*. 2003;81(1):1–10.
7466. Mazzantini D, Calvigioni M, Celandroni F, Lupetti A, Ghelardi E. Spotlight on the compositional quality of probiotic formulations marketed worldwide. *Front Microbiol*. 2021;12:693973.
7467. de Simone C. The unregulated probiotic market. *Clin Gastroenterol Hepatol*. 2019;17(5):809–17.
7468. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. *Nat Med*. 2019;25(5):716–29.
7469. Kristensen NB, Bryrup T, Allin KH, Nielsen T, Hansen TH, Pedersen O. Alterations in fecal microbiota composition by probiotic supplementation in healthy adults: a systematic review of randomized controlled trials. *Genome Med*. 2016;8(1):52.
7470. Khalesi S, Bellissimo N, Vandelanotte C, Williams S, Stanley D, Irwin C. A review of probiotic supplementation in healthy adults: helpful or hype? *Eur J Clin Nutr*. 2019;73(1):24–37.
7471. Tuohy KM, Conterno L, Gasperotti M, Viola R. Up-regulating the human intestinal microbiome using whole plant foods, polyphenols, and/or fiber. *J Agric Food Chem*. 2012;60(36):8776–82.
7472. Scrimshaw NS, Murray EB. The acceptability of milk and milk products in populations with a high prevalence of lactose intolerance. *Am J Clin Nutr*. 1988;48(4 Suppl):1079–159.
7473. Hertzler SR, Clancy SM. Kefir improves lactose digestion and tolerance in adults with lactose maldigestion. *J Am Diet Assoc*. 2003;103(5):582–7.

7474. Merenstein DJ, Foster J, D'Amico F. A randomized clinical trial measuring the influence of kefir on antibiotic-associated diarrhea: the Measuring the Influence of Kefir (MILK) Study. *Arch Pediatr Adolesc Med*. 2009;163(8):750–4.
7475. Nielsen ES, Garnås E, Jensen KJ, et al. Lacto-fermented sauerkraut improves symptoms in IBS patients independent of product pasteurisation—a pilot study. *Food Funct*. 2018;9(10):5323–35.
7476. Kim HJ, Lim SY, Lee JS, et al. Fresh and pickled vegetable consumption and gastric cancer in Japanese and Korean populations: a meta-analysis of observational studies. *Cancer Sci*. 2010;101(2):508–16.
7477. Morais S, Costa A, Albuquerque G, et al. Salt intake and gastric cancer: a pooled analysis within the Stomach cancer Pooling (StoP) Project. *Cancer Causes Control*. 2022;33(5):779–91.
7478. Matsuyama S, Sawada N, Tomata Y, et al. Association between adherence to the Japanese diet and all-cause and cause-specific mortality: the Japan Public Health Center-based Prospective Study. *Eur J Nutr*. 2021;60(3):1327–36.
7479. Ayala FR, Bauman C, Cogliati S, Lenini C, Bartolini M, Grau R. Microbial flora, probiotics, *Bacillus subtilis* and the search for a long and healthy human longevity. *Microb Cell*. 2017;4(4):133–6.
7480. Katagiri R, Sawada N, Goto A, et al. Association of soy and fermented soy product intake with total and cause specific mortality: prospective cohort study. *BMJ*. 2020;368:m34.
7481. Lo KKH, Wong AHC, Tam WWS, Ho SC. Citation classics in the nutrition and dietetics literature: 50 frequently cited articles: citation classics in nutrition and dietetics. *Nutr Diet*. 2016;73(4):356–68.
7482. Shurney D, Pauly K. The gut microbiome and food as medicine: healthy microbiomes = healthy humans. *Am J Health Promot*. 2019;33(5):821–4.
7483. Fechner A, Fenske K, Jahreis G. Effects of legume kernel fibres and citrus fibre on putative risk factors for colorectal cancer: a randomised, double-blind, crossover human intervention trial. *Nutr J*. 2013;12:101.
7484. Wedlake L, Shaw C, McNair H, et al. Randomized controlled trial of dietary fiber for the prevention of radiation-induced gastrointestinal

toxicity during pelvic radiotherapy. *Am J Clin Nutr*. 2017;106(3):849–57.

7485. So D, Whelan K, Rossi M, et al. Dietary fiber intervention on gut microbiota composition in healthy adults: a systematic review and meta-analysis. *Am J Clin Nutr*. 2018;107(6):965–83.

7486. Kumari M, Kozyrskyj AL. Gut microbial metabolism defines host metabolism: an emerging perspective in obesity and allergic inflammation. *Obes Rev*. 2017;18(1):18–31.

7487. Halnes I, Baines KJ, Berthon BS, MacDonald-Wicks LK, Gibson PG, Wood LG. Soluble fibre meal challenge reduces airway inflammation and expression of GPR43 and GPR41 in asthma. *Nutrients*. 2017;9(1):57.

7488. Kim YK, Shin C. The microbiota-gut-brain axis in neuropsychiatric disorders: pathophysiological mechanisms and novel treatments. *Curr Neuropharmacol*. 2018;16(5):559–73.

7489. Dai Z, Niu J, Zhang Y, Jacques P, Felson DT. Dietary intake of fibre and risk of knee osteoarthritis in two US prospective cohorts [published correction appears in *Ann Rheum Dis.* 2017;76(12):2103]. *Ann Rheum Dis*. 2017;76(8):1411–9.

7490. Dai Z, Lu N, Niu J, Felson DT, Zhang Y. Dietary fiber intake in relation to knee pain trajectory. *Arthritis Care Res (Hoboken)*. 2017;69(9):1331–9.

7491. Wedlake L, Shaw C, McNair H, et al. Randomized controlled trial of dietary fiber for the prevention of radiation-induced gastrointestinal toxicity during pelvic radiotherapy. *Am J Clin Nutr*. 2017;106(3):849–57.

7492. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Morenga LT. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. *Lancet*. 2019;393(10170):434–45.

7493. Gopinath B, Flood VM, Kifley A, Louie JCY, Mitchell P. Association between carbohydrate nutrition and successful aging over 10 years. *J Gerontol A Biol Sci Med Sci*. 2016;71(10):1335–40.

7494. Si Y, Liu X, Ye K, et al. Glucomannan hydrolysate promotes gut proliferative homeostasis and extends life span in *Drosophila melanogaster*. *J Gerontol A Biol Sci Med Sci*. 2019;74(10):1549–56.

7495. McDonald P, Maizi BM, Arking R. Chemical regulation of mid- and late-life longevities in *Drosophila*. *Exp Gerontol*. 2013;48(2):240–9.
7496. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Morenga LT. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. *Lancet*. 2019;393(10170):434–45.
7497. Buigues C, Fernández-Garrido J, Pruimboom L, et al. Effect of a prebiotic formulation on frailty syndrome: a randomized, double-blind clinical trial. *Int J Mol Sci.* 2016;17(6):E932.
7498. Hippe B, Zwielehner J, Liszt K, Lassl C, Unger F, Haslberger AG. Quantification of butyryl CoA:acetate CoA-transferase genes reveals different butyrate production capacity in individuals according to diet and age. *FEMS Microbiol Lett*. 2011;316(2):130–5.
7499. Duncan SH, Belenguer A, Holtrop G, Johnstone AM, Flint HJ, Lobley GE. Reduced dietary intake of carbohydrates by obese subjects results in decreased concentrations of butyrate and butyrate-producing bacteria in feces. *Appl Environ Microbiol*. 2007;73(4):1073–8.
7500. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science*. 2011;334(6052):105–8.
7501. Arumugam M, Raes J, Pelletier E, et al. Enterotypes of the human gut microbiome. *Nature*. 2011;473(7346):174–80.
7502. Chen T, Long W, Zhang C, Liu S, Zhao L, Hamaker BR. Fiber-utilizing capacity varies in *Prevotella*- versus *Bacteroides*-dominated gut microbiota. *Sci Rep*. 2017;7(1):2594.
7503. O'Keefe SJ, Chung D, Mahmoud N, et al. Why do African Americans get more colon cancer than Native Africans? *J Nutr*. 2007;137(1 Suppl):175S-82S.
7504. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;505(7484):559–63.
7505. Zhao F, Feng J, Li J, et al. Alterations of the gut microbiota in Hashimoto's thyroiditis patients. *Thyroid*. 2018;28(2):175–86.
7506. Tonstad S, Nathan E, Oda K, Fraser GE. Prevalence of hyperthyroidism according to type of vegetarian diet. *Public Health Nutr*. 2015;18(8):1482–7.

7507. Precup G, Vodnar DC. Gut *Prevotella* as a possible biomarker of diet and its eubiotic versus dysbiotic roles: a comprehensive literature review. *Br J Nutr*. 2019;122(2):131–40.
7508. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;505(7484):559–63.
7509. Kumar M, Babaei P, Ji B, Nielsen J. Human gut microbiota and healthy aging: recent developments and future prospective. *Nutr Healthy Aging*. 4(1):3–16.
7510. Wu YT, Shen SJ, Liao KF, Huang CY. Dietary plant and animal protein sources oppositely modulate fecal *Bilophila* and *Lachnoclostridium* in vegetarians and omnivores. *Microbiol Spectr*. 2022;10(2):e0204721.
7511. Singh RK, Chang HW, Yan D, et al. Influence of diet on the gut microbiome and implications for human health. *J Transl Med.* 2017;15(1):73.
7512. Franco-de-Moraes AC, de Almeida-Pititto B, da Rocha Fernandes G, Gomes EP, da Costa Pereira A, Ferreira SRG. Worse inflammatory profile in omnivores than in vegetarians associates with the gut microbiota composition. *Diabetol Metab Syndr*. 2017;9:62.
7513. Kim MS, Hwang SS, Park EJ, Bae JW. Strict vegetarian diet improves the risk factors associated with metabolic diseases by modulating gut microbiota and reducing intestinal inflammation. *Environ Microbiol Rep*. 2013;5(5):765–75.
7514. Zmora N, Suez J, Elinav E. You are what you eat: diet, health and the gut microbiota. *Nat Rev Gastroenterol Hepatol*. 2019;16(1):35–56.
7515. Asnicar F, Berry SE, Valdes AM, et al. Microbiome connections with host metabolism and habitual diet from 1,098 deeply phenotyped individuals. *Nat Med*. 2021;27(2):321–32.
7516. De Filippis F, Pellegrini N, Vannini L, et al. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut*. 2016;65(11):1812–21.
7517. Freeland KR, Wilson C, Wolever TM. Adaptation of colonic fermentation and glucagon-like peptide-1 secretion with increased wheat fibre intake for 1 year in hyperinsulinaemic human subjects. *Br J Nutr*. 2010;103(1):82–90.

7518. Wu GD, Compher C, Chen EZ, et al. Comparative metabolomics in vegans and omnivores reveal constraints on diet-dependent gut microbiota metabolite production. *Gut*. 2016;65(1):63–72.
7519. Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids*. National Academy Press; 2005.
7520. Jew S, Abumweis SS, Jones PJ. Evolution of the human diet: linking our ancestral diet to modern functional foods as a means of chronic disease prevention. *J Med Food.* 2009;12(5):925–34.
7521. Leach JD, Sobolik KD. High dietary intake of prebiotic inulin-type fructans in the prehistoric Chihuahuan Desert. *Br J Nutr*. 2010;103(11):1558–61.
7522. Institute of Medicine (U.S.). *Dietary Reference Intakes: Proposed Definition of Dietary Fiber*. National Academies Press; 2001.
7523. Burkitt DP, Meisner P. How to manage constipation with high-fiber diet. *Geriatrics*. 1979;34(2):33–5, 38–40.
7524. Requena T, Martínez-Cuesta MC, Peláez C. Diet and microbiota linked in health and disease. *Food Funct*. 2018;9(2):688–704.
7525. Han M, Wang C, Liu P, Li D, Li Y, Ma X. Dietary fiber gap and host gut microbiota. *Protein Pept Lett*. 2017;24(5):388–96.
7526. Venkatakrishnan A, Holzknecht ZE, Holzknecht R, et al. Evolution of bacteria in the human gut in response to changing environments: an invisible player in the game of health. *Comput Struct Biotechnol J*. 2021;19:752–8.
7527. Hamaker BR, Cantu-Jungles TM. Discrete fiber structures dictate human gut bacteria outcomes. *Trends Endocrinol Metab*. 2020;31(11):803–5.
7528. Tap J, Furet JP, Bensaada M, et al. Gut microbiota richness promotes its stability upon increased dietary fibre intake in healthy adults. *Environ Microbiol*. 2015;17(12):4954–64.
7529. Walter J, Martínez I, Rose DJ. Holobiont nutrition: considering the role of the gastrointestinal microbiota in the health benefits of whole grains. *Gut Microbes*. 2013;4(4):340–6.
7530. Toribio-Mateas M. Harnessing the power of microbiome assessment tools as part of neuroprotective nutrition and lifestyle medicine interventions. *Microorganisms*. 2018;6(2):35.

7531. McRorie J. Clinical data support that psyllium is not fermented in the gut. *Am J Gastroenterol*. 2013;108(9):1541.
7532. Almeida A, Mitchell AL, Boland M, et al. A new genomic blueprint of the human gut microbiota. *Nature*. 2019;568(7753):499–504.
7533. Pereira FC, Berry D. Microbial nutrient niches in the gut. *Environ Microbiol*. 2017;19(4):1366–78.
7534. O'Keefe SJD. The need to reassess dietary fiber requirements in healthy and critically ill patients. *Gastroenterol Clin North Am*. 2018;47(1):219–29.
7535. Swain Ewald HA, Ewald PW. Natural selection, the microbiome, and public health. *Yale J Biol Med*. 2018;91(4):445–55.
7536. Dewulf EM, Cani PD, Claus SP, et al. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. *Gut*. 2013;62(8):1112–21.
7537. Hill P, Muir JG, Gibson PR. Controversies and recent developments of the low-FODMAP diet. *Gastroenterol Hepatol (N Y)*. 2017;13(1):36–45.
7538. Yadav BS, Sharma A, Yadav RB. Studies on effect of multiple heating/cooling cycles on the resistant starch formation in cereals, legumes and tubers. *Int J Food Sci Nutr*. 2009;60 Suppl 4:258–72.
7539. Fernando WMU, Hill JE, Zello GA, Tyler RT, Dahl WJ, Van Kessel AG. Diets supplemented with chickpea or its main oligosaccharide component raffinose modify faecal microbial composition in healthy adults. *Benef Microbes*. 2010;1(2):197–207.
7540. Jin S, Je Y. Nuts and legumes consumption and risk of colorectal cancer: a systematic review and meta-analysis. *Eur J Epidemiol*. 2022;37(6):569–85.
7541. Hangen L, Bennink MR. Consumption of black beans and navy beans (*Phaseolus vulgaris*) reduced azoxymethane-induced colon cancer in rats. *Nutr Cancer*. 2002;44(1):60–5.
7542. Holscher HD. Diet affects the gastrointestinal microbiota and health. *J Acad Nutr Diet*. 2020;120(4):495–9.
7543. Venkataraman A, Sieber JR, Schmidt AW, Waldron C, Theis KR, Schmidt TM. Variable responses of human microbiomes to dietary supplementation with resistant starch. *Microbiome*. 2016;4(1):33.

7544. Liu S, Ren F, Zhao L, et al. Starch and starch hydrolysates are favorable carbon sources for bifidobacteria in the human gut. *BMC Microbiol*. 2015;15:54.
7545. Hellström PM, Grybäck P, Jacobsson H. The physiology of gastric emptying. *Best Pract Res Clin Anaesthesiol*. 2006;20(3):397–407.
7546. Grundy MM, Edwards CH, Mackie AR, Gidley MJ, Butterworth PJ, Ellis PR. Re-evaluation of the mechanisms of dietary fibre and implications for macronutrient bioaccessibility, digestion and postprandial metabolism. *Br J Nutr*. 2016;116(5):816–33.
7547. Edwards CH, Grundy MM, Grassby T, et al. Manipulation of starch bioaccessibility in wheat endosperm to regulate starch digestion, postprandial glycemia, insulinemia, and gut hormone responses: a randomized controlled trial in healthy ileostomy participants. *Am J Clin Nutr*. 2015;102(4):791–800.
7548. Hareland G. Evaluation of flour particle size distribution by laser diffraction, sieve analysis and near-infrared reflectance spectroscopy. *J Cereal Sci*. 1994;20(2):183–90.
7549. Holscher HD, Taylor AM, Swanson KS, Novotny JA, Baer DJ. Almond consumption and processing affects the composition of the gastrointestinal microbiota of healthy adult men and women: a randomized controlled trial. *Nutrients*. 2018;10(2):126.
7550. McCarty MF, DiNicolantonio JJ. Acarbose, lente carbohydrate, and prebiotics promote metabolic health and longevity by stimulating intestinal production of GLP-1. *Open Heart*. 2015;2(1):e000205.
7551. Helander HF, Fändriks L. The enteroendocrine “letter cells”—time for a new nomenclature? *Scand J Gastroenterol*. 2012;47(1):3–12.
7552. FDA approves new drug treatment for chronic weight management, first since 2014. U.S. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014. Published June 4, 2021. Accessed February 25, 2023.
7553. Kumari M, Kozyrskyj AL. Gut microbial metabolism defines host metabolism: an emerging perspective in obesity and allergic inflammation. *Obes Rev*. 2017;18(1):18–31.
7554. Freeland KR, Wolever TM. Acute effects of intravenous and rectal acetate on glucagon-like peptide-1, peptide YY, ghrelin, adiponectin

and tumour necrosis factor-alpha. *Br J Nutr*. 2010;103(3):460–6.
7555. Greenway F, O'Neil CE, Stewart L, Rood J, Keenan M, Martin R. Fourteen weeks of treatment with Viscofiber increased fasting levels of glucagon-like peptide-1 and peptide-YY. *J Med Food*. 2007;10(4):720–4.
7556. Sandberg JC, Björck IM, Nilsson AC. Rye-based evening meals favorably affected glucose regulation and appetite variables at the following breakfast; a randomized controlled study in healthy subjects. *PLoS ONE*. 2016;11(3):e0151985.
7557. Han Y, Xiao H. Whole food–based approaches to modulating gut microbiota and associated diseases. *Annu Rev Food Sci Technol*. 2020;11:119–43.
7558. Kahle K, Kraus M, Scheppach W, Ackermann M, Ridder F, Richling E. Studies on apple and blueberry fruit constituents: do the polyphenols reach the colon after ingestion? *Mol Nutr Food Res*. 2006;50(4–5):418–23.
7559. Martel J, Ojcius DM, Ko YF, Young JD. Phytochemicals as prebiotics and biological stress inducers. *Trends Biochem Sci*. 2020;45(6):462–71.
7560. Routray W, Orsat V. Blueberries and their anthocyanins: factors affecting biosynthesis and properties. *Comp Rev Food Sci and Food Saf*. 2011;10(6):303–20.
7561. Hidalgo M, Oruna-Concha MJ, Kolida S, et al. Metabolism of anthocyanins by human gut microflora and their influence on gut bacterial growth. *J Agric Food Chem*. 2012;60:3882–90.
7562. Stevenson D, Scalzo J. Anthocyanin composition and content of blueberries. *J Berry Res*. 2012;2(4):179–89.
7563. Vendrame S, Guglielmetti S, Riso P, Arioli S, Klimis-Zacas D, Porrini M. Six-week consumption of a wild blueberry powder drink increases bifidobacteria in the human gut. *J Agric Food Chem*. 2011;59(24):12815–20.
7564. Shinohara K, Ohashi Y, Kawasumi K, Terada A, Fujisawa T. Effect of apple intake on fecal microbiota and metabolites in humans. *Anaerobe*. 2010;16(5):510–5.
7565. Drasar B, Jenkins D. Bacteria, diet, and large bowel cancer. *Am J Clin Nutr*. 1976;29:1410–6.

7566. Mitsou EK, Kougia E, Nomikos T, Yannakoulia M, Mountzouris KC, Kyriacou A. Effect of banana consumption on faecal microbiota: a randomised, controlled trial. *Anaerobe*. 2011;17(6):384–7.
7567. Del Bo' C, Bernardi S, Cherubini A, et al. A polyphenol-rich dietary pattern improves intestinal permeability, evaluated as serum zonulin levels, in older subjects: the MaPLE randomised controlled trial. *Clin Nutr*. 2021;40(5):3006–18.
7568. Jin JS, Touyama M, Hisada T, Benno Y. Effects of green tea consumption on human fecal microbiota with special reference to *Bifidobacterium* species. *Microbiol Immunol*. 2012;56(11):729–39.
7569. Jaquet M, Rochat I, Moulin J, Cavin C, Bibiloni R. Impact of coffee consumption on the gut microbiota: a human volunteer study. *Int J Food Microbiol*. 2009;130(2):117–21.
7570. Jaquet M, Rochat I, Moulin J, Cavin C, Bibiloni R. Impact of coffee consumption on the gut microbiota: a human volunteer study. *Int J Food Microbiol*. 2009;130(2):117–21.
7571. Sarin S, Marya C, Nagpal R, Oberoi SS, Rekhi A. Preliminary clinical evidence of the antiplaque, antigingivitis efficacy of a mouthwash containing 2% green tea—a randomised clinical trial. *Oral Health Prev Dent*. 2015;13(3):197–203.
7572. Elsaie ML, Abdelhamid MF, Elsaaiee LT, Emam HM. The efficacy of topical 2% green tea lotion in mild-to-moderate acne vulgaris. *J Drugs Dermatol*. 2009;8(4):358–64.
7573. Ikeda S, Kanoya Y, Nagata S. Effects of a foot bath containing green tea polyphenols on interdigital tinea pedis. *Foot (Edinb)*. 2013;23(2–3):58–62.
7574. Jin JS, Touyama M, Hisada T, Benno Y. Effects of green tea consumption on human fecal microbiota with special reference to *Bifidobacterium* species. *Microbiol Immunol*. 2012;56(11):729–39.
7575. Sun H, Chen Y, Cheng M, Zhang X, Zheng X, Zhang Z. The modulatory effect of polyphenols from green tea, oolong tea and black tea on human intestinal microbiota in vitro. *J Food Sci Technol*. 2018;55(1):399–407.
7576. Ma ZJ, Wang HJ, Ma XJ, et al. Modulation of gut microbiota and intestinal barrier function during alleviation of antibiotic-associated

diarrhea with Rhizoma *Zingiber officinale* (Ginger) extract. *Food Funct*. 2020;11(12):10839–51.

7577. Hazan S. Rapid improvement in Alzheimer's disease symptoms following fecal microbiota transplantation: a case report. *J Int Med Res*. 2020;48(6):300060520925930.

7578. Marx W, Scholey A, Firth J, et al. Prebiotics, probiotics, fermented foods and cognitive outcomes: a meta-analysis of randomized controlled trials. *Neurosci Biobehav Rev*. 2020;118:472–84.

7579. Frontiers Editorial Office. Expression of concern: effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. *Front Aging Neurosci*. 2020;12:602204.

7580. [Information on the investigation and handling of suspected fraudulent thesis]. Ministry of Science and Technology of the People's Republic of China. https://www.most.gov.cn/tztg/202101/t20210121_172330.html. Published January 21, 2021. Accessed November 7, 2021.

7581. Syed YY. Sodium oligomannate: first approval. *Drugs*. 2020;80(4):441–4.

7582. Czank C, Cassidy A, Zhang Q, et al. Human metabolism and elimination of the anthocyanin, cyanidin-3-glucoside: a ^{13}C-tracer study. *Am J Clin Nutr*. 2013;97(5):995–1003.

7583. Djedjibegovic J, Marjanovic A, Panieri E, Saso L. Ellagic acid-derived urolithins as modulators of oxidative stress. *Oxid Med Cell Longev*. 2020;2020:1–15.

7584. Bakkalbaşi E, Menteş O, Artik N. Food ellagitannins–occurrence, effects of processing and storage. *Crit Rev Food Sci Nutr*. 2009;49(3):283–98.

7585. Ryu D, Mouchiroud L, Andreux PA, et al. Urolithin A induces mitophagy and prolongs lifespan in *C. elegans* and increases muscle function in rodents. *Nat Med*. 2016;22(8):879–88.

7586. Djedjibegovic J, Marjanovic A, Panieri E, Saso L. Ellagic acid-derived urolithins as modulators of oxidative stress. *Oxid Med Cell Longev*. 2020;2020:1–15.

7587. Ryu D, Mouchiroud L, Andreux PA, et al. Urolithin A induces mitophagy and prolongs lifespan in *C. elegans* and increases muscle

function in rodents. *Nat Med*. 2016;22(8):879–88.

7588. Drummond MJ, Addison O, Brunker L, et al. Downregulation of E3 ubiquitin ligases and mitophagy-related genes in skeletal muscle of physically inactive, frail older women: a cross-sectional comparison. *J Gerontol A Biol Sci Med Sci*. 2014;69(8):1040–8.

7589. Ryu D, Mouchiroud L, Andreux PA, et al. Urolithin A induces mitophagy and prolongs lifespan in *C. elegans* and increases muscle function in rodents. *Nat Med*. 2016;22(8):879–88.

7590. Andreux PA, Blanco-Bose W, Ryu D, et al. The mitophagy activator urolithin A is safe and induces a molecular signature of improved mitochondrial and cellular health in humans. *Nat Metab*. 2019;1(6):595–603.

7591. Liu S, D'Amico D, Shankland E, et al. Effect of urolithin A supplementation on muscle endurance and mitochondrial health in older adults. *JAMA Netw Open*. 2022;5(1):e2144279.

7592. Singh A, D'Amico D, Andreux PA, et al. Direct supplementation with Urolithin A overcomes limitations of dietary exposure and gut microbiome variability in healthy adults to achieve consistent levels across the population. *Eur J Clin Nutr*. 2022;76(2):297–308.

7593. González-Sarrías A, García-Villalba R, Romo-Vaquero M, et al. Clustering according to urolithin metabotype explains the interindividual variability in the improvement of cardiovascular risk biomarkers in overweight-obese individuals consuming pomegranate: a randomized clinical trial. *Mol Nutr Food Res*. 2017;61(5):1600830.

7594. Wu YT, Shen SJ, Liao KF, Huang CY. Dietary plant and animal protein sources oppositely modulate fecal *Bilophila* and *Lachnoclostridium* in vegetarians and omnivores. *Microbiol Spectr*. 2022;10(2):e0204721.

7595. Alfei S, Marengo B, Zuccari G. Oxidative stress, antioxidant capabilities, and bioavailability: ellagic acid or urolithins? *Antioxidants (Basel)*. 2020;9(8):E707.

7596. Prentice AM. Starvation in humans: evolutionary background and contemporary implications. *Mech Ageing Dev*. 2005;126(9):976–81.

7597. Wilhelmi de Toledo F, Buchinger A, Burggrabe H, et al. Fasting therapy—an expert panel update of the 2002 consensus guidelines. *Forsch Komplementmed*. 2013;20(6):434–43.

7598. Longo VD, Mattson MP. Fasting: molecular mechanisms and clinical applications. *Cell Metab*. 2014;19(2):181–92.
7599. Michalsen A, Li C. Fasting therapy for treating and preventing disease—current state of evidence. *Forsch Komplementmed*. 2013;20(6):444–53.
7600. Kozubík A, Pospísil M. Protective effect of intermittent fasting on the mortality of gamma-irradiated mice. *Strahlentherapie*. 1982;158(12):734–8.
7601. Dossey L. Longevity. *Altern Ther Health Med*. 2002;8(3):12–6, 125–34.
7602. Ziegler CC, Sidani MA. Diets for successful aging. *Clin Geriatr Med*. 2011;27(4):577–89.
7603. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: an update. *Ageing Res Rev*. 2017;39:36–45.
7604. Hindhede M. The effect of food restriction during war on mortality in Copenhagen. *JAMA*. 1920;74(6):381–2.
7605. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: an update. *Ageing Res Rev*. 2017;39:36–45.
7606. Austad SN, Hoffman JM. Beyond calorie restriction: aging as a biological target for nutrient therapies. *Curr Opin Biotechnol*. 2021;70:56–60.
7607. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: an update. *Ageing Res Rev*. 2017;39:36–45.
7608. Austad SN. Life extension by dietary restriction in the bowl and doily spider, *Frontinella pyramitela*. *Exp Gerontol*. 1989;24(1):83–92.
7609. Burkewitz K, Zhang Y, Mair WB. AMPK at the nexus of energetics and aging. *Cell Metab*. 2014;20(1):10–25.
7610. Speakman JR. Why does caloric restriction increase life and healthspan? The “clean cupboards” hypothesis. *Natl Sci Rev*. 2020;7(7):1153–6.
7611. Mani K, Javaheri A, Diwan A. Lysosomes mediate benefits of intermittent fasting in cardiometabolic disease: the janitor is the undercover boss. *Compr Physiol*. 2018;8(4):1639–67.
7612. Dulloo AG. Explaining the failures of obesity therapy: willpower attenuation, target miscalculation or metabolic compensation? *Int J Obes (Lond)*. 2012;36(11):1418–20.

7613. Redman LM, Heilbronn LK, Martin CK, et al. Metabolic and behavioral compensations in response to caloric restriction: implications for the maintenance of weight loss. *PLoS ONE*. 2009;4(2):e4377.
7614. Hall KD. Metabolic adaptations to weight loss. *Obesity (Silver Spring)*. 2018;26(5):790–1.
7615. Schwartz A, Doucet E. Relative changes in resting energy expenditure during weight loss: a systematic review. *Obes Rev*. 2010;11(7):531–47.
7616. Osborne TB, Mendel LB, Ferry EL. The effect of retardation of growth upon the breeding period and duration of life of rats. *Science*. 1917;45(1160):294–5.
7617. Redman LM, Smith SR, Burton JH, Martin CK, Il'yasova D, Ravussin E. Metabolic slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging. *Cell Metab*. 2018;27(4):805–15.e4.
7618. European hare (*Lepus europaeus*) longevity, ageing, and life history. *Human Ageing Genomic Resources*. https://genomics.senescence.info/species/entry.php?species=Lepus_europaeus. Published October 14, 2017. December 9, 2022.
7619. Galapagos tortoise (*Chelonoidis nigra*) longevity, ageing, and life history. *Human Ageing Genomic Resources*. https://genomics.senescence.info/species/entry.php?species=Chelonoidis_nigra. Published 2018. Accessed December 9, 2022.
7620. Civitarese AE, Carling S, Heilbronn LK, et al. Calorie restriction increases muscle mitochondrial biogenesis in healthy humans. *PLoS MED*. 2007;4(3):e76.
7621. Redman LM, Smith SR, Burton JH, Martin CK, Il'yasova D, Ravussin E. Metabolic slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging. *Cell Metab*. 2018;27(4):805–15.e4.
7622. Tamakoshi A, Tamakoshi K, Lin Y, Yagyu K, Kikuchi S, JACC Study Group. Healthy lifestyle and preventable death: findings from the

Japan Collaborative Cohort (JACC) Study. *Prev Med*. 2009;48(5):486–92.
7623. Bourzac K. Interventions: live long and prosper. *Nature*. 2012;492(7427):S18–20.
7624. Rebrin I, Forster MJ, Sohal RS. Association between life-span extension by caloric restriction and thiol redox state in two different strains of mice. *Free Radic Biol Med*. 2011;51(1):225–33.
7625. Life expectancy. Centers for Disease Control and Prevention. https://www.cdc.gov/nchs/fastats/life-expectancy.htm. Updated September 6, 2022. Accessed December 9, 2022.
7626. Speakman JR, Hambly C. Starving for life: what animal studies can and cannot tell us about the use of caloric restriction to prolong human lifespan. *J Nutr*. 2007;137(4):1078–86.
7627. Speakman JR, Hambly C. Starving for life: what animal studies can and cannot tell us about the use of caloric restriction to prolong human lifespan. *J Nutr*. 2007;137(4):1078–86.
7628. Liao CY, Rikke BA, Johnson TE, Diaz V, Nelson JF. Genetic variation in the murine lifespan response to dietary restriction: from life extension to life shortening. *Aging Cell*. 2010;9(1):92–5.
7629. Wolf AM. Rodent diet aids and the fallacy of caloric restriction. *Mech Ageing Dev*. 2021;200:111584.
7630. Weichhart T. mTOR as regulator of lifespan, aging, and cellular senescence: a mini-review. *Gerontology*. 2018;64(2):127–34.
7631. Ingram DK, de Cabo R. Calorie restriction in rodents: caveats to consider. *Ageing Res Rev*. 2017;39:15–28.
7632. Lawler DF, Larson BT, Ballam JM, et al. Diet restriction and ageing in the dog: major observations over two decades. *Br J Nutr*. 2008;99(4):793–805.
7633. Fryar CD, Carroll MD, Afful J. Prevalence of overweight, obesity, and extreme obesity among adults aged 20 and over: United States, 1960–1962 through 2017–2018. Centers for Disease Control and Prevention. https://www.cdc.gov/nchs/data/hestat/obesity-adult-17–18/overweight-obesity-adults-H.pdf. Published December 2020. Accessed November 22, 2022.
7634. Grover SA, Kaouache M, Rempel P, et al. Years of life lost and healthy life-years lost from diabetes and cardiovascular disease in

overweight and obese people: a modelling study. *Lancet Diabetes Endocrinol*. 2015;3(2):114–22.
7635. Bodkin NL, Alexander TM, Ortmeyer HK, Johnson E, Hansen BC. Mortality and morbidity in laboratory-maintained rhesus monkeys and effects of long-term dietary restriction. *J Gerontol A Biol Sci Med Sci*. 2003;58(3):212–9.
7636. Colman RJ, Beasley TM, Kemnitz JW, Johnson SC, Weindruch R, Anderson RM. Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys. *Nat Commun*. 2014;5(1):3557.
7637. Mattison JA, Roth GS, Beasley TM, et al. Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. *Nature*. 2012;489(7415):318–21.
7638. Pifferi F, Terrien J, Marchal J, et al. Caloric restriction increases lifespan but affects brain integrity in grey mouse lemur primates. *Commun Biol*. 2018;1:30.
7639. Le Bourg E. Dietary restriction studies in humans: focusing on obesity, forgetting longevity. *Gerontology*. 2012;58(2):126–8.
7640. Harbottle EJ, Birmingham CL, Sayani F. Anorexia nervosa: a survival analysis. *Eat Weight Disord*. 2008;13(2):e32–4.
7641. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: an update. *Ageing Res Rev*. 2017;39:36–45.
7642. Harbottle EJ, Birmingham CL, Sayani F. Anorexia nervosa: a survival analysis. *Eat Weight Disord*. 2008;13(2):e32–4.
7643. Machado PPP, Grilo CM, Crosby RD. Evaluation of the DSM-5 severity indicator for anorexia nervosa. *Eur Eat Disord Rev*. 2017;25(3):221–3.
7644. Fryar CD, Kruszon-Moran D, Gu Q, Ogden CL. Mean body weight, height, waist circumference, and body mass index among adults: United States, 1999–2000 through 2015–2016. *Natl Health Stat Report*. 2018;(122):1–16.
7645. Mehler PS, Koutsavlis A. Anorexia nervosa, albumin, and inflammation. *Am J Med*. 2021;134(6):e401.
7646. Arcelus J, Mitchell AJ, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders: a meta-analysis of 36 studies. *Arch Gen Psychiatry*. 2011;68(7):724–31.

7647. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: an update. *Ageing Res Rev*. 2017;39:36–45.
7648. Lee MB, Hill CM, Bitto A, Kaeberlein M. Antiaging diets: separating fact from fiction. *Science*. 2021;374(6570):eabe7365.
7649. Most J, Gilmore LA, Smith SR, Han H, Ravussin E, Redman LM. Significant improvement in cardiometabolic health in healthy nonobese individuals during caloric restriction-induced weight loss and weight loss maintenance. *Am J Physiol Endocrinol Metab*. 2018;314(4):E396–405.
7650. Anderson RM, Le Couteur DG, de Cabo R. Caloric restriction research: new perspectives on the biology of aging. *J Gerontol A Biol Sci Med Sci*. 2017;73(1):1–3.
7651. Richardson A, Austad SN, Ikeno Y, Unnikrishnan A, McCarter RJ. Significant life extension by ten percent dietary restriction. *Ann N Y Acad Sci.* 2016;1363(1):11–7.
7652. Dirks AJ, Leeuwenburgh C. Caloric restriction in humans: potential pitfalls and health concerns. *Mech Ageing Dev*. 2006;127(1):1–7.
7653. Martin CK, Bhapkar M, Pittas AG, et al. Effect of calorie restriction on mood, quality of life, sleep, and sexual function in healthy nonobese adults: the CALERIE 2 randomized clinical trial. *JAMA Intern Med*. 2016;176(6):743–52.
7654. Most J, Gilmore LA, Smith SR, Han H, Ravussin E, Redman LM. Significant improvement in cardiometabolic health in healthy nonobese individuals during caloric restriction-induced weight loss and weight loss maintenance. *Am J Physiol Endocrinol Metab*. 2018;314(4):E396–405.
7655. Ravussin E, Redman LM, Rochon J, et al. A 2-year randomized controlled trial of human caloric restriction: feasibility and effects on predictors of health span and longevity. *J Gerontol A Biol Sci Med Sci*. 2015;70(9):1097–104.
7656. Das SK, Roberts SB, Bhapkar MV, et al. Body-composition changes in the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE)-2 study: a 2-y randomized controlled trial of calorie restriction in nonobese humans. *Am J Clin Nutr*. 2017;105(4):913–27.

7657. Franklin JC, Scheile BC. Observations on human behavior in experimental semi-starvation and rehabilitation. *J Clin Psychol*. 1948;4(1):28–45.
7658. Dulloo AG, Jacquet J, Montani JP. How dieting makes some fatter: from a perspective of human body composition autoregulation. *Proc Nutr Soc*. 2012;71(3):379–89.
7659. Redman LM, Smith SR, Burton JH, Martin CK, Il'yasova D, Ravussin E. Metabolic slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging. *Cell Metab*. 2018;27(4):805–15.e4.
7660. Marlatt KL, Redman LM, Burton JH, Martin CK, Ravussin E. Persistence of weight loss and acquired behaviors 2 y after stopping a 2-y calorie restriction intervention. *Am J Clin Nutr*. 2017;105(4):928–35.
7661. Dorling JL, van Vliet S, Huffman KM, et al. Effects of caloric restriction on human physiological, psychological, and behavioral outcomes: highlights from CALERIE phase 2. *Nutr Rev*. 2020;79(1):98–113.
7662. Kahathuduwa CN, Binks M, Martin CK, Dawson JA. Extended calorie restriction suppresses overall and specific food cravings: a systematic review and a meta-analysis. *Obes Rev*. 2017;18(10):1122–35.
7663. Redman LM, Smith SR, Burton JH, Martin CK, Il'yasova D, Ravussin E. Metabolic slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging. *Cell Metab*. 2018;27(4):805–15.e4.
7664. Il'yasova D, Fontana L, Bhapkar M, et al. Effects of 2 years of caloric restriction on oxidative status assessed by urinary F2-isoprostanes: the CALERIE 2 randomized clinical trial. *Aging Cell*. 2018;17(2):e12719.
7665. Omodei D, Licastro D, Salvatore F, Crosby SD, Fontana L. Serum from humans on long-term calorie restriction enhances stress resistance in cell culture. *Aging (Albany NY)*. 2013;5(8):599–606.
7666. Dorling JL, van Vliet S, Huffman KM, et al. Effects of caloric restriction on human physiological, psychological, and behavioral

outcomes: highlights from CALERIE phase 2. *Nutr Rev*. 2020;79(1):98–113.
7667. Dorling JL, van Vliet S, Huffman KM, et al. Effects of caloric restriction on human physiological, psychological, and behavioral outcomes: highlights from CALERIE phase 2. *Nutr Rev*. 2020;79(1):98–113.
7668. Block G, Dresser CM, Hartman AM, Carroll MD. Nutrient sources in the American diet: quantitative data from the NHANES II survey. II. Macronutrients and fats. *Am J Epidemiol*. 1985;122(1):13–26.
7669. Dorling JL, van Vliet S, Huffman KM, et al. Effects of caloric restriction on human physiological, psychological, and behavioral outcomes: highlights from CALERIE phase 2. *Nutr Rev*. 2020;79(1):98–113.
7670. Tang X, Zhao W, Lu M, et al. Relationship between central obesity and the incidence of cognitive impairment and dementia from cohort studies involving 5,060,687 participants. *Neurosci Biobehav Rev*. 2021;130:301–13.
7671. Yu Q, Zou L, Kong Z, Yang L. Cognitive impact of calorie restriction: a narrative review. *J Am Med Dir Assoc*. 2020;21(10):1394–401.
7672. Phillips MCL. Fasting as a therapy in neurological disease. *Nutrients*. 2019;11(10):2501.
7673. Lü W, Yu T, Kuang W. Effects of dietary restriction on cognitive function: a systematic review and meta-analysis. *Nutr Neurosci*. Published online April 25, 2022:1–11.
7674. Lü W, Yu T, Kuang W. Effects of dietary restriction on cognitive function: a systematic review and meta-analysis. *Nutr Neurosci*. Published online April 25, 2022:1–11.
7675. Witte AV, Fobker M, Gellner R, Knecht S, Flöel A. Caloric restriction improves memory in elderly humans. *Proc Natl Acad Sci U S A*. 2009;106(4):1255–60.
7676. Leclerc E, Trevizol AP, Grigolon RB, et al. The effect of caloric restriction on working memory in healthy non-obese adults. *CNS Spectr*. 2020;25(1):2–8.
7677. Lindseth GN, Lindseth PD, Jensen WC, Petros TV, Helland BD, Fossum DL. Dietary effects on cognition and pilots' flight

performance. *Int J Aviat Psychol*. 2011;21(3):269–82.
7678. Benau EM, Orloff NC, Janke EA, Serpell L, Timko CA. A systematic review of the effects of experimental fasting on cognition. *Appetite*. 2014;77:52–61.
7679. Zajac I, Herreen D, Hunkin H, et al. Modified fasting compared to true fasting improves blood glucose levels and subjective experiences of hunger, food cravings and mental fatigue, but not cognitive function: results of an acute randomised cross-over trial. *Nutrients*. 2020;13(1):E65.
7680. Lieberman HR, Caruso CM, Niro PJ, et al. A double-blind, placebo-controlled test of 2 d of calorie deprivation: effects on cognition, activity, sleep, and interstitial glucose concentrations. *Am J Clin Nutr*. 2008;88(3):667–76.
7681. Dar BA, Dar MA, Bashir S. Calorie restriction the fountain of youth. *Food Nutr Sci.* 2012;3(11):1522–6.
7682. Dirks AJ, Leeuwenburgh C. Caloric restriction in humans: potential pitfalls and health concerns. *Mech Ageing Dev.* 2006;127(1):1–7.
7683. Hunt ND, Li GD, Zhu M, et al. Effect of calorie restriction and refeeding on skin wound healing in the rat. *Age (Dordr).* 2012;34(6):1453–8.
7684. Reed MJ, Penn PE, Li Y, et al. Enhanced cell proliferation and biosynthesis mediate improved wound repair in refed, caloric-restricted mice. *Mech Ageing Dev*. 1996;89(1):21–43.
7685. Bergendahl M, Vance ML, Iranmanesh A, Thorner MO, Veldhuis JD. Fasting as a metabolic stress paradigm selectively amplifies cortisol secretory burst mass and delays the time of maximal nyctohemeral cortisol concentrations in healthy men. *J Clin Endocrinol Metab*. 1996;81(2):692–9.
7686. Nakamura Y, Walker BR, Ikuta T. Systematic review and meta-analysis reveals acutely elevated plasma cortisol following fasting but not less severe calorie restriction. *Stress*. 2016;19(2):151–7.
7687. Speakman JR, Hambly C. Starving for life: what animal studies can and cannot tell us about the use of caloric restriction to prolong human lifespan. *J Nutr*. 2007;137(4):1078–86.
7688. Mattison JA, Roth GS, Beasley TM, et al. Impact of caloric restriction on health and survival in rhesus monkeys from the NIA

study. *Nature*. 2012;489(7415):318–21.
7689. Sun D, Muthukumar AR, Lawrence RA, Fernandes G. Effects of calorie restriction on polymicrobial peritonitis induced by cecum ligation and puncture in young C57BL/6 mice. *Clin Diagn Lab Immunol*. 2001;8(5):1003–11.
7690. Gardner EM, Beli E, Clinthorne JF, Duriancik DM. Energy intake and response to infection with influenza. *Annu Rev Nutr*. 2011;31:353–67.
7691. Barbosa ASAA, Diório SM, Pedrini SCB, et al. Nutritional status and immune response in murine experimental Jorge Lobo's disease. *Mycoses*. 2015;58(9):522–30.
7692. Kristan DM. Chronic calorie restriction increases susceptibility of laboratory mice (*Mus musculus*) to a primary intestinal parasite infection. *Aging Cell*. 2007;6(6):817–25.
7693. Clinthorne JF, Adams DJ, Fenton JI, Ritz BW, Gardner EM. Short-term re-feeding of previously energy-restricted C57BL/6 male mice restores body weight and body fat and attenuates the decline in natural killer cell function after primary influenza infection. *J Nutr*. 2010;140(8):1495–501.
7694. Clinthorne JF, Adams DJ, Fenton JI, Ritz BW, Gardner EM. Short-term re-feeding of previously energy-restricted C57BL/6 male mice restores body weight and body fat and attenuates the decline in natural killer cell function after primary influenza infection. *J Nutr*. 2010;140(8):1495–501.
7695. Nicoll R, Henein MY. Caloric restriction and its effect on blood pressure, heart rate variability and arterial stiffness and dilatation: a review of the evidence. *Int J Mol Sci*. 2018;19(3):751.
7696. Florian JP, Baisch FJ, Heer M, Pawelczyk JA. Caloric restriction decreases orthostatic tolerance independently from 6° head-down bedrest. *PLoS ONE*. 2015;10(4):e0118812.
7697. Lu CC, Diedrich A, Tung CS, et al. Water ingestion as prophylaxis against syncope. *Circulation*. 2003;108(21):2660–5.
7698. Racette SB, Rochon J, Uhrich ML, et al. Effects of two years of calorie restriction on aerobic capacity and muscle strength. *Med Sci Sports Exerc*. 2017;49(11):2240–9.

7699. Cava E, Yeat NC, Mittendorfer B. Preserving healthy muscle during weight loss. *Adv Nutr*. 2017;8(3):511–9.
7700. Smith GI, Yoshino J, Kelly SC, et al. High-protein intake during weight loss therapy eliminates the weight-loss-induced improvement in insulin action in obese postmenopausal women. *Cell Rep*. 2016;17(3):849–61.
7701. Sardeli AV, Komatsu TR, Mori MA, Gáspari AF, Chacon-Mikahil MPT. Resistance training prevents muscle loss induced by caloric restriction in obese elderly individuals: a systematic review and meta-analysis. *Nutrients*. 2018;10(4):423.
7702. Villareal DT, Fontana L, Weiss EP, et al. Bone mineral density response to caloric restriction-induced weight loss or exercise-induced weight loss: a randomized controlled trial. *Arch Intern Med*. 2006;166(22):2502–10.
7703. Romashkan SV, Das SK, Villareal DT, et al. Safety of two-year caloric restriction in non-obese healthy individuals. *Oncotarget*. 2016;7(15):19124–33.
7704. Villareal DT, Kotyk JJ, Armamento-Villareal RC, et al. Reduced bone mineral density is not associated with significantly reduced bone quality in men and women practicing long-term calorie restriction with adequate nutrition. *Aging Cell.* 2011;10(1):96–102.
7705. Lee YM, Kim KS, Jacobs DR, Lee DH. Persistent organic pollutants in adipose tissue should be considered in obesity research. *Obes Rev*. 2017;18(2):129–39.
7706. Vaz R, Slorach SA, Hofvander Y. Organochlorine contaminants in Swedish human milk: studies conducted at the National Food Administration 1981–1990. *Food Addit Contam*. 1993;10(4):407–18.
7707. Jandacek RJ, Heubi JE, Buckley DD, et al. Reduction of the body burden of PCBs and DDE by dietary intervention in a randomized trial. *J Nutr Biochem*. 2014;25(4):483–8.
7708. Sera N, Morita K, Nagasoe M, Tokieda H, Kitaura T, Tokiwa H. Binding effect of polychlorinated compounds and environmental carcinogens on rice bran fiber. *J Nutr Biochem*. 2005;16(1):50–8.
7709. Tufan F, Soyluk O, Karan MA. Healthy behaviors potentially due to calorie restriction. *JAMA Intern Med*. 2016;176(11):1724.

7710. Villareal DT, Fontana L, Das SK, et al. Effect of two-year caloric restriction on bone metabolism and bone mineral density in non-obese younger adults: a randomized clinical trial. *J Bone Miner Res*. 2016;31(1):40–51.
7711. Khong TK, Kimpton J. Moderate calorie restriction improves cardiometabolic risk factors in healthy individuals. *Drug Ther Bull*. 2020;58(9):135–6.
7712. Key T, Davey G. Prevalence of obesity is low in people who do not eat meat. *BMJ*. 1996;313(7060):816–7.
7713. Kennedy ET, Bowman SA, Spence JT, Freedman M, King J. Popular diets: correlation to health, nutrition, and obesity. *J Am Diet Assoc*. 2001;101(4):411–20.
7714. Rizzo NS, Jaceldo-Siegl K, Sabate J, Fraser GE. Nutrient profiles of vegetarian and nonvegetarian dietary patterns. *J Acad Nutr Diet*. 2013;113(12):1610–9.
7715. Sinclair DA, LaPlante MD. *Lifespan: The Revolutionary Science of Why We Age—and Why We Don't Have To*. Atria Books; 2019.
7716. Willcox DC, Willcox BJ, Todoriki H, Curb JD, Suzuki M. Caloric restriction and human longevity: what can we learn from the Okinawans? *Biogerontology*. 2006;7(3):173–7.
7717. Kouda K, Iki M. Beneficial effects of mild stress (hormetic effects): dietary restriction and health. *J Physiol Anthropol*. 2010;29(4):127–32.
7718. Twain M. *My Debut As A Literary Person: With Other Essays and Stories*. American Pub Co; 1903.
7719. Twain M. *A Connecticut Yankee in King Arthur's Court*. Charles L. Webster and Co; 1889.
7720. Harris L, McGarty A, Hutchison L, Ells L, Hankey C. Short-term intermittent energy restriction interventions for weight management: a systematic review and meta-analysis. *Obes Rev*. 2018;19(1):1–13.
7721. Trepanowski JF, Kroeger CM, Barnosky A, et al. Effect of alternate-day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults: a randomized clinical trial. *JAMA Intern Med*. 2017;177(7):930–8.
7722. Arguin H, Dionne IJ, Sénéchal M, et al. Short- and long-term effects of continuous versus intermittent restrictive diet approaches on body

composition and the metabolic profile in overweight and obese postmenopausal women: a pilot study. *Menopause*. 2012;19(8):870–6.

7723. Corley BT, Carroll RW, Hall RM, Weatherall M, Parry-Strong A, Krebs JD. Intermittent fasting in type 2 diabetes mellitus and the risk of hypoglycaemia: a randomized controlled trial. *Diabet Med*. 2018;35(5):588–94.

7724. Lammers LA, Achterbergh R, de Vries EM, et al. Short-term fasting alters cytochrome P450-mediated drug metabolism in humans. *Drug Metab Dispos*. 2015;43(6):819–28.

7725. de Cabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. *N Engl J Med*. 2019;381(26):2541–51.

7726. da Luz FQ, Hay P, Gibson AA, et al. Does severe dietary energy restriction increase binge eating in overweight or obese individuals? A systematic review. *Obes Rev*. 2015;16(8):652–65.

7727. Horne BD, May HT, Anderson JL, et al. Usefulness of routine periodic fasting to lower risk of coronary artery disease among patients undergoing coronary angiography. *Am J Cardiol*. 2008;102(7):814–9.

7728. Enstrom JE. Cancer and total mortality among active Mormons. *Cancer*. 1978;42(4):1943–51.

7729. Horne BD, Muhlestein JB, May HT, et al. Relation of routine, periodic fasting to risk of diabetes mellitus, and coronary artery disease in patients undergoing coronary angiography. *Am J Cardiol*. 2012;109(11):1558–62.

7730. Bartholomew CL, Muhlestein JB, Anderson JL, et al. Association of periodic fasting lifestyles with survival and incident major adverse cardiovascular events in patients undergoing cardiac catheterization. *Eur J Prev Cardiol*. 2022;28(16):1774–81.

7731. Tsaban G. Routine periodic fasting reduces all-cause mortality and heart failure incidence: new insights on old habits. *Eur J Prev Cardiol*. 2022;28(16):1782–3.

7732. Enstrom JE. Cancer and total mortality among active Mormons. *Cancer*. 1978;42(4):1943–51.

7733. *The Doctrine and Covenants of The Church of Jesus Christ of Latter-day Saints*. *Section 89:12.* The Church of Jesus Christ of Latter-day

Saints; 2013. https://www.churchofjesuschrist.org/study/scriptures/dc-testament/dc/89?lang=eng. Accessed December 9, 2022.
7734. Vallejo EA. La dieta de hambre a dias alternos en la alimentacion de los viejos. *Rev Clin Esp.* 1956;63:25–7.
7735. Stunkard AJ. Nutrition, aging and obesity: a critical review of a complex relationship. *Int J Obes*. 1983;7(3):201–20.
7736. Brandhorst S, Choi IY, Wei M, et al. A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan. *Cell Metab*. 2015;22(1):86–99.
7737. Abbasi J. Can a diet that mimics fasting turn back the clock? *JAMA*. 2017;318(3):227–9.
7738. Wei M, Brandhorst S, Shelehchi M, et al. Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease. *Sci Transl Med*. 2017;9(377):8700.
7739. Gill S, Panda S. A smartphone app reveals erratic diurnal eating patterns in humans that can be modulated for health benefits. *Cell Metab*. 2015;22(5):789–98.
7740. Anton SD, Moehl K, Donahoo WT, et al. Flipping the metabolic switch: understanding and applying the health benefits of fasting. *Obesity (Silver Spring)*. 2018;26(2):254–68.
7741. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. *Cell Metab*. 2018;27(6):1212–21.e3.
7742. Schloss J, Steel A. Medical synopsis: nightly fasting may assist breast cancer patients and other people with cancer. *Adv Integr Med*. 2016;3(2):66–7.
7743. Fraser GE, Shavlik DJ. Ten years of life: is it a matter of choice? *Arch Intern Med*. 2001;161(13):1645–52.
7744. Currenti W, Godos J, Castellano S, et al. Association between time restricted feeding and cognitive status in older Italian adults. *Nutrients*. 2021;13(1):E191.
7745. Mayer J. Should you starve yourself thin? *Family Health/Today's Health*. February, 1977.

7746. Keys A. Caloric undernutrition and starvation, with notes on protein deficiency. *J Am Med Assoc*. 1948;138(7):500–11.
7747. Michalsen A, Li C. Fasting therapy for treating and preventing disease—current state of evidence. *Forsch Komplementmed*. 2013;20(6):444–53.
7748. Schnitker MA, Mattman PE, Bliss TL. A clinical study of malnutrition in Japanese prisoners of war. *Ann Intern Med*. 1951;35(1):69–96.
7749. Boateng AA, Sriram K, Meguid MM, Crook M. Refeeding syndrome: treatment considerations based on collective analysis of literature case reports. *Nutrition.* 2010;26(2):156–67.
7750. Finnell JS, Saul BC, Goldhamer AC, Myers TR. Is fasting safe? A chart review of adverse events during medically supervised, water-only fasting. *BMC Complement Altern Med*. 2018;18:67.
7751. Michalsen A, Li C. Fasting therapy for treating and preventing disease—current state of evidence. *Forsch Komplementmed*. 2013;20(6):444–53.
7752. Runcie J, Thomson TJ. Prolonged starvation—a dangerous procedure? *Br Med J*. 1970;3(5720):432–5.
7753. Sailaja BS, He XC, Li L. Stem cells matter in response to fasting. *Cell Rep*. 2015;13(11):2325–6.
7754. Raffaghello L, Lee C, Safdie FM, et al. Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy. *Proc Natl Acad Sci U S A*. 2008;105(24):8215–20.
7755. Dorff TB, Groshen S, Garcia A, et al. Safety and feasibility of fasting in combination with platinum-based chemotherapy. *BMC Cancer*. 2016;16:360.
7756. Nencioni A, Caffa I, Cortellino S, Longo VD. Fasting and cancer: molecular mechanisms and clinical application. *Nat Rev Cancer*. 2018;18(11):707–19.
7757. Lugtenberg RT, de Groot S, Kaptein AA, et al. Quality of life and illness perceptions in patients with breast cancer using a fasting mimicking diet as an adjunct to neoadjuvant chemotherapy in the phase 2 DIRECT (BOOG 2013–14) trial. *Breast Cancer Res Treat*. 2021;185(3):741–58.

7758. Caffa I, Spagnolo V, Vernieri C, et al. Fasting-mimicking diet and hormone therapy induce breast cancer regression. *Nature*. 2020;583(7817):620–4.
7759. de Groot S, Lugtenberg RT, Cohen D, et al. Fasting mimicking diet as an adjunct to neoadjuvant chemotherapy for breast cancer in the multicentre randomized phase 2 DIRECT trial. *Nat Commun*. 2020;11(1):3083.
7760. Vernieri C, Ligorio F, Zattarin E, Rivoltini L, de Braud F. Fasting-mimicking diet plus chemotherapy in breast cancer treatment. *Nat Commun*. 2020;11(1):4274.
7761. de Groot S, Lugtenberg RT, Cohen D, et al. Fasting mimicking diet as an adjunct to neoadjuvant chemotherapy for breast cancer in the multicentre randomized phase 2 DIRECT trial. *Nat Commun*. 2020;11(1):3083.
7762. Vernieri C, Ligorio F, Zattarin E, Rivoltini L, de Braud F. Fasting-mimicking diet plus chemotherapy in breast cancer treatment. *Nat Commun*. 2020;11(1):4274.
7763. Lee C, Longo VD. Fasting vs dietary restriction in cellular protection and cancer treatment: from model organisms to patients. *Oncogene*. 2011;30(30):3305–16.
7764. Lee C, Safdie FM, Raffaghello L, et al. Reduced levels of IGF-I mediate differential protection of normal and cancer cells in response to fasting and improve chemotherapeutic index. *Cancer Res*. 2010;70(4):1564–72.
7765. Lee C, Raffaghello L, Brandhorst S, et al. Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy. *Sci Transl Med*. 2012;4(124):124ra27.
7766. Longo VD, Lieber MR, Vijg J. Turning anti-ageing genes against cancer. *Nat Rev Mol Cell Biol*. 2008;9(11):903–10.
7767. Clemmons DR, Klibanski A, Underwood LE, et al. Reduction of plasma immunoreactive somatomedin C during fasting in humans. *J Clin Endocrinol Metab*. 1981;53(6):1247–50.
7768. Fontana L, Weiss EP, Villareal DT, Klein S, Holloszy JO. Long-term effects of calorie or protein restriction on serum IGF-1 and IGFBP-3 concentration in humans. *Aging Cell*. 2008;7(5):681–7.

7769. Kazemi A, Speakman JR, Soltani S, Djafarian K. Effect of calorie restriction or protein intake on circulating levels of insulin like growth factor I in humans: a systematic review and meta-analysis. *Clin Nutr*. 2020;39(6):1705–16.
7770. Fontana L, Villareal DT, Das SK, et al. Effects of 2-year calorie restriction on circulating levels of IGF-1, IGF-binding proteins and cortisol in nonobese men and women: a randomized clinical trial. *Aging Cell*. 2016;15(1):22–7.
7771. Most J, Tosti V, Redman LM, Fontana L. Calorie restriction in humans: an update. *Ageing Res Rev*. 2017;39:36–45.
7772. Kazemi A, Speakman JR, Soltani S, Djafarian K. Effect of calorie restriction or protein intake on circulating levels of insulin like growth factor I in humans: a systematic review and meta-analysis. *Clin Nutr*. 2020;39(6):1705–16.
7773. Fontana L, Weiss EP, Villareal DT, Klein S, Holloszy JO. Long-term effects of calorie or protein restriction on serum IGF-1 and IGFBP-3 concentration in humans. *Aging Cell*. 2008;7(5):681–7.
7774. Solon-Biet SM, Mitchell SJ, de Cabo R, Raubenheimer D, Le Couteur DG, Simpson SJ. Macronutrients and caloric intake in health and longevity. *J Endocrinol*. 2015;226(1):R17–28.
7775. Piper MDW, Partridge L, Raubenheimer D, Simpson SJ. Dietary restriction and ageing: a unifying perspective. *Cell Metab*. 2011;14(2):154–60.
7776. Pamplona R, Barja G. Mitochondrial oxidative stress, aging and caloric restriction: the protein and methionine connection. *Biochim Biophys Acta*. 2006;1757(5–6):496–508.
7777. Speakman JR, Mitchell SE, Mazidi M. Calories or protein? The effect of dietary restriction on lifespan in rodents is explained by calories alone. *Exp Gerontol*. 2016;86:28–38.
7778. Solon-Biet SM, McMahon AC, Ballard JWO, et al. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. *Cell Metab*. 2014;19(3):418–30
7779. Nishimura T, Nakatake Y, Konishi M, Itoh N. Identification of a novel FGF, FGF-21, preferentially expressed in the liver. *Biochim Biophys Acta*. 2000;1492(1):203–6.

7780. McCarty MF. Practical prospects for boosting hepatic production of the “pro-longevity” hormone FGF21. *Horm Mol Biol Clin Investig*. 2017;30(2).
7781. Andersen B, Straarup EM, Heppner KM, et al. FGF21 decreases body weight without reducing food intake or bone mineral density in high-fat fed obese rhesus macaque monkeys. *Int J Obes (Lond)*. 2018;42(6):1151–60.
7782. Zhang Y, Xie Y, Berglund ED, et al. The starvation hormone, fibroblast growth factor-21, extends lifespan in mice. *eLife*. 2012;1:e00065.
7783. Solon-Biet SM, Mitchell SJ, de Cabo R, Raubenheimer D, Le Couteur DG, Simpson SJ. Macronutrients and caloric intake in health and longevity. *J Endocrinol*. 2015;226(1):R17–28.
7784. Lee MB, Hill CM, Bitto A, Kaeberlein M. Antiaging diets: Separating fact from fiction. *Science*. 2021;374(6570):eabe7365.
7785. Riera CE, Dillin A. Can aging be ‘drugged’?. *Nat Med*. 2015;21(12):1400–5.
7786. Huang Z, Xu A, Cheung BMY. The potential role of fibroblast growth factor 21 in lipid metabolism and hypertension. *Curr Hypertens Rep*. 2017;19(4):28.
7787. Pérez-Martí A, Sandoval V, Marrero PF, Haro D, Relat J. Nutritional regulation of fibroblast growth factor 21: from macronutrients to bioactive dietary compounds. *Horm Mol Biol Clin Investig*. 2016;30(1).
7788. Sonoda J, Chen MZ, Baruch A. FGF21-receptor agonists: an emerging therapeutic class for obesity-related diseases. *Horm Mol Biol Clin Investig*. 2017;30(2).
7789. Talukdar S, Zhou Y, Li D, et al. A long-acting FGF21 molecule, PF-05231023, decreases body weight and improves lipid profile in non-human primates and type 2 diabetic subjects. *Cell Metab*. 2016;23(3):427–40.
7790. Harrison SA, Ruane PJ, Freilich BL, et al. Efruxifermin in non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled, phase 2a trial. *Nat Med*. 2021;27(7):1262–71.
7791. Jimenez V, Jambrina C, Casana E, et al. FGF21 gene therapy as treatment for obesity and insulin resistance. *EMBO Mol Med*.

2018;10(8):e8791.
7792. Cuevas-Ramos D, Almeda-Valdés P, Meza-Arana CE, et al. Exercise increases serum fibroblast growth factor 21 (FGF21) levels. *PLoS One*. 2012;7(5):e38022.
7793. Cuevas-Ramos D, Almeda-Valdés P, Meza-Arana CE, et al. Exercise increases serum fibroblast growth factor 21 (FGF21) levels. *PLoS One*. 2012;7(5):e38022.
7794. Khalafi M, Alamdari KA, Symonds ME, Nobari H, Carlos-Vivas J. Impact of acute exercise on immediate and following early post-exercise FGF-21 concentration in adults: systematic review and meta-analysis. *Hormones (Athens)*. 2021;20(1):23–33.
7795. Keihanian A, Arazi H, Kargarfard M. Effects of aerobic versus resistance training on serum fetuin-A, fetuin-B, and fibroblast growth factor-21 levels in male diabetic patients. *Physiol Int*. 2019;106(1):70–80.
7796. Erickson A, Moreau R. The regulation of *FGF21* gene expression by metabolic factors and nutrients. *Horm Mol Biol Clin Investig*. 2016;30(1).
7797. Zhang Y, Xie Y, Berglund ED, et al. The starvation hormone, fibroblast growth factor-21, extends lifespan in mice. *eLife*. 2012;1:e00065.
7798. Salminen A, Kauppinen A, Kaarniranta K. FGF21 activates AMPK signaling: impact on metabolic regulation and the aging process. *J Mol Med (Berl)*. 2017;95(2):123–31.
7799. Holmes D. Fasting induces FGF21 in humans. *Nat Rev Endocrinol*. 2016;12(1):3.
7800. Fazeli PK, Lun M, Kim SM, et al. FGF21 and the late adaptive response to starvation in humans. *J Clin Invest*. 2015;125(12):4601–11.
7801. Gälman C, Lundåsen T, Kharitonenkov A, et al. The circulating metabolic regulator FGF21 is induced by prolonged fasting and PPARα activation in man. *Cell Metab*. 2008;8(2):169–74.
7802. Murata Y, Nishio K, Mochiyama T, et al. Fgf21 impairs adipocyte insulin sensitivity in mice fed a low-carbohydrate, high-fat ketogenic diet. *PLoS One*. 2013;8(7):e69330.

7803. Gälman C, Lundåsen T, Kharitonenkov A, et al. The circulating metabolic regulator FGF21 is induced by prolonged fasting and PPARα activation in man. *Cell Metab*. 2008;8(2):169–74.
7804. Crujeiras AB, Gomez-Arbelaez D, Zulet MA, et al. Plasma FGF_{21} levels in obese patients undergoing energy-restricted diets or bariatric surgery: a marker of metabolic stress? *Int J Obes*. 2017;41(10):1570–8.
7805. Christodoulides C, Dyson P, Sprecher D, Tsintzas K, Karpe F. Circulating fibroblast growth factor 21 is induced by peroxisome proliferator-activated receptor agonists but not ketosis in man. *J Clin Endocrinol Metab*. 2009;94(9):3594–601.
7806. Asle Mohammadi Zadeh M, Kargarfard M, Marandi SM, Habibi A. Diets along with interval training regimes improves inflammatory & anti-inflammatory condition in obesity with type 2 diabetes subjects. *J Diabetes Metab Disord*. 2018;17(2):253–67.
7807. Salminen A, Kaarniranta K, Kauppinen A. Integrated stress response stimulates FGF21 expression: systemic enhancer of longevity. *Cell Signal*. 2017;40:10–21.
7808. Fazeli PK, Lun M, Kim SM, et al. FGF21 and the late adaptive response to starvation in humans. *J Clin Invest*. 2015;125(12):4601–11.
7809. Lundsgaard AM, Fritzen AM, Sjøberg KA, et al. Circulating FGF21 in humans is potently induced by short term overfeeding of carbohydrates. *Mol Metab*. 2017;6(1):22–9.
7810. Li H, Gao Z, Zhang J, et al. Sodium butyrate stimulates expression of fibroblast growth factor 21 in liver by inhibition of histone deacetylase 3. *Diabetes*. 2012;61(4):797–806.
7811. Erickson A, Moreau R. The regulation of *FGF21* gene expression by metabolic factors and nutrients. *Horm Mol Biol Clin Investig*. 2016;30(1).
7812. Harrison DE, Strong R, Allison DB, et al. Acarbose, 17-α-estradiol, and nordihydroguaiaretic acid extend mouse lifespan preferentially in males. *Aging Cell*. 2014;13(2):273–82.
7813. McCarty MF. Practical prospects for boosting hepatic production of the “pro-longevity” hormone FGF21. *Horm Mol Biol Clin Invest*.

2015;30(2).
7814. Laeger T, Henagan TM, Albarado DC, et al. FGF21 is an endocrine signal of protein restriction. *J Clin Invest*. 2014;124(9):3913–22.
7815. Trumbo P, Schlicker S, Yates AA, Poos M. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. *J Am Diet Assoc*. 2002;102(11):1621–30.
7816. Nutrient intakes from food: mean amounts and percentages of calories from protein, carbohydrate, fat, and alcohol, one day, 2005–2006. Agricultural Research Service, United States Department of Agriculture. https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/0506/table_2_nif_05.pdf. Published 2008. Accessed January 19, 2023.
7817. Fontana L, Cummings NE, Arriola Apelo SI, et al. Decreased consumption of branched-chain amino acids improves metabolic health. *Cell Rep*. 2016;16(2):520–30.
7818. Fontana L, Cummings NE, Arriola SI, et al. Supplemental information: decreased consumption of branched-chain amino acids improves metabolic health. *Cell Rep*. https://www.cell.com/cms/10.1016/j.celrep.2016.05.092/attachment/1cc73bb8-d48a-497a-8cb6–16828f45777b/mmc1.pdf. Published July 12, 2016. Accessed January 1, 2023.
7819. Fontana L, Cummings NE, Arriola Apelo SI, et al. Decreased consumption of branched-chain amino acids improves metabolic health. *Cell Rep*. 2016;16(2):520–30.
7820. Müller TD, Tschöp MH. Play down protein to play up metabolism? *J Clin Invest*. 2014;124(9):3691–3.
7821. Fontana L, Cummings NE, Arriola Apelo SI, et al. Decreased consumption of branched-chain amino acids improves metabolic health. *Cell Rep*. 2016;16(2):520–30.
7822. Maida A, Zota A, Sjøberg KA, et al. A liver stress-endocrine nexus promotes metabolic integrity during dietary protein dilution. *J Clin Invest*. 2016;126(9):3263–78.
7823. Gosby AK, Conigrave AD, Lau NS, et al. Testing protein leverage in lean humans: a randomised controlled experimental study. *PLoS One*. 2011;6(10):e25929.

7824. Gosby AK, Lau NS, Tam CS, et al. Raised FGF-21 and triglycerides accompany increased energy intake driven by protein leverage in lean, healthy individuals: a randomised trial. *PLoS One*. 2016;11(8):e0161003.
7825. Fontana L, Cummings NE, Arriola Apelo SI, et al. Decreased consumption of branched-chain amino acids improves metabolic health. *Cell Rep*. 2016;16(2):520–30.
7826. Kitada M, Ogura Y, Monno I, Koya D. The impact of dietary protein intake on longevity and metabolic health. *EBioMedicine*. 2019;43:632–40.
7827. Mladenović D, Radosavljević T, Hrnčić D, Rasic-Markovic A, Stanojlović O. The effects of dietary methionine restriction on the function and metabolic reprogramming in the liver and brain—implications for longevity. *Rev Neurosci*. 2019;30(6):581–93.
7828. Cole JT. Metabolism of BCAAs. In: Rajendram R, et al, eds. *Branched Chain Amino Acids in Clinical Nutrition.* Vol 1. Springer Science+Business Media; 2015:13–24.
7829. Kitada M, Ogura Y, Monno I, Koya D. The impact of dietary protein intake on longevity and metabolic health. *EBioMedicine*. 2019;43:632–40.
7830. Ables GP, Johnson JE. Pleiotropic responses to methionine restriction. *Exp Gerontol*. 2017;94:83–8.
7831. McCarty MF. GCN2 and FGF21 are likely mediators of the protection from cancer, autoimmunity, obesity, and diabetes afforded by vegan diets. *Med Hypotheses*. 2014;83(3):365–71.
7832. McCarty MF. The moderate essential amino acid restriction entailed by low-protein vegan diets may promote vascular health by stimulating FGF21 secretion. *Horm Mol Biol Clin Investig*. 2016;30(1).
7833. Lonnie M, Johnstone AM. The public health rationale for promoting plant protein as an important part of a sustainable and healthy diet. *Nutr Bull*. 2020;45(3):281–93.
7834. McCarty MF. Practical prospects for boosting hepatic production of the “pro-longevity” hormone FGF21. *Horm Mol Biol Clin Investig*. 2015;30(2).

7835. Castaño-Martinez T, Schumacher F, Schumacher S, et al. Methionine restriction prevents onset of type 2 diabetes in NZO mice. *FASEB J.* 2019;33(6):7092–102.
7836. Castaño-Martinez T, Schumacher F, Schumacher S, et al. Methionine restriction prevents onset of type 2 diabetes in NZO mice. *FASEB J.* 2019;33(6):7092–102.
7837. Longo VD, Mattson MP. Fasting: molecular mechanisms and clinical applications. *Cell Metab*. 2014;19(2):181–92.
7838. Hill CM, Albarado DC, Coco LG, et al. FGF21 is required for protein restriction to extend lifespan and improve metabolic health in male mice. *Nat Commun*. 2022;13(1):1897.
7839. Estévez M, Xiong Y. Intake of oxidized proteins and amino acids and causative oxidative stress and disease: recent scientific evidences and hypotheses. *J Food Sci*. 2019;84(3):387–96.
7840. Seyedsadjadi N, Berg J, Bilgin AA, Braidy N, Salonikas C, Grant R. High protein intake is associated with low plasma NAD^+ levels in a healthy human cohort. *PLoS One*. 2018;13(8):e0201968.
7841. Solon-Biet SM, Mitchell SJ, de Cabo R, Raubenheimer D, Le Couteur DG, Simpson SJ. Macronutrients and caloric intake in health and longevity. *J Endocrinol*. 2015;226(1):R17–28.
7842. Brandhorst S, Longo VD. Protein quantity and source, fasting-mimicking diets, and longevity. *Adv Nutr*. 2019;10(Suppl_4):S340–50.
7843. Lee C, Longo VD. Fasting vs dietary restriction in cellular protection and cancer treatment: from model organisms to patients. *Oncogene*. 2011;30(30):3305–16.
7844. Lee C, Safdie FM, Raffaghello L, et al. Reduced levels of IGF-I mediate differential protection of normal and cancer cells in response to fasting and improve chemotherapeutic index. *Cancer Res*. 2010;70(4):1564–72.
7845. Lee C, Raffaghello L, Brandhorst S, et al. Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy. *Sci Transl Med*. 2012;4(124):124ra27.
7846. Thissen JP, Ketelslegers JM, Underwood LE. Nutritional regulation of the insulin-like growth factors. *Endocr Rev*. 1994;15(1):80–101.

7847. Fontana L, Weiss EP, Villareal DT, Klein S, Holloszy JO. Long-term effects of calorie or protein restriction on serum IGF-1 and IGFBP-3 concentration in humans. *Aging Cell*. 2008;7(5):681–7.
7848. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. *Cancer Epidemiol Biomarkers Prev*. 2002;11(11):1441–8.
7849. Allen NE, Appleby PN, Davey GK, Key TJ. Hormones and diet: low insulin-like growth factor-I but normal bioavailable androgens in vegan men. *Br J Cancer*. 2000;83(1):95–7.
7850. Fontana L, Klein S, Holloszy JO. Long-term low-protein, low-calorie diet and endurance exercise modulate metabolic factors associated with cancer risk. *Am J Clin Nutr*. 2006;84(6):1456–62.
7851. Dunn SE, Kari FW, French J, et al. Dietary restriction reduces insulin-like growth factor I levels, which modulates apoptosis, cell proliferation, and tumor progression in p53-deficient mice. *Cancer Res*. 1997;57(21):4667–72.
7852. Fontana L, Weiss EP, Villareal DT, Klein S, Holloszy JO. Long-term effects of calorie or protein restriction on serum IGF-1 and IGFBP-3 concentration in humans. *Aging Cell*. 2008;7(5):681–7.
7853. McCarty MF. A low-fat, whole-food vegan diet, as well as other strategies that down-regulate IGF-I activity, may slow the human aging process. *Med Hypotheses*. 2003;60(6):784–92.
7854. Murphy N, Carreras-Torres R, Song M, et al. Circulating levels of insulin-like growth factor 1 and insulin-like growth factor binding protein 3 associate with risk of colorectal cancer based on serologic and Mendelian randomization analyses. *Gastroenterology*. 2020;158(5):1300–12.e20.
7855. Larsson SC, Michaëlsson K, Burgess S. IGF-1 and cardiometabolic diseases: a Mendelian randomisation study. *Diabetologia*. 2020;63(9):1775–82.
7856. Hartley A, Sanderson E, Paternoster L, et al. Mendelian randomization provides evidence for a causal effect of higher serum IGF-1 concentration on risk of hip and knee osteoarthritis. *Rheumatology (Oxford)*. 2021;60(4):1676–86.

7857. Nashiro K, Guevara-Aguirre J, Braskie MN, et al. Brain structure and function associated with younger adults in growth hormone receptor-deficient humans. *J Neurosci*. 2017;37(7):1696–707.
7858. Schut AFC, Janssen JAMJL, Deinum J, et al. Polymorphism in the promoter region of the insulin-like growth factor I gene is related to carotid intima-media thickness and aortic pulse wave velocity in subjects with hypertension. *Stroke*. 2003;34(7):1623–7.
7859. Potassium-rich foods linked to lower stroke risk. Harvard Health Publishing. https://www.health.harvard.edu/heart-health/potassium-rich-foods-linked-to-lower-stroke-risk-. Published November 14, 2014. Accessed January 2, 2023.
7860. McCay CM, Dilley WE, Crowell MF. Growth rates of brook trout reared upon purified rations, upon dry skim milk diets, and upon feed combinations of cereal grains. *J Nutr*. 1929;1(3):233–46.
7861. McDonald RB, Ramsey JJ. Honoring Clive McCay and 75 years of calorie restriction research. *J Nutr*. 2010;140(7):1205–10.
7862. Speakman JR, Mitchell SE, Mazidi M. Calories or protein? The effect of dietary restriction on lifespan in rodents is explained by calories alone. *Exp Gerontol*. 2016;86:28–38.
7863. Nakagawa S, Lagisz M, Hector KL, Spencer HG. Comparative and meta-analytic insights into life extension via dietary restriction. *Aging Cell*. 2012;11(3):401–9.
7864. Solon-Biet SM, McMahon AC, Ballard JWO, et al. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. *Cell Metab*. 2014;19(3):418–30.
7865. Solon-Biet SM, McMahon AC, Ballard JWO, et al. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. *Cell Metab*. 2014;19(3):418–30.
7866. Simpson SJ, Le Couteur DG, Raubenheimer D. Putting the balance back in diet. *Cell*. 2015;161(1):18–23.
7867. Le Couteur DG, Tay SS, Solon-Biet S, et al. The influence of macronutrients on splanchnic and hepatic lymphocytes in aging mice. *J Gerontol A Biol Sci Med Sci*. 2015;70(12):1499–507.

7868. Solon-Biet SM, Mitchell SJ, Coogan SCP, et al. Dietary protein to carbohydrate ratio and caloric restriction: comparing metabolic outcomes in mice. *Cell Rep*. 2015;11(10):1529–34.
7869. Le Couteur DG, Tay SS, Solon-Biet S, et al. The influence of macronutrients on splanchnic and hepatic lymphocytes in aging mice. *J Gerontol A Biol Sci Med Sci*. 2015;70(12):1499–507.
7870. Solon-Biet SM, McMahon AC, Ballard JWO, et al. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. *Cell Metab*. 2014;19(3):418–30.
7871. Ingram DK, de Cabo R. Calorie restriction in rodents: caveats to consider. *Ageing Res Rev*. 2017;39:15–28.
7872. Speakman JR, Mitchell SE, Mazidi M. Calories or protein? The effect of dietary restriction on lifespan in rodents is explained by calories alone. *Exp Gerontol*. 2016;86:28–38.
7873. Swindell WR. Dietary restriction in rats and mice: a meta-analysis and review of the evidence for genotype-dependent effects on lifespan. *Ageing Res Rev*. 2012;11(2):254–70.
7874. Solon-Biet SM, McMahon AC, Ballard JWO, et al. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. *Cell Metab*. 2014;19(3):418–30.
7875. Speakman JR, Mitchell SE, Mazidi M. Calories or protein? The effect of dietary restriction on lifespan in rodents is explained by calories alone. *Exp Gerontol*. 2016;86:28–38.
7876. Simpson SJ, Le Couteur DG, Raubenheimer D. Putting the balance back in diet. *Cell*. 2015;161(1):18–23.
7877. Speakman JR, Mitchell SE, Mazidi M. Calories or protein? The effect of dietary restriction on lifespan in rodents is explained by calories alone. *Exp Gerontol*. 2016;86:28–38.
7878. Solon-Biet SM, McMahon AC, Ballard JWO, et al. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. *Cell Metab*. 2014;19(3):418–30.
7879. Solon-Biet SM, Mitchell SJ, de Cabo R, Raubenheimer D, Le Couteur DG, Simpson SJ. Macronutrients and caloric intake in health

and longevity. *J Endocrinol*. 2015;226(1):R17–28.
7880. Wali JA, Raubenheimer D, Senior AM, Le Couteur DG, Simpson SJ. Cardio-metabolic consequences of dietary carbohydrates: reconciling contradictions using nutritional geometry. *Cardiovasc Res*. 2021;117(2):386–401.
7881. Wali JA, Milner AJ, Luk AWS, et al. Impact of dietary carbohydrate type and protein-carbohydrate interaction on metabolic health. *Nat Metab*. 2021;3(6):810–28.
7882. Vogtschmidt YD, Raben A, Faber I, et al. Is protein the forgotten ingredient: effects of higher compared to lower protein diets on cardiometabolic risk factors. A systematic review and meta-analysis of randomised controlled trials. *Atherosclerosis*. 2021;328:124–35.
7883. Wali JA, Raubenheimer D, Senior AM, Le Couteur DG, Simpson SJ. Cardio-metabolic consequences of dietary carbohydrates: reconciling contradictions using nutritional geometry. *Cardiovasc Res*. 2021;117(2):386–401.
7884. Simpson SJ, Le Couteur DG, Raubenheimer D, et al. Dietary protein, aging and nutritional geometry. *Ageing Res Rev*. 2017;39:78–86.
7885. Le Couteur DG, Solon-Biet S, Wahl D, et al. New horizons: dietary protein, ageing and the Okinawan ratio. *Age Ageing*. 2016;45(4):443–7.
7886. Willcox BJ, Willcox DC, Todoriki H, et al. Caloric restriction, the traditional Okinawan diet, and healthy aging: the diet of the world's longest-lived people and its potential impact on morbidity and life span. *Ann N Y Acad Sci*. 2007;1114:434–55.
7887. Rizza W, Veronese N, Fontana L. What are the roles of calorie restriction and diet quality in promoting healthy longevity? *Ageing Res Rev*. 2014;13:38–45.
7888. Willcox BJ, Willcox DC, Todoriki H, et al. Caloric restriction, the traditional Okinawan diet, and healthy aging: the diet of the world's longest-lived people and its potential impact on morbidity and life span. *Ann N Y Acad Sci*. 2007;1114:434–55.
7889. Willcox BJ, Willcox DC, Todoriki H, et al. Caloric restriction, the traditional Okinawan diet, and healthy aging: the diet of the world's longest-lived people and its potential impact on morbidity and life span. *Ann N Y Acad Sci*. 2007;1114:434–55.

7890. Abraham S, Lowenstein FW, Johnson CL. *Preliminary Findings of the First Health and Nutrition Examination Survey, United States, 1971–1972*. U.S. Department of Health, Education, and Welfare, Public Health Service, Health Resources Administration, National Center for Health Statistics; 1974.
7891. Le Couteur DG, Solon-Biet S, Wahl D, et al. New horizons: dietary protein, ageing and the Okinawan ratio. *Age Ageing*. 2016;45(4):443–7.
7892. Chen Z, Glisic M, Song M, et al. Dietary protein intake and all-cause and cause-specific mortality: results from the Rotterdam Study and a meta-analysis of prospective cohort studies. *Eur J Epidemiol*. 2020;35(5):411–29.
7893. Green CL, Lamming DW, Fontana L. Molecular mechanisms of dietary restriction promoting health and longevity. *Nat Rev Mol Cell Biol*. 2022;23(1):56–73.
7894. Chen Z, Glisic M, Song M, et al. Dietary protein intake and all-cause and cause-specific mortality: results from the Rotterdam Study and a meta-analysis of prospective cohort studies. *Eur J Epidemiol*. 2020;35(5):411–29.
7895. Levine ME, Suarez JA, Brandhorst S, et al. Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. *Cell Metab*. 2014;19(3):407–17.
7896. Mirzaei H, Suarez JA, Longo VD. Protein and amino acid restriction, aging and disease: from yeast to humans. *Trends Endocrinol Metab*. 2014;25(11):558–66.
7897. Hoy MK, Clemens JC, Moshfegh A. Protein intake of adults: what we eat in America, NHANES 2015–2016. Food Surveys Research Group, Dietary Data Brief No. 29. https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/DBrief/29_Protein_Intake_of_Adults_1516.pdf. Published January 2021. Accessed December 26, 2022.
7898. Mirzaei H, Suarez JA, Longo VD. Protein and amino acid restriction, aging and disease: from yeast to humans. *Trends Endocrinol Metab*. 2014;25(11):558–66.

7899. Huang J, Liao LM, Weinstein SJ, Sinha R, Graubard BI, Albanes D. Association between plant and animal protein intake and overall and cause-specific mortality. *JAMA Intern Med*. 2020;180(9):1173–84.
7900. Meroño T, Zamora-Ros R, Hidalgo-Liberona N, et al. Animal protein intake is inversely associated with mortality in older adults: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci*. 2022;77(9):1866–72.
7901. Naghshi S, Sadeghi O, Willett WC, Esmaillzadeh A. Dietary intake of total, animal, and plant proteins and risk of all cause, cardiovascular, and cancer mortality: systematic review and dose-response meta-analysis of prospective cohort studies. *BMJ*. 2020;370:m2412.
7902. Ortolá R, Struijk EA, García-Esquinas E, Rodríguez-Artalejo F, Lopez-Garcia E. Changes in dietary intake of animal and vegetable protein and unhealthy aging. *Am J Med*. 2020;133(2):231–9.e7.
7903. Sun Y, Liu B, Snetselaar LG, et al. Association of major dietary protein sources with all-cause and cause-specific mortality: prospective cohort study. *J Am Heart Assoc*. 2021;10(5):e015553.
7904. Zhong VW, Allen NB, Greenland P, et al. Protein foods from animal sources, incident cardiovascular disease and all-cause mortality: a substitution analysis. *Int J Epidemiol*. 2021;50(1):223–33.
7905. Zheng J, Zhu T, Yang G, et al. The isocaloric substitution of plant-based and animal-based protein in relation to aging-related health outcomes: a systematic review. *Nutrients*. 2022;14(2):272.
7906. Willcox BJ, Willcox DC, Todoriki H, et al. Caloric restriction, the traditional Okinawan diet, and healthy aging: the diet of the world's longest-lived people and its potential impact on morbidity and life span. *Ann N Y Acad Sci*. 2007;1114:434–55.
7907. Fraser GE, Shavlik DJ. Ten years of life: is it a matter of choice? *Arch Intern Med*. 2001;161(13):1645–52.
7908. Rizzo NS, Jaceldo-Siegl K, Sabate J, Fraser GE. Nutrient profiles of vegetarian and nonvegetarian dietary patterns. *J Acad Nutr Diet*. 2013;113(12):1610–9.
7909. Kitada M, Ogura Y, Monno I, Koya D. The impact of dietary protein intake on longevity and metabolic health. *EBioMedicine*. 2019;43:632–40.

7910. Schüler R, Markova M, Osterhoff MA, et al. Similar dietary regulation of IGF-1-and IGF-binding proteins by animal and plant protein in subjects with type 2 diabetes. *Eur J Nutr*. 2021;60(6):3499–504.
7911. Kahleova H, Fleeman R, Hlozkova A, Holubkov R, Barnard ND. A plant-based diet in overweight individuals in a 16-week randomized clinical trial: metabolic benefits of plant protein. *Nutr Diabetes*. 2018;8(1):58.
7912. Dorling JL, Martin CK, Redman LM. Calorie restriction for enhanced longevity: the role of novel dietary strategies in the present obesogenic environment. *Ageing Res Rev*. 2020;64:101038.
7913. Appleton BS, Campbell TC. Inhibition of aflatoxin-initiated preneoplastic liver lesions by low dietary protein. *Nutr Cancer*. 1982;3(4):200–6.
7914. Solon-Biet SM, McMahon AC, Ballard JWO, et al. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. *Cell Metab*. 2014;19(3):418–30.
7915. Solon-Biet SM, Mitchell SJ, de Cabo R, Raubenheimer D, Le Couteur DG, Simpson SJ. Macronutrients and caloric intake in health and longevity. *J Endocrinol*. 2015;226(1):R17–28.
7916. Fontana L, Adelaiye RM, Rastelli AL, et al. Dietary protein restriction inhibits tumor growth in human xenograft models. *Oncotarget*. 2013;4(12):2451–61.
7917. Fontana L, Adelaiye RM, Rastelli AL, et al. Dietary protein restriction inhibits tumor growth in human xenograft models. *Oncotarget*. 2013;4(12):2451–61.
7918. Rubio-Patiño C, Bossowski JP, De Donatis GM, et al. Low-protein diet induces IRE1α-dependent anticancer immunosurveillance. *Cell Metab*. 2018;27(4):828–42.e7.
7919. Orillion A, Damayanti NP, Shen L, et al. Dietary protein restriction reprograms tumor-associated macrophages and enhances immunotherapy. *Clin Cancer Res*. 2018;24(24):6383–95.
7920. Pili R, Fontana L. Low-protein diet in cancer: ready for prime time? *Nat Rev Endocrinol*. 2018;14(7):384–6.

7921. Gao X, Sanderson SM, Dai Z, et al. Dietary methionine influences therapy in mouse cancer models and alters human metabolism. *Nature*. 2019;572(7769):397–401.
7922. Solon-Biet SM, McMahon AC, Ballard JWO, et al. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. *Cell Metab*. 2014;19(3):418–30.
7923. Trepanowski JF, Canale RE, Marshall KE, Kabir MM, Bloomer RJ. Impact of caloric and dietary restriction regimens on markers of health and longevity in humans and animals: a summary of available findings. *Nutr J*. 2011;10:107.
7924. Pamplona R, Barja G. Mitochondrial oxidative stress, aging and caloric restriction: the protein and methionine connection. *Biochim Biophys Acta*. 2006;1757(5–6):496–508.
7925. McIsaac RS, Lewis KN, Gibney PA, Buffenstein R. From yeast to human: exploring the comparative biology of methionine restriction in extending eukaryotic life span. *Ann N Y Acad Sci*. 2016;1363:155–70.
7926. Gorbunova V, Bozzella MJ, Seluanov A. Rodents for comparative aging studies: from mice to beavers. *Age (Dordr)*. 2008;30(2–3):111–9.
7927. Zimmerman JA, Malloy V, Krajcik R, Orentreich N. Nutritional control of aging. *Exp Gerontol*. 2003;38(1–2):47–52.
7928. Swindell WR. Dietary restriction in rats and mice: a meta-analysis and review of the evidence for genotype-dependent effects on lifespan. *Ageing Res Rev*. 2012;11(2):254–70.
7929. Miller RA, Buehner G, Chang Y, Harper JM, Sigler R, Smith-Wheelock M. Methionine-deficient diet extends mouse lifespan, slows immune and lens aging, alters glucose, T4, IGF-I and insulin levels, and increases hepatocyte MIF levels and stress resistance. *Aging Cell*. 2005;4(3):119–25.
7930. Yu D, Yang SE, Miller BR, et al. Short-term methionine deprivation improves metabolic health *via* sexually dimorphic, mTORC1-independent mechanisms. *FASEB J*. 2018;32(6):3471–82.
7931. Miller RA, Buehner G, Chang Y, Harper JM, Sigler R, Smith-Wheelock M. Methionine-deficient diet extends mouse lifespan,

slows immune and lens aging, alters glucose, T4, IGF-I and insulin levels, and increases hepatocyte MIF levels and stress resistance. *Aging Cell*. 2005;4(3):119–25.

7932. Miller RA, Buehner G, Chang Y, Harper JM, Sigler R, Smith-Wheelock M. Methionine-deficient diet extends mouse lifespan, slows immune and lens aging, alters glucose, T4, IGF-I and insulin levels, and increases hepatocyte MIF levels and stress resistance. *Aging Cell*. 2005;4(3):119–25.

7933. Yu D, Yang SE, Miller BR, et al. Short-term methionine deprivation improves metabolic health *via* sexually dimorphic, mTORC1-independent mechanisms. *FASEB J*. 2018;32(6):3471–82.

7934. Ruckenstuhl C, Netzberger C, Entfellner I, et al. Lifespan extension by methionine restriction requires autophagy-dependent vacuolar acidification. *PLoS Genet*. 2014;10(5):e1004347.

7935. Sharma S, Dixon T, Jung S, et al. Dietary methionine restriction reduces inflammation independent of FGF21 action. *Obesity (Silver Spring)*. 2019;27(8):1305–13.

7936. Miller RA, Buehner G, Chang Y, Harper JM, Sigler R, Smith-Wheelock M. Methionine-deficient diet extends mouse lifespan, slows immune and lens aging, alters glucose, T4, IGF-I and insulin levels, and increases hepatocyte MIF levels and stress resistance. *Aging Cell*. 2005;4(3):119–25.

7937. Brown-Borg HM, Rakoczy SG, Wonderlich JA, et al. Growth hormone signaling is necessary for lifespan extension by dietary methionine. *Aging Cell*. 2014;13(6):1019–27.

7938. Harper AE, Benevenga NJ, Wohlhueter RM. Effects of ingestion of disproportionate amounts of amino acids. *Physiol Rev*. 1970;50(3):428–558.

7939. López-Torres M, Barja G. Lowered methionine ingestion as responsible for the decrease in rodent mitochondrial oxidative stress in protein and dietary restriction. Possible implications for humans. *Biochim Biophys Acta*. 2008;1780(11):1337–47.

7940. Mori N, Hirayama K. Long-term consumption of a methionine-supplemented diet increases iron and lipid peroxide levels in rat liver. *J Nutr.* 2000;130(9):2349–55.

7941. Hidiroglou N, Gilani GS, Long L, et al. The influence of dietary vitamin E, fat, and methionine on blood cholesterol profile, homocysteine levels, and oxidizability of low density lipoprotein in the gerbil. *J Nutr Biochem.* 2004;15(12):730–40.
7942. Sanz A, Caro P, Ayala V, Portero-Otin M, Pamplona R, Barja G. Methionine restriction decreases mitochondrial oxygen radical generation and leak as well as oxidative damage to mitochondrial DNA and proteins. *FASEB J*. 2006;20(8):1064–73.
7943. Caro P, Gomez J, Sanchez I, et al. Effect of 40% restriction of dietary amino acids (except methionine) on mitochondrial oxidative stress and biogenesis, AIF and SIRT1 in rat liver. *Biogerontology*. 2009;10(5):579–92.
7944. Moskovitz J, Bar-Noy S, Williams WM, Requena J, Berlett BS, Stadtman ER. Methionine sulfoxide reductase (MsrA) is a regulator of antioxidant defense and lifespan in mammals. *Proc Natl Acad Sci U S A*. 2001;98(23):12920–5.
7945. Pamplona R, Barja G. Mitochondrial oxidative stress, aging and caloric restriction: the protein and methionine connection. *Biochim Biophys Acta*. 2006;1757(5–6):496–508.
7946. Lushchak O, Strilbytska OM, Yurkevych I, Vaiserman AM, Storey KB. Implications of amino acid sensing and dietary protein to the aging process. *Exp Gerontol*. 2019;115:69–78.
7947. Ruan H, Tang XD, Chen ML, et al. High-quality life extension by the enzyme peptide methionine sulfoxide reductase. *Proc Natl Acad Sci U S A*. 2002;99(5):2748–53.
7948. Takauji Y, Wada T, Takeda A, et al. Restriction of protein synthesis abolishes senescence features at cellular and organismal levels. *Sci Rep*. 2016;6:18722.
7949. Green CL, Lamming DW, Fontana L. Molecular mechanisms of dietary restriction promoting health and longevity. *Nat Rev Mol Cell Biol*. 2022;23(1):56–73.
7950. Kozieł R, Ruckenstuhl C, Albertini E, et al. Methionine restriction slows down senescence in human diploid fibroblasts. *Aging Cell*. 2014;13(6):1038–48.
7951. Brown-Borg HM, Buffenstein R. Cutting back on the essentials: can manipulating intake of specific amino acids modulate health and

lifespan? *Ageing Res Rev*. 2017;39:87–95.
7952. Johnson JE, Johnson FB. Methionine restriction activates the retrograde response and confers both stress tolerance and lifespan extension to yeast, mouse and human cells. *PLoS One*. 2014;9(5):e97729.
7953. Agrawal V, Alpini SEJ, Stone EM, Frenkel EP, Frankel AE. Targeting methionine auxotrophy in cancer: discovery & exploration. *Expert Opin Biol Ther*. 2012;12(1):53–61.
7954. Han Q, Tan Y, Hoffman RM. Oral dosing of recombinant methioninase is associated with a 70% drop in PSA in a patient with bone-metastatic prostate cancer and 50% reduction in circulating methionine in a high-stage ovarian cancer patient. *Anticancer Res*. 2020;40(5):2813–9.
7955. Cavuoto P, Fenech MF. A review of methionine dependency and the role of methionine restriction in cancer growth control and life-span extension. *Cancer Treat Rev*. 2012;38(6):726–36.
7956. Heilbronn LK, Panda S. Alternate-day fasting gets a safe bill of health. *Cell Metab*. 2019;30(3):411–3.
7957. Stekovic S, Hofer SJ, Tripolt N, et al. Alternate day fasting improves physiological and molecular markers of aging in healthy, non-obese humans. *Cell Metab*. 2019;30(3):462–76.
7958. McCarty MF, Barroso-Aranda J, Contreras F. The low-methionine content of vegan diets may make methionine restriction feasible as a life extension strategy. *Med Hypotheses*. 2009;72(2):125–8.
7959. Kitada M, Ogura Y, Monno I, Koya D. The impact of dietary protein intake on longevity and metabolic health. *EBioMedicine*. 2019;43:632–40.
7960. Yamamoto J, Han Q, Simon M, Thomas D, Hoffman RM. Methionine restriction: ready for prime time in the cancer clinic? *Anticancer Res*. 2022;42(2):641–4.
7961. Product information: Hominex®-2. Abbott Laboratories Inc. Updated May 3, 2022.
7962. Yamamoto J, Han Q, Simon M, Thomas D, Hoffman RM. Methionine restriction: ready for prime time in the cancer clinic? *Anticancer Res*. 2022;42(2):641–4.

7963. McCarty MF, Barroso-Aranda J, Contreras F. The low-methionine content of vegan diets may make methionine restriction feasible as a life extension strategy. *Med Hypotheses*. 2009;72(2):125–8.
7964. Agricultural Research Service, United States Department of Agriculture. Component search: methionine. FoodData Central. https://fdc.nal.usda.gov/fdc-app.html#/food-search?component=1215. Accessed January 25, 2023.
7965. Gaudichon C, Calvez J. Determinants of amino acid bioavailability from ingested protein in relation to gut health. *Curr Opin Clin Nutr Metab Care*. 2021;24(1):55–61.
7966. McCarty MF, Barroso-Aranda J, Contreras F. The low-methionine content of vegan diets may make methionine restriction feasible as a life extension strategy. *Med Hypotheses*. 2009;72(2):125–8.
7967. Cavuoto P, Fenech MF. A review of methionine dependency and the role of methionine restriction in cancer growth control and life-span extension. *Cancer Treat Rev*. 2012;38(6):726–36.
7968. Cavuoto P, Fenech MF. A review of methionine dependency and the role of methionine restriction in cancer growth control and life-span extension. *Cancer Treat Rev*. 2012;38(6):726–36.
7969. Krajcovicova-Kudlackova M, Babinska K, Valachovicova M. Health benefits and risks of plant proteins. *Bratisl Lek Listy*. 2005;106(6–7):231–4.
7970. Schmidt JA, Rinaldi S, Scalbert A, et al. Plasma concentrations and intakes of amino acids in male meat-eaters, fish-eaters, vegetarians and vegans: a cross-sectional analysis in the EPIC-Oxford cohort. *Eur J Clin Nutr*. 2016;70(3):306–12.
7971. Wu G, Han L, Shi Y, et al. Effect of different levels of dietary methionine restriction on relieving oxidative stress and behavioral deficits in middle-aged mice fed low-, medium-, or high-fat diet. *J Funct Foods*. 2020;65:103782.
7972. Trepanowski JF, Canale RE, Marshall KE, Kabir MM, Bloomer RJ. Impact of caloric and dietary restriction regimens on markers of health and longevity in humans and animals: a summary of available findings. *Nutr J*. 2011;10:107.
7973. Schmidt JA, Rinaldi S, Scalbert A, et al. Plasma concentrations and intakes of amino acids in male meat-eaters, fish-eaters, vegetarians

and vegans: a cross-sectional analysis in the EPIC-Oxford cohort. *Eur J Clin Nutr*. 2016;70(3):306–12.

7974. Green CL, Lamming DW, Fontana L. Molecular mechanisms of dietary restriction promoting health and longevity. *Nat Rev Mol Cell Biol*. 2022;23(1):56–73.

7975. Yu D, Yang SE, Miller BR, et al. Short-term methionine deprivation improves metabolic health *via* sexually dimorphic, mTORC1-independent mechanisms. *FASEB J*. 2018;32(6):3471–82.

7976. Elshorbagy AK, Valdivia-Garcia M, Mattocks DAL, et al. Cysteine supplementation reverses methionine restriction effects on rat adiposity: significance of stearoyl-coenzyme A desaturase. *J Lipid Res*. 2011;52(1):104–12.

7977. Le LT, Sabaté J. Beyond meatless, the health effects of vegan diets: findings from the Adventist cohorts. *Nutrients.* 2014;6(6):2131–47.

7978. Tonstad S, Stewart K, Oda K, Batech M, Herring RP, Fraser GE. Vegetarian diets and incidence of diabetes in the Adventist Health Study-2. *Nutr Metab Cardiovasc Dis*. 2013;23(4):292–9.

7979. Dong Z, Gao X, Chinchilli VM, et al. Association of dietary sulfur amino acid intake with mortality from diabetes and other causes. *Eur J Nutr*. 2022;61(1):289–98.

7980. Dong Z, Gao X, Chinchilli VM, et al. Association of dietary sulfur amino acid intake with mortality from diabetes and other causes. *Eur J Nutr*. 2022;61(1):289–98.

7981. Dong Z, Gao X, Chinchilli VM, et al. Association of sulfur amino acid consumption with cardiometabolic risk factors: cross-sectional findings from NHANES III. *EClinicalMedicine*. 2020;19:100248.

7982. López-Torres M, Barja G. Lowered methionine ingestion as responsible for the decrease in rodent mitochondrial oxidative stress in protein and dietary restriction possible implications for humans. *Biochim Biophys Acta*. 2008;1780(11):1337–47.

7983. Di Buono M, Wykes LJ, Ball RO, Pencharz PB. Dietary cysteine reduces the methionine requirement in men. *Am J Clin Nutr*. 2001;74(6):761–6.

7984. Elshorbagy AK, Valdivia-Garcia M, Mattocks DAL, et al. Cysteine supplementation reverses methionine restriction effects on rat

adiposity: significance of stearoyl-coenzyme A desaturase. *J Lipid Res*. 2011;52(1):104–12.

7985. Duran-Ortiz S, List EO, Basu R, Kopchick JJ. Extending lifespan by modulating the growth hormone/insulin-like growth factor-1 axis: coming of age. *Pituitary*. 2021;24(3):438–56.

7986. Schmidt JA, Rinaldi S, Scalbert A, et al. Plasma concentrations and intakes of amino acids in male meat-eaters, fish-eaters, vegetarians and vegans: a cross-sectional analysis in the EPIC-Oxford cohort. *Eur J Clin Nutr*. 2016;70(3):306–12.

7987. Lederer AK, Maul-Pavicic A, Hannibal L, et al. Vegan diet reduces neutrophils, monocytes and platelets related to branched-chain amino acids—a randomized, controlled trial. *Clin Nutr*. 2020;39(11):3241–50.

7988. Tanrikulu-Kucuk S, Ademoglu E. Dietary restriction of amino acids other than methionine prevents oxidative damage during aging: involvement of telomerase activity and telomere length. *Life Sci*. 2012;90(23–24):924–8.

7989. Solon-Biet SM, Mitchell SJ, de Cabo R, Raubenheimer D, Le Couteur DG, Simpson SJ. Macronutrients and caloric intake in health and longevity. *J Endocrinol*. 2015;226(1):R17–28.

7990. Solon-Biet SM, Cogger VC, Pulpitel T, et al. Branched chain amino acids impact health and lifespan indirectly via amino acid balance and appetite control. *Nat Metab*. 2019;1(5):532–45.

7991. Lu J, Temp U, Müller-Hartmann A, Esser J, Grönke S, Partridge L. Sestrin is a key regulator of stem cell function and lifespan in response to dietary amino acids. *Nat Aging*. 2021;1(1):60–72.

7992. Richardson NE, Konon EN, Schuster HS, et al. Lifelong restriction of dietary branched-chain amino acids has sex-specific benefits for frailty and lifespan in mice. *Nat Aging*. 2021;1(1):73–86.

7993. Richardson NE, Konon EN, Schuster HS, et al. Lifelong restriction of dietary branched-chain amino acids has sex-specific benefits for frailty and lifespan in mice. *Nat Aging*. 2021;1(1):73–86.

7994. Green CL, Lamming DW, Fontana L. Molecular mechanisms of dietary restriction promoting health and longevity. *Nat Rev Mol Cell Biol*. 2022;23(1):56–73.

7995. Solon-Biet SM, Mitchell SJ, de Cabo R, Raubenheimer D, Le Couteur DG, Simpson SJ. Macronutrients and caloric intake in health and longevity. *J Endocrinol*. 2015;226(1):R17–28.
7996. Lee MB, Hill CM, Bitto A, Kaeberlein M. Antiaging diets: Separating fact from fiction. *Science*. 2021;374(6570):eabe7365.
7997. Cordain L, Lindeberg S, Hurtado M, Hill K, Eaton SB, Brand-Miller J. Acne vulgaris: a disease of Western civilization. *Arch Dermatol*. 2002;138(12):1584–90.
7998. Melnik BC, John SM, Plewig G. Acne: risk indicator for increased body mass index and insulin resistance. *Acta Derm Venereol*. 2013;93(6):644–9.
7999. Blair MC, Neinast MD, Arany Z. Whole-body metabolic fate of branched-chain amino acids. *Biochem J.* 2021;478(4):765–76.
8000. Neinast M, Murashige D, Arany Z. Branched chain amino acids. *Annu Rev Physiol*. 2019;81:139–64.
8001. Tournissac M, Vandal M, Tremblay C, et al. Dietary intake of branched-chain amino acids in a mouse model of Alzheimer's disease: effects on survival, behavior, and neuropathology. *Alzheimers Dement (N Y)*. 2018;4:677–87.
8002. Larsson SC, Markus HS. Branched-chain amino acids and Alzheimer's disease: a Mendelian randomization analysis. *Sci Rep*. 2017;7(1):13604.
8003. Tynkkynen J, Chouraki V, van der Lee SJ, et al. Association of branched-chain amino acids and other circulating metabolites with risk of incident dementia and Alzheimer's disease: a prospective study in eight cohorts. *Alzheimers Dement*. 2018;14(6):723–33.
8004. Le Couteur DG, Solon-Biet SM, Cogger VC, et al. Branched chain amino acids, aging and age-related health. *Ageing Res Rev*. 2020;64:101198.
8005. Xu B, Wang M, Pu L, Shu C, Li L, Han L. Association of dietary intake of branched-chain amino acids with long-term risks of CVD, cancer and all-cause mortality. *Public Health Nutr*. 2022;25(12):3390–400.
8006. Le Couteur DG, Solon-Biet SM, Cogger VC, et al. Branched chain amino acids, aging and age-related health. *Ageing Res Rev*. 2020;64:101198.

8007. Insulin resistance. Cleveland Clinic. https://my.clevelandclinic.org/health/diseases/22206-insulin-resistance. Updated December 16, 2021. Accessed December 26, 2022.
8008. Zhang X, Li J, Zheng S, Luo Q, Zhou C, Wang C. Fasting insulin, insulin resistance, and risk of cardiovascular or all-cause mortality in non-diabetic adults: a meta-analysis. *Biosci Rep*. 2017;37(5):BSR20170947.
8009. Ju SY, Lee JY, Kim DH. Association of metabolic syndrome and its components with all-cause and cardiovascular mortality in the elderly: a meta-analysis of prospective cohort studies. *Medicine (Baltimore)*. 2017;96(45):e8491.
8010. Bishop CA, Machate T, Henning T, et al. Detrimental effects of branched-chain amino acids in glucose tolerance can be attributed to valine induced glucotoxicity in skeletal muscle. *Nutr Diabetes*. 2022;12(1):1–9.
8011. Jang C, Oh SF, Wada S, et al. A branched-chain amino acid metabolite drives vascular fatty acid transport and causes insulin resistance. *Nat Med*. 2016;22(4):421–6.
8012. Williams KJ, Wu X. Imbalanced insulin action in chronic over nutrition: clinical harm, molecular mechanisms, and a way forward. *Atherosclerosis*. 2016;247:225–82.
8013. Cummings NE, Williams EM, Kasza I, et al. Restoration of metabolic health by decreased consumption of branched-chain amino acids. *J Physiol*. 2018;596(4):623–45.
8014. Solon-Biet SM, Cogger VC, Pulpitel T, et al. Branched chain amino acids impact health and lifespan indirectly via amino acid balance and appetite control. *Nat Metab*. 2019;1(5):532–45.
8015. Nie C, He T, Zhang W, Zhang G, Ma X. Branched chain amino acids: beyond nutrition metabolism. *Int J Mol Sci*. 2018;19(4):954.
8016. Bishop CA, Machate T, Henning T, et al. Detrimental effects of branched-chain amino acids in glucose tolerance can be attributed to valine induced glucotoxicity in skeletal muscle. *Nutr Diabetes*. 2022;12(1):1–9.
8017. Rhee EP, Ho JE, Chen MH, et al. A genome-wide association study of the human metabolome in a community-based cohort. *Cell Metab*.

2013;18(1):130–43.
8018. Lotta LA, Scott RA, Sharp SJ, et al. Genetic predisposition to an impaired metabolism of the branched-chain amino acids and risk of type 2 diabetes: a Mendelian randomisation analysis. *PLoS Med*. 2016;13(11):e1002179.
8019. Mahendran Y, Jonsson A, Have CT, et al. Genetic evidence of a causal effect of insulin resistance on branched-chain amino acid levels. *Diabetologia*. 2017;60(5):873–8.
8020. White PJ, Newgard CB. Branched-chain amino acids in disease. *Science*. 2019;363(6427):582–3.
8021. Okekunle AP, Zhang M, Wang Z, et al. Dietary branched-chain amino acids intake exhibited a different relationship with type 2 diabetes and obesity risk: a meta-analysis. *Acta Diabetol*. 2019;56(2):187–95.
8022. Ridaura VK, Faith JJ, Rey FE, et al. Cultured gut microbiota from twins discordant for obesity modulate adiposity and metabolic phenotypes in mice. *Science*. 2013;341(6150):1241214.
8023. Bachmann OP, Dahl DB, Brechtel K, et al. Effects of intravenous and dietary lipid challenge on intramyocellular lipid content and the relation with insulin sensitivity in humans. *Diabetes.* 2001;50(11):2579–84.
8024. Arany Z, Neinast M. Branched chain amino acids in metabolic disease. *Curr Diab Rep*. 2018;18(10):76.
8025. Smith GI, Yoshino J, Stromsdorfer KL, et al. Protein ingestion induces muscle insulin resistance independent of leucine-mediated mTOR activation. *Diabetes*. 2015;64(5):1555–63.
8026. Manco M, Bertuzzi A, Salinari S, et al. The ingestion of saturated fatty acid triacylglycerols acutely affects insulin secretion and insulin sensitivity in human subjects. *Br J Nutr*. 2004;92(6):895–903.
8027. Fontana L, Cummings NE, Arriola Apelo SI, et al. Decreased consumption of branched-chain amino acids improves metabolic health. *Cell Rep*. 2016;16(2):520–30.
8028. Cummings NE, Williams EM, Kasza I, et al. Restoration of metabolic health by decreased consumption of branched-chain amino acids. *J Physiol*. 2018;596(4):623–45.
8029. Wolfe RR. Branched-chain amino acids and muscle protein synthesis in humans: myth or reality? *J Int Soc Sports Nutr*. 2017;14(1):30.

8030. Buse MG. In vivo effects of branched chain amino acids on muscle protein synthesis in fasted rats. *Horm Metab Res*. 1981;13(9):502–5.
8031. Louard RJ, Barrett EJ, Gelfand RA. Effect of infused branched-chain amino acids on muscle and whole-body amino acid metabolism in man. *Clin Sci (Lond)*. 1990;79(5):457–66.
8032. Louard RJ, Barrett EJ, Gelfand RA. Overnight branched-chain amino acid infusion causes sustained suppression of muscle proteolysis. *Metabolism*. 1995;44(4):424–9.
8033. Plotkin DL, Delcastillo K, Van Every DW, Tipton KD, Aragon AA, Schoenfeld BJ. Isolated leucine and branched-chain amino acid supplementation for enhancing muscular strength and hypertrophy: a narrative review. *Int J Sport Nutr Exerc Metab*. 2021;31(3):292–301.
8034. Isanejad M, LaCroix AZ, Thomson CA, et al. Branched-chain amino acid, meat intake and risk of type 2 diabetes in the Women's Health Initiative. *Br J Nutr*. 2017;117(11):1523–30.
8035. Adeva-Andany MM, González-Lucán M, Fernández-Fernández C, Carneiro-Freire N, Seco-Filgueira M, Pedre-Piñeiro AM. Effect of diet composition on insulin sensitivity in humans. *Clin Nutr ESPEN*. 2019;33:29–38.
8036. Isanejad M, Lacroix AZ, Thomson CA, et al. Branched-chain amino acid, meat intake and risk of type 2 diabetes in the Women's Health Initiative. *Br J Nutr*. 2017;117(11):1523–30.
8037. Malik VS, Li Y, Tobias DK, Pan A, Hu FB. Dietary protein intake and risk of type 2 diabetes in US men and women. *Am J Epidemiol*. 2016;183(8):715–28.
8038. Le Couteur DG, Solon-Biet SM, Cogger VC, et al. Branched chain amino acids, aging and age-related health. *Ageing Res Rev*. 2020;64:101198.
8039. Hagve M, Simbo SY, Ruebush LE, et al. Postprandial concentration of circulating branched chain amino acids are able to predict the carbohydrate content of the ingested mixed meal. *Clin Nutr*. 2021;40(8):5020–9.
8040. Hosseinpour-Niazi S, Mirmiran P, Hedayati M, Azizi F. Substitution of red meat with legumes in the therapeutic lifestyle change diet based on dietary advice improves cardiometabolic risk factors in

overweight type 2 diabetes patients: a cross-over randomized clinical trial. *Eur J Clin Nutr*. 2015;69(5):592–7.

8041. Viguiliouk E, Stewart SE, Jayalath VH, et al. Effect of replacing animal protein with plant protein on glycemic control in diabetes: a systematic review and meta-analysis of randomized controlled trials. *Nutrients*. 2015;7(12):9804–24.

8042. Schmidt JA, Rinaldi S, Scalbert A, et al. Plasma concentrations and intakes of amino acids in male meat-eaters, fish-eaters, vegetarians and vegans: a cross-sectional analysis in the EPIC-Oxford cohort. *Eur J Clin Nutr*. 2016;70(3):306–12.

8043. Lederer AK, Maul-Pavicic A, Hannibal L, et al. Vegan diet reduces neutrophils, monocytes and platelets related to branched-chain amino acids—a randomized, controlled trial. *Clin Nutr*. 2020;39(11):3241–50.

8044. Kahleova H, Klementova M, Herynek V, et al. The effect of a vegetarian vs conventional hypocaloric diabetic diet on thigh adipose tissue distribution in subjects with type 2 diabetes: a randomized study. *J Am Coll Nutr*. 2017;36(5):364–9.

8045. Lee Y, Park K. Adherence to a vegetarian diet and diabetes risk: a systematic review and meta-analysis of observational studies. *Nutrients*. 2017;9(6):603.

8046. Kahleova H, Klementova M, Herynek V, et al. The effect of a vegetarian vs conventional hypocaloric diabetic diet on thigh adipose tissue distribution in subjects with type 2 diabetes: a randomized study. *J Am Coll Nutr*. 2017;36(5):364–9.

8047. Goff LM, Bell JD, So PW, Dornhorst A, Frost GS. Veganism and its relationship with insulin resistance and intramyocellular lipid. *Eur J Clin Nutr*. 2005;59(2):291–8.

8048. Valachovicová M, Krajcovicová-Kudlácková M, Blazícek P, Babinská K. No evidence of insulin resistance in normal weight vegetarians. A case control study. *Eur J Nutr*. 2006;45(1):52–4.

8049. Kuo CS, Lai NS, Ho LT, Lin CL. Insulin sensitivity in Chinese ovo-lactovegetarians compared with omnivores. *Eur J Clin Nutr*. 2004;58(2):312–6.

8050. Toth MJ, Poehlman ET. Sympathetic nervous system activity and resting metabolic rate in vegetarians. *Metab Clin Exp*.

1994;43(5):621–5.
8051. Hung CJ, Huang PC, Li YH, Lu SC, Ho LT, Chou HF. Taiwanese vegetarians have higher insulin sensitivity than omnivores. *Br J Nutr*. 2006;95(1):129–35.
8052. Kahleova H, Petersen KF, Shulman GI, et al. Effect of a low-fat vegan diet on body weight, insulin sensitivity, postprandial metabolism, and intramyocellular and hepatocellular lipid levels in overweight adults: a randomized clinical trial. *JAMA Netw Open*. 2020;3(11):e2025454.
8053. McCarty MF. The origins of western obesity: a role for animal protein? *Med Hypotheses*. 2000;54(3):488–94.
8054. Remer T, Pietrzik K, Manz F. A moderate increase in daily protein intake causing an enhanced endogenous insulin secretion does not alter circulating levels or urinary excretion of dehydroepiandrosterone sulfate. *Metab Clin Exp*. 1996;45(12):1483–6.
8055. Gulliford MC, Bicknell EJ, Scarpello JH. Differential effect of protein and fat ingestion on blood glucose responses to high- and low-glycemic-index carbohydrates in noninsulin-dependent diabetic subjects. *Am J Clin Nutr*. 1989;50(4):773–7.
8056. Ballance S, Knutsen SH, Fosvold ØW, Wickham M, Trenado CD, Monro J. Glyceamic and insulinaemic response to mashed potato alone, or with broccoli, broccoli fibre or cellulose in healthy adults. *Eur J Nutr*. 2018;57(1):199–207.
8057. Gannon MC, Nuttall FQ, Neil BJ, Westphal SA. The insulin and glucose responses to meals of glucose plus various proteins in type II diabetic subjects. *Metab Clin Exp*. 1988;37(11):1081–8.
8058. Gojda J, Rossmeislová L, Straková R, et al. Chronic dietary exposure to branched chain amino acids impairs glucose disposal in vegans but not in omnivores. *Eur J Clin Nutr*. 2017;71(5):594–601.
8059. Draper CF, Vassallo I, Di Cara A, et al. A 48-hour vegan diet challenge in healthy women and men induces a branch-chain amino acid related, health associated, metabolic signature. *Mol Nutr Food Res*. 2018;62(3):1700703.
8060. Le Couteur DG, Solon-Biet S, Cogger VC, et al. The impact of low-protein high-carbohydrate diets on aging and lifespan. *Cell Mol Life*

Sci. 2016;73(6):1237–52.
8061. Draper CF, Vassallo I, Di Cara A, et al. A 48-hour vegan diet challenge in healthy women and men induces a BRANCH-chain amino acid related, health associated, metabolic signature. *Mol Nutr Food Res*. 2018;62(3):1700703.
8062. Kalantar-Zadeh K, Kramer HM, Fouque D. High-protein diet is bad for kidney health: unleashing the taboo. *Nephrol Dial Transplant*. 2020;35(1):1–4.
8063. Mittendorfer B, Klein S, Fontana L. A word of caution against excessive protein intake. *Nat Rev Endocrinol*. 2020;16(1):59–66.
8064. Larsen TM, Dalskov SM, van Baak M, et al. Diets with high or low protein content and glycemic index for weight-loss maintenance. *N Engl J Med*. 2010;363(22):2102–13.
8065. Brandhorst S, Longo VD. Protein quantity and source, fasting-mimicking diets, and longevity. *Adv Nutr*. 2019;10(Suppl_4):S340–50.
8066. Sifferlin A. What diet helps people live the longest? *Time*. 2015;185(6–7):93.
8067. Fontana L. The Path to Longevity: How to Reach 100 with the Health and Stamina of a 40-Year-Old. Hardie Grant Books; 2020.
8068. Harden A, Young WJ. The alcoholic ferment of yeast-juice. Part II.—The coferment of yeast-juice. *Proc R Soc Lond B*. 1906;78(526):369–75.
8069. Reiten OK, Wilvang MA, Mitchell SJ, Hu Z, Fang EF. Preclinical and clinical evidence of NAD^+ precursors in health, disease, and ageing. *Mech Ageing Dev*. 2021;199:111567.
8070. Strømland Ø, Diab J, Ferrario E, Sverkeli LJ, Ziegler M. The balance between NAD^+ biosynthesis and consumption in ageing. *Mech Ageing Dev*. 2021;199:111569.
8071. Rajman L, Chwalek K, Sinclair DA. Therapeutic potential of NAD-boosting molecules: the *in vivo* evidence. *Cell Metab*. 2018;27(3):529–47.
8072. Katsyuba E, Romani M, Hofer D, Auwerx J. NAD^+ homeostasis in health and disease. *Nat Metab*. 2020;2(1):9–31.
8073. Zapata-Pérez R, Wanders RJA, van Karnebeek CDM, Houtkooper RH. NAD^+ homeostasis in human health and disease. *EMBO Mol*

Med. 2021;13(7):e13943.
8074. Giblin W, Skinner ME, Lombard DB. Sirtuins: guardians of mammalian healthspan. *Trends Genet*. 2014;30(7):271–86.
8075. Rajman L, Chwalek K, Sinclair DA. Therapeutic potential of NAD-boosting molecules: the *in vivo* evidence. *Cell Metab*. 2018;27(3):529–47.
8076. Liu L, Su X, Quinn WJ, et al. Quantitative analysis of NAD synthesis-breakdown fluxes. *Cell Metab*. 2018;27(5):1067–80.e5.
8077. Ziegler M, Nikiforov AA. NAD on the rise again. *Nat Metab*. 2020;2(4):291–2.
8078. Zapata-Pérez R, Wanders RJA, van Karnebeek CDM, Houtkooper RH. NAD^+ homeostasis in human health and disease. *EMBO Mol Med*. 2021;13(7):e13943.
8079. Jacobson MK, Jacobson EL. Vitamin B3 in health and disease: toward the second century of discovery. *Methods Mol Biol*. 2018;1813:3–8.
8080. Chini CCS, Tarragó MG, Chini EN. NAD and the aging process: role in life, death and everything in between. *Mol Cell Endocrinol*. 2017;455:62–74.
8081. Bogan KL, Brenner C. Nicotinic acid, nicotinamide, and nicotinamide riboside: a molecular evaluation of NAD^+ precursor vitamins in human nutrition. *Annu Rev Nutr*. 2008;28:115–30.
8082. Kirkland JB, Meyer-Ficca ML. Niacin. In: *Advances in Food and Nutrition Research*. Elsevier; 2018;83:83–149.
8083. Yang Y, Sauve AA. NAD^+ metabolism: bioenergetics, signaling and manipulation for therapy. *Biochim Biophys Acta*. 2016;1864(12):1787–800.
8084. Rajman L, Chwalek K, Sinclair DA. Therapeutic potential of NAD-boosting molecules: the *in vivo* evidence. *Cell Metab*. 2018;27(3):529–47.
8085. Soma M, Lalam SK. The role of nicotinamide mononucleotide (NMN) in anti-aging, longevity, and its potential for treating chronic conditions. *Mol Biol Rep*. 2022;49(10):9737–48.
8086. Rajman L, Chwalek K, Sinclair DA. Therapeutic potential of NAD-boosting molecules: the *in vivo* evidence. *Cell Metab*. 2018;27(3):529–47.

8087. She J, Sheng R, Qin ZH. Pharmacology and potential implications of nicotinamide adenine dinucleotide precursors. *Aging Dis*. 2021;12(8):1879–97.
8088. Pflanzer LR. A startup that's developed an anti-aging supplement just raised $20 million. Business Insider. https://www.businessinsider.com/elysium-health-raises-20-million-and-presents-clinical-data-2016–12. Published December 7, 2016. Accessed January 10, 2023.
8089. Goldstein J. Harvard researcher tied to Shaklee "anti-aging tonic" Vivix. *Wall Street Journal*. https://www.wsj.com/articles/BL-HEB-3860. Published December 26, 2008. Accessed January 10, 2023.
8090. Peluso A, Damgaard MV, Mori MAS, Treebak JT. Age-dependent decline of NAD^+—universal truth or confounded consensus? *Nutrients*. 2021;14(1):101.
8091. McReynolds MR, Chellappa K, Chiles E, et al. NAD^+ flux is maintained in aged mice despite lower tissue concentrations. *Cell Syst*. 2021;12(12):1160–72.e4.
8092. Peluso A, Damgaard MV, Mori MAS, Treebak JT. Age-dependent decline of NAD^+—universal truth or confounded consensus? *Nutrients*. 2021;14(1):101.
8093. Rajman L, Chwalek K, Sinclair DA. Therapeutic potential of NAD-boosting molecules: the *in vivo* evidence. *Cell Metab*. 2018;27(3):529–47.
8094. Mills KF, Yoshida S, Stein LR, et al. Long-term administration of nicotinamide mononucleotide mitigates age-associated physiological decline in mice. *Cell Metab*. 2016;24(6):795–806.
8095. Cerutti R, Pirinen E, Lamperti C, et al. NAD^+-dependent activation of Sirt1 corrects the phenotype in a mouse model of mitochondrial disease. *Cell Metab*. 2014;19(6):1042–9.
8096. Fang EF, Lautrup S, Hou Y, et al. NAD^+ in aging: molecular mechanisms and translational implications. *Trends Mol Med*. 2017;23(10):899–916.
8097. Okur MN, Mao B, Kimura R, et al. Short-term NAD^+ supplementation prevents hearing loss in mouse models of Cockayne syndrome. *NPJ Aging Mech Dis*. 2020;6:1.

8098. Yang Q, Cong L, Wang Y, et al. Increasing ovarian NAD^+ levels improve mitochondrial functions and reverse ovarian aging. *Free Radic Biol Med*. 2020;156:1–10.
8099. Gong B, Pan Y, Vempati P, et al. Nicotinamide riboside restores cognition through an upregulation of proliferator-activated receptor-γ coactivator 1α regulated β-secretase 1 degradation and mitochondrial gene expression in Alzheimer's mouse models. *Neurobiol Aging*. 2013;34(6):1581–8.
8100. Rajman L, Chwalek K, Sinclair DA. Therapeutic potential of NAD-boosting molecules: the *in vivo* evidence. *Cell Metab*. 2018;27(3):529–47.
8101. de Picciotto NE, Gano LB, Johnson LC, et al. Nicotinamide mononucleotide supplementation reverses vascular dysfunction and oxidative stress with aging in mice. *Aging Cell*. 2016;15(3):522–30.
8102. Yao Z, Yang W, Gao Z, Jia P. Nicotinamide mononucleotide inhibits JNK activation to reverse Alzheimer disease. *Neurosci Lett*. 2017;647:133–40.
8103. Ryu D, Zhang H, Ropelle ER, et al. NAD+ repletion improves muscle function in muscular dystrophy and counters global PARylation. *Sci Transl Med*. 2016;8(361):361ra139.
8104. Takeda K, Okumura K. Nicotinamide mononucleotide augments the cytotoxic activity of natural killer cells in young and elderly mice. *Biomed Res*. 2021;42(5):173–9.
8105. Tran MT, Zsengeller ZK, Berg AH, et al. PGC1α drives NAD biosynthesis linking oxidative metabolism to renal protection. *Nature*. 2016;531(7595):528–32.
8106. Mukherjee S, Chellappa K, Moffitt A, et al. Nicotinamide adenine dinucleotide biosynthesis promotes liver regeneration. *Hepatology*. 2017;65(2):616–30.
8107. Gomes AP, Price NL, Ling AJY, et al. Declining NAD^+ induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. *Cell*. 2013;155(7):1624–38.
8108. Dutta S, Sengupta P. Men and mice: relating their ages. *Life Sci*. 2016;152:244–8.
8109. Giblin W, Skinner ME, Lombard DB. Sirtuins: guardians of mammalian healthspan. *Trends Genet*. 2014;30(7):271–86.

8110. Anderson RM, Bitterman KJ, Wood JG, et al. Manipulation of a nuclear NAD^+ salvage pathway delays aging without altering steady-state NAD^+ levels. *J Biol Chem*. 2002;277(21):18881–90.
8111. Mouchiroud L, Houtkooper RH, Moullan N, et al. The NAD^+/sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling. *Cell*. 2013;154(2):430–41.
8112. Zhang H, Ryu D, Wu Y, et al. NAD^+ repletion improves mitochondrial and stem cell function and enhances life span in mice. *Science*. 2016;352(6292):1436–43.
8113. Rajman L, Chwalek K, Sinclair DA. Therapeutic potential of NAD-boosting molecules: the *in vivo* evidence. *Cell Metab*. 2018;27(3):529–47.
8114. Conlon N, Ford D. A systems-approach to NAD+ restoration. *Biochem Pharmacol.* 2022;198:114946.
8115. Bogan KL, Brenner C. Nicotinic acid, nicotinamide, and nicotinamide riboside: a molecular evaluation of NAD^+ precursor vitamins in human nutrition. *Annu Rev Nutr*. 2008;28:115–30.
8116. Liu L, Su X, Quinn WJ, et al. Quantitative analysis of NAD synthesis-breakdown fluxes. *Cell Metab*. 2018;27(5):1067–80.e5.
8117. Shats I, Williams JG, Liu J, et al. Bacteria boost mammalian host NAD metabolism by engaging the deamidated biosynthesis pathway. *Cell Metab*. 2020;31(3):564–79.e7.
8118. Romani M, Hofer DC, Katsyuba E, Auwerx J. Niacin: an old lipid drug in a new NAD^+ dress. *J Lipid Res*. 2019;60(4):741–6.
8119. Gasperi V, Sibilano M, Savini I, Catani MV. Niacin in the central nervous system: an update of biological aspects and clinical applications. *Int J Mol Sci*. 2019;20(4):974.
8120. Altschul R, Hoffer A. Effects of salts of nicotinic acid on serum cholesterol. *Br Med J*. 1958;2(5098):713–4.
8121. Schandelmaier S, Briel M, Saccilotto R, et al. Niacin for primary and secondary prevention of cardiovascular events. *Cochrane Database Syst Rev*. 2017;6(6):CD009744.
8122. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986;8(6):1245–55.

8123. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365(24):2255–67.
8124. Landray MJ, Haynes R, Hopewell JC, et al. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014;371(3):203–12.
8125. Schandelmaier S, Briel M, Saccilotto R, et al. Niacin for primary and secondary prevention of cardiovascular events. *Cochrane Database Syst Rev*. 2017;6(6):CD009744.
8126. Superko HR, Zhao XQ, Hodis HN, Guyton JR. Niacin and heart disease prevention: engraving its tombstone is a mistake. *J Clin Lipidol*. 2017;11(6):1309–17.
8127. Krumholz HM. Niacin: time to believe outcomes over surrogate outcomes: if not now, when? *Circ Cardiovasc Qual Outcomes*. 2016;9(4):343–4.
8128. Knopp RH, Ginsberg J, Albers JJ, et al. Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: clues to mechanism of action of niacin. *Metabolism*. 1985;34(7):642–50.
8129. Goldie C, Taylor AJ, Nguyen P, McCoy C, Zhao XQ, Preiss D. Niacin therapy and the risk of new-onset diabetes: a meta-analysis of randomised controlled trials. *Heart*. 2016;102(3):198–203.
8130. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2016;68(1):92–125.
8131. Kent S, Haynes R, Hopewell JC, et al. Effects of vascular and nonvascular adverse events and of extended-release niacin with laropiprant on health and healthcare costs. *Circ Cardiovasc Qual Outcomes*. 2016;9(4):348–54.
8132. Pirinen E, Auranen M, Khan NA, et al. Niacin cures systemic NAD^+ deficiency and improves muscle performance in adult-onset mitochondrial myopathy. *Cell Metab*. 2020;31(6):1078–90.e5.

8133. Zapata-Pérez R, Wanders RJA, van Karnebeek CDM, Houtkooper RH. NAD^+ homeostasis in human health and disease. *EMBO Mol Med*. 2021;13(7):e13943.
8134. Pirinen E, Auranen M, Khan NA, et al. Niacin cures systemic NAD^+ deficiency and improves muscle performance in adult-onset mitochondrial myopathy. *Cell Metab*. 2020;31(6):1078–90.e5.
8135. Pirinen E, Auranen M, Khan NA, et al. Niacin cures systemic NAD^+ deficiency and improves muscle performance in adult-onset mitochondrial myopathy. *Cell Metab*. 2020;31(6):1078–90.e5.
8136. Morris BJ. Seven sirtuins for seven deadly diseases of aging. *Free Radic Biol Med*. 2013;56:133–71.
8137. Zhong O, Wang J, Tan Y, Lei X, Tang Z. Effects of NAD+ precursor supplementation on glucose and lipid metabolism in humans: a meta-analysis. *Nutr Metab (Lond)*. 2022;19(1):20.
8138. Goldie C, Taylor AJ, Nguyen P, McCoy C, Zhao XQ, Preiss D. Niacin therapy and the risk of new-onset diabetes: a meta-analysis of randomised controlled trials. *Heart*. 2016;102(3):198–203.
8139. Meyer-Ficca M, Kirkland JB. Niacin. *Adv Nutr*. 2016;7(3):556–8.
8140. Williamson G, Holst B. Dietary reference intake (DRI) value for dietary polyphenols: are we heading in the right direction? *Br J Nutr*. 2008;99 Suppl 3:S55–8.
8141. Pitkin RM, Allen LH, Bailey LB, et al. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline: a report of the Standing Committee of the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins and Choline and Subcommittee on Upper Reference Levels of Nutrients. National Academies Press (US); 1998.
8142. Benyó Z, Gille A, Kero J, et al. GPR109A (PUMA-g/HM74A) mediates nicotinic acid-induced flushing. *J Clin Invest*. 2005;115(12):3634–40.
8143. DiPalma JR, Thayer WS. Use of niacin as a drug. *Annu Rev Nutr*. 1991;11:169–87.
8144. Fukushima T. Niacin metabolism and Parkinson's disease. *Environ Health Prev Med*. 2005;10(1):3–8.

8145. Abdellatif M, Sedej S, Kroemer G. NAD^+ metabolism in cardiac health, aging, and disease. *Circulation*. 2021;144(22):1795–817.
8146. Elvehjem CA, Madden RJ, Strong FM, Woolley DW. Relation of nicotinic acid and nicotinic acid amide to canine black tongue. *J Am Chem Soc*. 1937;59(9):1767–8.
8147. Yoshino J, Baur JA, Imai SI. NAD^+ intermediates: the biology and therapeutic potential of NMN and NR. *Cell Metab*. 2018;27(3):513–28.
8148. Giacalone S, Spigariolo CB, Bortoluzzi P, Nazzaro G. Oral nicotinamide: the role in skin cancer chemoprevention. *Dermatol Ther*. 2021;34(3):e14892.
8149. Kelly G. A review of the sirtuin system, its clinical implications, and the potential role of dietary activators like resveratrol: part 1. *Altern Med Rev*. 2010;15(3):245–63.
8150. Morris BJ. Seven sirtuins for seven deadly diseases of aging. *Free Radic Biol Med*. 2013;56:133–71.
8151. Schmeisser K, Mansfeld J, Kuhlow D, et al. Role of sirtuins in lifespan regulation is linked to methylation of nicotinamide. *Nat Chem Biol*. 2013;9(11):693–700.
8152. Mitchell SJ, Bernier M, Aon MA, et al. Nicotinamide improves aspects of healthspan, but not lifespan, in mice. *Cell Metab*. 2018;27(3):667–76.e4.
8153. Elliott RB, Pilcher CC, Stewart A, Fergusson D, McGregor MA. The use of nicotinamide in the prevention of type 1 diabetes. *Ann N Y Acad Sci*. 1993;696:333–41.
8154. Pozzilli P, Browne PD, Kolb H, et al. Meta-analysis of nicotinamide treatment in patients with recent-onset IDDM. *Diabetes Care*. 1996;19(12):1357–63.
8155. Connell NJ, Grevendonk L, Fealy CE, et al. NAD^+-precursor supplementation with L-tryptophan, nicotinic acid, and nicotinamide does not affect mitochondrial function or skeletal muscle function in physically compromised older adults. J Nutr. 2021;151(10):2917–31.
8156. Gasperi V, Sibilano M, Savini I, Catani MV. Niacin in the central nervous system: an update of biological aspects and clinical applications. *Int J Mol Sci*. 2019;20(4):974.

8157. Winter SL, Boyer JL. Hepatic toxicity from large doses of vitamin B_3 (nicotinamide). *N Engl J Med*. 1973;289(22):1180–2.
8158. Reddi KK, Kodicek E. Metabolism of nicotinic acid and related compounds in man and rat. *Biochem J*. 1953;53(2):286–94.
8159. Braidy N, Liu Y. NAD+ therapy in age-related degenerative disorders: a benefit/risk analysis. *Exp Gerontol*. 2020;132:110831.
8160. Willets JM, Lunec J, Williams AC, Griffiths HR. Neurotoxicity of nicotinamide derivatives: their role in the aetiology of Parkinson's disease. *Biochem Soc Trans*. 1993;21 (Pt 3)(3):299S.
8161. Harrison IF, Powell NM, Dexter DT. The histone deacetylase inhibitor nicotinamide exacerbates neurodegeneration in the lactacystin rat model of Parkinson's disease. *J Neurochem*. 2019;148(1):136–56.
8162. Parsons RB, Smith ML, Williams AC, Waring RH, Ramsden DB. Expression of nicotinamide N-methyltransferase (E.C. 2.1.1.1) in the Parkinsonian brain. *J Neuropathol Exp Neurol*. 2002;61(2):111–24.
8163. Li D, Tian YJ, Guo J, et al. Nicotinamide supplementation induces detrimental metabolic and epigenetic changes in developing rats. *Br J Nutr*. 2013;110(12):2156–64.
8164. Kang-Lee YA, McKee RW, Wright SM, Swendseid ME, Jenden DJ, Jope RS. Metabolic effects of nicotinamide administration in rats. *J Nutr.* 1983;113(2):215–21.
8165. Hwang ES, Song SB. Possible adverse effects of high-dose nicotinamide: mechanisms and safety assessment. *Biomolecules*. 2020;10(5):687.
8166. Tian YJ, Li D, Ma Q, et al. Excess nicotinamide increases plasma serotonin and histamine levels. *Sheng Li Xue Bao*. 2013;65(1):33–8.
8167. Sun WP, Li D, Lun YZ, et al. Excess nicotinamide inhibits methylation-mediated degradation of catecholamines in normotensives and hypertensives. *Hypertens Res*. 2012;35(2):180–5.
8168. Tinelli C, Di Pino A, Ficulle E, Marcelli S, Feligioni M. Hyperhomocysteinemia as a risk factor and potential nutraceutical target for certain pathologies. *Front Nutr*. 2019;6:49.
8169. Avalos JL, Bever KM, Wolberger C. Mechanism of sirtuin inhibition by nicotinamide: altering the NAD^+ cosubstrate specificity of a Sir2

enzyme. *Mol Cell*. 2005;17(6):855–68.
8170. Mitchell SJ, Bernier M, Aon MA, et al. Nicotinamide improves aspects of healthspan, but not lifespan, in mice. *Cell Metab*. 2018;27(3):667–76.e4.
8171. Bitterman KJ, Anderson RM, Cohen HY, Latorre-Esteves M, Sinclair DA. Inhibition of silencing and accelerated aging by nicotinamide, a putative negative regulator of yeast Sir2 and human SIRT1. *J Biol Chem*. 2002;277(47):45099–107.
8172. Rajman L, Chwalek K, Sinclair DA. Therapeutic potential of NAD-boosting molecules: the *in vivo* evidence. *Cell Metab*. 2018;27(3):529–47.
8173. Cantó C, Houtkooper RH, Pirinen E, et al. The NAD^+ precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity. *Cell Metab*. 2012;15(6):838–47.
8174. Rajman L, Chwalek K, Sinclair DA. Therapeutic potential of NAD-boosting molecules: the *in vivo* evidence. *Cell Metab*. 2018;27(3):529–47.
8175. Conlon N, Ford D. A systems-approach to NAD^+ restoration. *Biochem Pharmacol.* 2022;198:114946.
8176. Conze D, Brenner C, Kruger CL. Safety and metabolism of long-term administration of NIAGEN (Nicotinamide riboside chloride) in a randomized, double-blind, placebo-controlled clinical trial of healthy overweight adults. *Sci Rep*. 2019;9(1):9772.
8177. Elhassan YS, Kluckova K, Fletcher RS, et al. Nicotinamide riboside augments the aged human skeletal muscle NAD^+ metabolome and induces transcriptomic and anti-inflammatory signatures. *Cell Rep*. 2019;28(7):1717–28.e6.
8178. Dollerup OL, Chubanava S, Agerholm M, et al. Nicotinamide riboside does not alter mitochondrial respiration, content or morphology in skeletal muscle from obese and insulin-resistant men. *J Physiol*. 2020;598(4):731–54.
8179. Remie CME, Roumans KHM, Moonen MPB, et al. Nicotinamide riboside supplementation alters body composition and skeletal muscle acetylcarnitine concentrations in healthy obese humans. *Am J Clin Nutr*. 2020;112(2):413–26.

8180. Stocks B, Ashcroft SP, Joanisse S, et al. Nicotinamide riboside supplementation does not alter whole-body or skeletal muscle metabolic responses to a single bout of endurance exercise. *J Physiol*. 2021;599(5):1513–31.
8181. Mehmel M, Jovanović N, Spitz U. Nicotinamide riboside—the current state of research and therapeutic uses. *Nutrients*. 2020;12(6):1616.
8182. Katsyuba E, Romani M, Hofer D, Auwerx J. NAD^+ homeostasis in health and disease. *Nat Metab*. 2020;2(1):9–31.
8183. Martens CR, Denman BA, Mazzo MR, et al. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD^+ in healthy middle-aged and older adults. *Nat Commun*. 2018;9(1):1286.
8184. Dolopikou CF, Kourtzidis IA, Margaritelis NV, et al. Acute nicotinamide riboside supplementation improves redox homeostasis and exercise performance in old individuals: a double-blind cross-over study. *Eur J Nutr*. 2020;59(2):505–15.
8185. Martens CR, Denman BA, Mazzo MR, et al. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD^+ in healthy middle-aged and older adults. *Nat Commun*. 2018;9(1):1286.
8186. Dolopikou CF, Kourtzidis IA, Margaritelis NV, et al. Acute nicotinamide riboside supplementation improves redox homeostasis and exercise performance in old individuals: a double-blind cross-over study. *Eur J Nutr*. 2020;59(2):505–15.
8187. Elhassan YS, Kluckova K, Fletcher RS, et al. Nicotinamide riboside augments the aged human skeletal muscle NAD^+ metabolome and induces transcriptomic and anti-inflammatory signatures. *Cell Rep*. 2019;28(7):1717–28.e6.
8188. Remie CME, Roumans KHM, Moonen MPB, et al. Nicotinamide riboside supplementation alters body composition and skeletal muscle acetylcarnitine concentrations in healthy obese humans. *Am J Clin Nutr*. 2020;112(2):413–26.
8189. Martens CR, Denman BA, Mazzo MR, et al. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD^+ in healthy middle-aged and older adults. *Nat Commun*. 2018;9(1):1286.
8190. Dolopikou CF, Kourtzidis IA, Margaritelis NV, et al. Acute nicotinamide riboside supplementation improves redox homeostasis

and exercise performance in old individuals: a double-blind cross-over study. *Eur J Nutr*. 2020;59(2):505–15.

8191. Remie CME, Roumans KHM, Moonen MPB, et al. Nicotinamide riboside supplementation alters body composition and skeletal muscle acetylcarnitine concentrations in healthy obese humans. *Am J Clin Nutr*. 2020;112(2):413–26.

8192. Martens CR, Denman BA, Mazzo MR, et al. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD^+ in healthy middle-aged and older adults. *Nat Commun*. 2018;9(1):1286.

8193. Dolopikou CF, Kourtzidis IA, Margaritelis NV, et al. Acute nicotinamide riboside supplementation improves redox homeostasis and exercise performance in old individuals: a double-blind cross-over study. *Eur J Nutr*. 2020;59(2):505–15.

8194. Elhassan YS, Kluckova K, Fletcher RS, et al. Nicotinamide riboside augments the aged human skeletal muscle NAD^+ metabolome and induces transcriptomic and anti-inflammatory signatures. *Cell Rep*. 2019;28(7):1717–28.e6.

8195. Remie CME, Roumans KHM, Moonen MPB, et al. Nicotinamide riboside supplementation alters body composition and skeletal muscle acetylcarnitine concentrations in healthy obese humans. *Am J Clin Nutr*. 2020;112(2):413–26.

8196. Dollerup OL, Christensen B, Svart M, et al. A randomized placebo-controlled clinical trial of nicotinamide riboside in obese men: safety, insulin-sensitivity, and lipid-mobilizing effects. *Am J Clin Nutr*. 2018;108(2):343–53.

8197. Stocks B, Ashcroft SP, Joanisse S, et al. Nicotinamide riboside supplementation does not alter whole-body or skeletal muscle metabolic responses to a single bout of endurance exercise. *J Physiol*. 2021;599(5):1513–31.

8198. Dollerup OL, Chubanava S, Agerholm M, et al. Nicotinamide riboside does not alter mitochondrial respiration, content or morphology in skeletal muscle from obese and insulin-resistant men. *J Physiol*. 2020;598(4):731–54.

8199. Elhassan YS, Kluckova K, Fletcher RS, et al. Nicotinamide riboside augments the aged human skeletal muscle NAD^+ metabolome and

induces transcriptomic and anti-inflammatory signatures. *Cell Rep*. 2019;28(7):1717–28.e6.

8200. Martens CR, Denman BA, Mazzo MR, et al. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD^+ in healthy middle-aged and older adults. *Nat Commun*. 2018;9(1):1286.

8201. Dolopikou CF, Kourtzidis IA, Margaritelis NV, et al. Acute nicotinamide riboside supplementation improves redox homeostasis and exercise performance in old individuals: a double-blind cross-over study. *Eur J Nutr*. 2020;59(2):505–15.

8202. Dollerup OL, Trammell SAJ, Hartmann B, et al. Effects of nicotinamide riboside on endocrine pancreatic function and incretin hormones in nondiabetic men with obesity. *J Clin Endocrinol Metab*. 2019;104(11):5703–14.

8203. Brakedal B, Dölle C, Riemer F, et al. The NADPARK study: a randomized phase I trial of nicotinamide riboside supplementation in Parkinson's disease. *Cell Metab*. 2022;34(3):396–407.e6.

8204. Martens CR, Denman BA, Mazzo MR, et al. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD^+ in healthy middle-aged and older adults. *Nat Commun*. 2018;9(1):1286.

8205. Dolopikou CF, Kourtzidis IA, Margaritelis NV, et al. Acute nicotinamide riboside supplementation improves redox homeostasis and exercise performance in old individuals: a double-blind cross-over study. *Eur J Nutr*. 2020;59(2):505–15.

8206. Brenner C. Anti-inflammatory plus this observation among the men. Twitter. https://twitter.com/charlesmbrenner/status/1161314766176083968. Published August 14, 2019. Accessed January 13, 2023.

8207. Elhassan YS, Kluckova K, Fletcher RS, et al. Nicotinamide riboside augments the aged human skeletal muscle NAD^+ metabolome and induces transcriptomic and anti-inflammatory signatures. *Cell Rep*. 2019;28(7):1717–28.e6.

8208. Remie CME, Roumans KHM, Moonen MPB, et al. Nicotinamide riboside supplementation alters body composition and skeletal muscle acetylcarnitine concentrations in healthy obese humans. *Am J Clin Nutr*. 2020;112(2):413–26.

8209. Chi Y, Sauve AA. Nicotinamide riboside, a trace nutrient in foods, is a Vitamin B3 with effects on energy metabolism and neuroprotection. *Curr Opin Clin Nutr Metab Care*. 2013;16(6):657–61.
8210. Katsyuba E, Romani M, Hofer D, Auwerx J. NAD^+ homeostasis in health and disease. *Nat Metab*. 2020;2(1):9–31.
8211. Stocks B, Ashcroft SP, Joanisse S, et al. Nicotinamide riboside supplementation does not alter whole-body or skeletal muscle metabolic responses to a single bout of endurance exercise. *J Physiol*. 2021;599(5):1513–31.
8212. Campbell MTD, Jones DS, Andrews GP, Li S. Understanding the physicochemical properties and degradation kinetics of nicotinamide riboside, a promising vitamin B_3 nutritional supplement. *Food Nutr Res*. 2019;63.
8213. Shats I, Williams JG, Liu J, et al. Bacteria boost mammalian host NAD metabolism by engaging the deamidated biosynthesis pathway. *Cell Metab*. 2020;31(3):564–79.e7.
8214. Stocks B, Ashcroft SP, Joanisse S, et al. Nicotinamide riboside supplementation does not alter whole-body or skeletal muscle metabolic responses to a single bout of endurance exercise. *J Physiol*. 2021;599(5):1513–31.
8215. Dollerup OL, Chubanava S, Agerholm M, et al. Nicotinamide riboside does not alter mitochondrial respiration, content or morphology in skeletal muscle from obese and insulin-resistant men. *J Physiol*. 2020;598(4):731–54.
8216. Sauve AA. Metabolic disease, NAD metabolism, nicotinamide riboside, and the gut microbiome: connecting the dots from the gut to physiology. *mSystems*. 2022;7(1):e01223–21.
8217. Conze D, Brenner C, Kruger CL. Safety and metabolism of long-term administration of NIAGEN (Nicotinamide riboside chloride) in a randomized, double-blind, placebo-controlled clinical trial of healthy overweight adults. *Sci Rep*. 2019;9(1):9772.
8218. Dellinger RW, Santos SR, Morris M, et al. Repeat dose NRPT (nicotinamide riboside and pterostilbene) increases NAD^+ levels in humans safely and sustainably: a randomized, double-blind, placebo-controlled study. *NPJ Aging Mech Dis*. 2017;3:17.

8219. Wolf AM. Rodent diet aids and the fallacy of caloric restriction. *Mech Ageing Dev*. 2021;200:111584.
8220. Brenner C, Boileau AC. Pterostilbene raises low density lipoprotein cholesterol in people. *Clin Nutr*. 2019;38(1):480–1.
8221. Martens CR, Denman BA, Mazzo MR, et al. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD^+ in healthy middle-aged and older adults. *Nat Commun*. 2018;9(1):1286.
8222. Dollerup OL, Christensen B, Svart M, et al. A randomized placebo-controlled clinical trial of nicotinamide riboside in obese men: safety, insulin-sensitivity, and lipid-mobilizing effects. *Am J Clin Nutr*. 2018;108(2):343–53.
8223. Riche DM, Riche KD, Blackshear CT, et al. Pterostilbene on metabolic parameters: a randomized, double-blind, and placebo-controlled trial. *Evid Based Complement Alternat Med*. 2014;2014:459165.
8224. Airhart SE, Shireman LM, Risler LJ, et al. An open-label, non-randomized study of the pharmacokinetics of the nutritional supplement nicotinamide riboside (NR) and its effects on blood NAD+ levels in healthy volunteers. *PLoS One*. 2017;12(12):e0186459.
8225. Palmer RD, Elnashar MM, Vaccarezza M. Precursor comparisons for the upregulation of nicotinamide adenine dinucleotide. Novel approaches for better aging. *Aging Med (Milton).* 2021;4(3):214–20.
8226. Kourtzidis IA, Stoupas AT, Gioris IS, et al. The NAD^+ precursor nicotinamide riboside decreases exercise performance in rats. *J Int Soc Sports Nutr*. 2016;13:32.
8227. Kourtzidis IA, Dolopikou CF, Tsiftsis AN, et al. Nicotinamide riboside supplementation dysregulates redox and energy metabolism in rats: implications for exercise performance. *Exp Physiol*. 2018;103(10):1357–66.
8228. Shi W, Hegeman MA, Doncheva A, Bekkenkamp-Grovenstein M, de Boer VCJ, Keijer J. High dose of dietary nicotinamide riboside induces glucose intolerance and white adipose tissue dysfunction in mice fed a mildly obesogenic diet. *Nutrients*. 2019;11(10):2439.
8229. Sun P, Qie S, Pan B. Nicotinamide riboside will play an important role in anti-aging therapy in humans, especially in the face skin anti-

aging treatment. *Aesthetic Plast Surg*. 2022;46(Suppl 1):192–4.
8230. Turck D, Castenmiller J, de Henauw S, et al. Safety of nicotinamide riboside chloride as a novel food pursuant to Regulation (EU) 2015/2283 and bioavailability of nicotinamide from this source, in the context of Directive 2002/46/EC. *EFSA J*. 2019;17(8):5775.
8231. Leduc-Gaudet JP, Dulac M, Reynaud O, Ayoub MB, Gouspillou G. Nicotinamide riboside supplementation to improve skeletal muscle mitochondrial health and whole-body glucose homeostasis: does it actually work in humans? *J Physiol*. 2020;598(4):619–20.
8232. Yoshino J, Baur JA, Imai SI. NAD^+ intermediates: the biology and therapeutic potential of NMN and NR. *Cell Metab*. 2018;27(3):513–28.
8233. Okabe K, Yaku K, Uchida Y, et al. Oral administration of nicotinamide mononucleotide is safe and efficiently increases blood nicotinamide adenine dinucleotide levels in healthy subjects. *Front Nutr*. 2022;9:868640.
8234. Airhart SE, Shireman LM, Risler LJ, et al. An open-label, non-randomized study of the pharmacokinetics of the nutritional supplement nicotinamide riboside (NR) and its effects on blood NAD+ levels in healthy volunteers. *PLoS One*. 2017;12(12):e0186459.
8235. Soma M, Lalam SK. The role of nicotinamide mononucleotide (NMN) in anti-aging, longevity, and its potential for treating chronic conditions. *Mol Biol Rep*. 2022;49(10):9737–48.
8236. Poddar SK, Sifat AE, Haque S, Nahid NA, Chowdhury S, Mehedi I. Nicotinamide mononucleotide: exploration of diverse therapeutic applications of a potential molecule. *Biomolecules*. 2019;9(1):34.
8237. Schmidt MS, Brenner C. Absence of evidence that Slc12a8 encodes a nicotinamide mononucleotide transporter. *Nat Metab*. 2019;1(7):660–1.
8238. Grozio A, Mills KF, Yoshino J, et al. Slc12a8 is a nicotinamide mononucleotide transporter. *Nat Metab*. 2019;1(1):47–57.
8239. Mills KF, Yoshida S, Stein LR, et al. Long-term administration of nicotinamide mononucleotide mitigates age-associated physiological decline in mice. *Cell Metab*. 2016;24(6):795–806.

8240. Zhang H, Ryu D, Wu Y, et al. NAD^+ repletion improves mitochondrial and stem cell function and enhances life span in mice. *Science*. 2016;352(6292):1436–43.
8241. Rajman L, Chwalek K, Sinclair DA. Therapeutic potential of NAD-boosting molecules: the *in vivo* evidence. *Cell Metab*. 2018;27(3):529–47.
8242. Irie J, Inagaki E, Fujita M, et al. Effect of oral administration of nicotinamide mononucleotide on clinical parameters and nicotinamide metabolite levels in healthy Japanese men. *Endocr J*. 2020;67(2):153–60.
8243. Okabe K, Yaku K, Uchida Y, et al. Oral administration of nicotinamide mononucleotide is safe and efficiently increases blood nicotinamide adenine dinucleotide levels in healthy subjects. *Front Nutr*. 2022;9:868640.
8244. Yoshino M, Yoshino J, Kayser BD, et al. Nicotinamide mononucleotide increases muscle insulin sensitivity in prediabetic women. *Science*. 2021;372(6547):1224–9.
8245. Liao B, Zhao Y, Wang D, Zhang X, Hao X, Hu M. Nicotinamide mononucleotide supplementation enhances aerobic capacity in amateur runners: a randomized, double-blind study. *J Int Soc Sports Nutr*. 2021;18(1):54.
8246. Kim M, Seol J, Sato T, Fukamizu Y, Sakurai T, Okura T. Effect of 12-week intake of nicotinamide mononucleotide on sleep quality, fatigue, and physical performance in older Japanese adults: a randomized, double-blind placebo-controlled study. *Nutrients*. 2022;14(4):755.
8247. Yoshino M, Yoshino J, Kayser BD, et al. Nicotinamide mononucleotide increases muscle insulin sensitivity in prediabetic women. *Science*. 2021;372(6547):1224–9.
8248. Abdellatif M, Baur JA. NAD^+ metabolism and cardiometabolic health: the human evidence. *Cardiovasc Res*. 2021;117(9):e106–9.
8249. Yoshino M, Yoshino J, Kayser BD, et al. Nicotinamide mononucleotide increases muscle insulin sensitivity in prediabetic women. *Science*. 2021;372(6547):1224–9.
8250. Benson D. Christopher W. Shade, PhD: nicotinamide mononucleotide. *Integr Med (Encinitas)*. 2019;18(6):42–4.

8251. Shade C. The science behind NMN—a stable, reliable NAD+ activator and anti-aging molecule. *Integr Med (Encinitas)*. 2020;19(1):12–4.
8252. Mills KF, Yoshida S, Stein LR, et al. Long-term administration of nicotinamide mononucleotide mitigates age-associated physiological decline in mice. *Cell Metab*. 2016;24(6):795–806.
8253. Ummarino S, Mozzon M, Zamporlini F, et al. Simultaneous quantitation of nicotinamide riboside, nicotinamide mononucleotide and nicotinamide adenine dinucleotide in milk by a novel enzyme-coupled assay. *Food Chem*. 2017;221:161–8.
8254. Turner J, Licollari A, Mihalcea E, Tan A. Safety evaluation for Restorin® NMN, a NAD^+ precursor. *Front Pharmacol*. 2021;12:749727.
8255. You Y, Gao Y, Wang H, et al. Subacute toxicity study of nicotinamide mononucleotide via oral administration. *Front Pharmacol*. 2020;11:604404.
8256. Poddar SK, Sifat AE, Haque S, Nahid NA, Chowdhury S, Mehedi I. Nicotinamide mononucleotide: exploration of diverse therapeutic applications of a potential molecule. *Biomolecules*. 2019;9(1):34.
8257. NDI 1259-B-Nicotinamide Mononucleotide (NMN) from Inner Mongolia Kingdomway Pharmaceutical Limited. U.S. Food and Drug Administration. https://www.regulations.gov/document/FDA-2022-S-0023–0051. Published November 8, 2022. Accessed February 25, 2023.
8258. Ramsey KM, Mills KF, Satoh A, Imai SI. Age-associated loss of Sirt1-mediated enhancement of glucose-stimulated insulin secretion in beta cell-specific Sirt1-overexpressing (BESTO) mice. *Aging Cell*. 2008;7(1):78–88.
8259. Li C, Wu LE. Risks and rewards of targeting NAD^+ homeostasis in the brain. *Mech Ageing Dev*. 2021;198:111545.
8260. Braidy N, Liu Y. NAD+ therapy in age-related degenerative disorders: a benefit/risk analysis. *Exp Gerontol*. 2020;132:110831.
8261. Cohen MS. Axon degeneration: too much NMN is actually bad? *Curr Biol*. 2017;27(8):R310–2.
8262. Williams PA, Harder JM, John SWM. Glaucoma as a metabolic optic neuropathy: making the case for nicotinamide treatment in glaucoma.

J Glaucoma. 2017;26(12):1161–8.
8263. Di Stefano M, Nascimento-Ferreira I, Orsomando G, et al. A rise in NAD precursor nicotinamide mononucleotide (NMN) after injury promotes axon degeneration. *Cell Death Differ*. 2015;22(5):731–42.
8264. Di Stefano M, Loreto A, Orsomando G, et al. NMN deamidase delays Wallerian degeneration and rescues axonal defects caused by NMNAT2 deficiency in vivo. *Curr Biol*. 2017;27(6):784–94.
8265. Cohen MS. Axon degeneration: too much NMN is actually bad? *Curr Biol*. 2017;27(8):R310–2.
8266. Quantitative analysis of twenty-two NMN consumer products. ChromaDex. https://s23.q4cdn.com/937095816/files/doc_downloads/2021/Quantitative-Analysis-of-22-NMN-Consumer-Products-Oct-2021.pdf. Published October 20, 2021. Accessed January 10, 2023.
8267. Cooperman T. NAD booster supplements review (NAD+/NADH, nicotinamide riboside, and NMN). ConsumerLab.com. https://www.consumerlab.com/reviews/nmn-nadh-nicotinamide-riboside/nmn-nadh-nicotinamide-riboside/#related-clinical-updates. Published November 2, 2021. Updated November 14, 2022. Accessed January 11, 2023.
8268. Correll WA, Viswanathan S. Warning letter: ChromaDex MARCS-CMS 607692–11/17/2020. U.S. Food and Drug Administration. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/chromadex-607692–11172020. Updated December 1, 2020. Accessed January 10, 2023.
8269. BBB National Programs. ChromaDex, Inc. Discontinues advertising claims for Tru Niagen dietary supplement following national advertising division challenge. Cision PR Newswire. https://www.prnewswire.com/news-releases/chromadex-inc-discontinues-advertising-claims-for-tru-niagen-dietary-supplement-following-national-advertising-division-challenge-301392733.html. Published October 5, 2021. Accessed January 10, 2023.
8270. Segall PE, Timiras PS. Patho-physiologic findings after chronic tryptophan deficiency in rats: a model for delayed growth and aging. *Mech Ageing Dev*. 1976;5(2):109–24.

8271. De Marte ML, Enesco HE. Influence of low tryptophan diet on survival and organ growth in mice. *Mech Ageing Dev*. 1986;36(2):161–71.
8272. Conlon N, Ford D. A systems-approach to NAD+ restoration. *Biochem Pharmacol.* 2022;198:114946.
8273. Kimura N, Fukuwatari T, Sasaki R, Shibata K. Comparison of metabolic fates of nicotinamide, NAD^+ and NADH administered orally and intraperitoneally; characterization of oral NADH. J Nutr Sci Vitaminol. 2006;52(2):142–8.
8274. Zapata-Pérez R, Tammaro A, Schomakers BV, et al. Reduced nicotinamide mononucleotide is a new and potent NAD^+ precursor in mammalian cells and mice. *FASEB J*. 2021;35(4):e21456.
8275. Giroud-Gerbetant J, Joffraud M, Giner MP, et al. A reduced form of nicotinamide riboside defines a new path for NAD^+ biosynthesis and acts as an orally bioavailable NAD^+ precursor. *Mol Metab*. 2019;30:192–202.
8276. Chini CCS, Peclat TR, Gomez LS, et al. Dihydronicotinamide riboside is a potent NAD^+ precursor promoting a pro-inflammatory phenotype in macrophages. *Front Immunol*. 2022;13:840246.
8277. Sonavane M, Hayat F, Makarov M, Migaud ME, Gassman NR. Dihydronicotinamide riboside promotes cell-specific cytotoxicity by tipping the balance between metabolic regulation and oxidative stress. *PLoS One*. 2020;15(11):e0242174.
8278. Chini CCS, Peclat TR, Gomez LS, et al. Dihydronicotinamide riboside is a potent NAD^+ precursor promoting a pro-inflammatory phenotype in macrophages. *Front Immunol*. 2022;13:840246.
8279. Poljsak B, Kovač V, Milisav I. Healthy lifestyle recommendations: do the beneficial effects originate from NAD^+ amount at the cellular level? *Oxid Med Cell Longev*. 2020;2020:8819627.
8280. Oakey LA, Fletcher RS, Elhassan YS, et al. Metabolic tracing reveals novel adaptations to skeletal muscle cell energy production pathways in response to NAD^+ depletion. *Wellcome Open Res*. 2018;3:147.
8281. Braidy N, Liu Y. NAD+ therapy in age-related degenerative disorders: a benefit/risk analysis. *Exp Gerontol*. 2020;132:110831.
8282. Palmer RD, Vaccarezza M. Nicotinamide adenine dinucleotide and the sirtuins caution: pro-cancer functions. *Aging Med (Milton)*.

2021;4(4):337–44.
8283. Poljsak B, Kovač V, Milisav I. Healthy lifestyle recommendations: do the beneficial effects originate from NAD^+ amount at the cellular level? *Oxid Med Cell Longev*. 2020;2020:8819627.
8284. Liu Y, Clement J, Grant R, Sachdev P, Braidy N. Quantitation of NAD+: why do we need to measure it? *Biochim Biophys Acta Gen Subj*. 2018;1862(12):2527–32.
8285. Chini EN. Of mice and men: NAD^+ boosting with niacin provides hope for mitochondrial myopathy patients. *Cell Metab*. 2020;31(6):1041–3.
8286. Conlon N, Ford D. A systems-approach to NAD+ restoration. *Biochem Pharmacol.* 2022;198:114946.
8287. McReynolds MR, Chellappa K, Baur JA. Age-related NAD^+ decline. *Exp Gerontol*. 2020;134:110888.
8288. Katsyuba E, Romani M, Hofer D, Auwerx J. NAD^+ homeostasis in health and disease. *Nat Metab*. 2020;2(1):9–31.
8289. Katsyuba E, Romani M, Hofer D, Auwerx J. NAD^+ homeostasis in health and disease. *Nat Metab*. 2020;2(1):9–31.
8290. Elysium Health. U. S. District Court invalidates Dartmouth patents asserted by ChromaDex. Cision PR Newswire. https://www.prnewswire.com/news-releases/us-district-court-invalidates-dartmouth-patents-asserted-by-chromadex-301381257.html. Published September 21, 2021. Accessed January 28, 2023.
8291. Conlon N, Ford D. A systems-approach to NAD+ restoration. *Biochem Pharmacol.* 2022;198:114946.
8292. Rajman L, Chwalek K, Sinclair DA. Therapeutic potential of NAD-boosting molecules: the *in vivo* evidence. *Cell Metab*. 2018;27(3):529–47.
8293. Conlon N, Ford D. A systems-approach to NAD+ restoration. *Biochem Pharmacol.* 2022;198:114946.
8294. de Guia RM, Agerholm M, Nielsen TS, et al. Aerobic and resistance exercise training reverses age-dependent decline in NAD^+ salvage capacity in human skeletal muscle. *Physiol Rep*. 2019;7(12):e14139.
8295. Zhou CC, Yang X, Hua X, et al. Hepatic NAD^+ deficiency as a therapeutic target for non-alcoholic fatty liver disease in ageing. *Br J*

Pharmacol. 2016;173(15):2352–68.
8296. Conlon N, Ford D. A systems-approach to NAD+ restoration. *Biochem Pharmacol.* 2022;198:114946.
8297. Koltai E, Szabo Z, Atalay M, et al. Exercise alters SIRT1, SIRT6, NAD and NAMPT levels in skeletal muscle of aged rats. *Mech Ageing Dev*. 2010;131(1):21–8.
8298. Liu LY, Wang F, Zhang XY, et al. Nicotinamide phosphoribosyltransferase may be involved in age-related brain diseases. *PLoS One*. 2012;7(10):e44933.
8299. Anderson RM, Bitterman KJ, Wood JG, Medvedik O, Sinclair DA. Nicotinamide and *PNC1* govern lifespan extension by calorie restriction in *Saccharomyces cerevisiae*. *Nature*. 2003;423(6936):181–5.
8300. Balan V, Miller GS, Kaplun L, et al. Life span extension and neuronal cell protection by *Drosophila* nicotinamidase. *J Biol Chem*. 2008;283(41):27810–9.
8301. Yoshida M, Satoh A, Lin JB, et al. Extracellular vesicle-contained eNAMPT delays aging and extends lifespan in mice. *Cell Metab*. 2019;30(2):329–42.e5.
8302. Brouwers B, Stephens NA, Costford SR, et al. Elevated nicotinamide phosphoribosyl transferase in skeletal muscle augments exercise performance and mitochondrial respiratory capacity following exercise training. *Front Physiol*. 2018;9:704.
8303. Costford SR, Brouwers B, Hopf ME, et al. Skeletal muscle overexpression of nicotinamide phosphoribosyl transferase in mice coupled with voluntary exercise augments exercise endurance. *Mol Metab*. 2018;7:1–11.
8304. Frederick DW, Davis JG, Dávila A Jr, et al. Increasing NAD synthesis in muscle via nicotinamide phosphoribosyltransferase is not sufficient to promote oxidative metabolism. *J Biol Chem*. 2015;290(3):1546–58.
8305. Dollerup OL, Chubanava S, Agerholm M, et al. Nicotinamide riboside does not alter mitochondrial respiration, content or morphology in skeletal muscle from obese and insulin-resistant men. *J Physiol*. 2020;598(4):731–54.

8306. Conlon N, Ford D. A systems-approach to NAD+ restoration. *Biochem Pharmacol.* 2022;198:114946.
8307. Costford SR, Bajpeyi S, Pasarica M, et al. Skeletal muscle NAMPT is induced by exercise in humans. *Am J Physiol Endocrinol Metab*. 2010;298(1):E117–26.
8308. Lamb DA, Moore JH, Mesquita PHC, et al. Resistance training increases muscle NAD^+ and NADH concentrations as well as NAMPT protein levels and global sirtuin activity in middle-aged, overweight, untrained individuals. *Aging (Albany NY)*. 2020;12(10):9447–60.
8309. Ruan Q, Ruan J, Zhang W, Qian F, Yu Z. Targeting NAD^+ degradation: the therapeutic potential of flavonoids for Alzheimer's disease and cognitive frailty. *Pharmacol Res*. 2018;128:345–58.
8310. Soma M, Lalam SK. The role of nicotinamide mononucleotide (NMN) in anti-aging, longevity, and its potential for treating chronic conditions. *Mol Biol Rep*. 2022;49(10):9737–48.
8311. Skidmore CJ, Davies MI, Goodwin PM, et al. The involvement of poly(ADP-ribose) polymerase in the degradation of NAD caused by γ-radiation and *N*-methyl-*N*-nitrosourea. *Eur J Biochem*. 1979;101(1):135–42.
8312. Pacher P, Szabó C. Role of poly(ADP-ribose) polymerase 1 (PARP-1) in cardiovascular diseases: the therapeutic potential of PARP inhibitors. *Cardiovasc Drug Rev*. 2007;25(3):235–60.
8313. Palmer RD, Vaccarezza M. Nicotinamide adenine dinucleotide and the sirtuins caution: pro-cancer functions. *Aging Med (Milton)*. 2021;4(4):337–44.
8314. Amici SA, Young NA, Narvaez-Miranda J, et al. CD38 is robustly induced in human macrophages and monocytes in inflammatory conditions. *Front Immunol*. 2018;9:1593.
8315. Polzonetti V, Carpi FM, Micozzi D, Pucciarelli S, Vincenzetti S, Napolioni V. Population variability in CD38 activity: correlation with age and significant effect of *TNF*-α-308G>A and *CD38* 184C>G SNPs. *Mol Genet Metab*. 2012;105(3):502–7.
8316. Conlon N, Ford D. A systems-approach to NAD+ restoration. *Biochem Pharmacol.* 2022;198:114946.

8317. Wu S, Zhang R. CD38-expressing macrophages drive age-related NAD^+ decline. *Nat Metab*. 2020;2(11):1186–7.
8318. Chini CCS, Peclat TR, Warner GM, et al. CD38 ecto-enzyme in immune cells is induced during aging and regulates NAD^+ and NMN levels. *Nat Metab*. 2020;2(11):1284–304.

8319. Larrick JW, Mendelsohn AR. Finally, a regimen to extend human life expectancy. *Rejuvenation Res*. 2018;21(3):278–82.
8320. Li Y, Pan A, Wang DD, et al. Impact of healthy lifestyle factors on life expectancies in the US population. *Circulation*. 2018;138(4):345–55.
8321. Ruby JG, Wright KM, Rand KA, et al. Estimates of the heritability of human longevity are substantially inflated due to assortative mating. *Genetics*. 2018;210(3):1109–24.
8322. Kaeberlein M, Creevy KE, Promislow DEL. The dog aging project: translational geroscience in companion animals. *Mamm Genome*. 2016;27(7–8):279–88.
8323. Scott CT, DeFrancesco L. Selling long life. *Nat Biotechnol*. 2015;33(1):31–40.
8324. Chase P, Mitchell K, Morley JE. In the steps of giants: the early geriatrics texts. *J Am Geriatr Soc*. 2000;48(1):89–94.
8325. King DE, Mainous AG III, Geesey ME. Turning back the clock: adopting a healthy lifestyle in middle age. *Am J Med.* 2007;120(7):598–603.
8326. Ma H, Xue Q, Wang X, et al. Adding salt to foods and hazard of premature mortality. *Eur Heart J*. 2022;43(30):2878–88.
8327. Cevenini E, Monti D, Franceschi C. Inflamm-ageing. *Curr Opin Clin Nutr Metab Care*. 2013;16(1):14–20.
8328. Ioannidis JPA. The challenge of reforming nutritional epidemiologic research. *JAMA*. 2018;320(10):969–70.
8329. The US Burden of Disease Collaborators, Mokdad AH, Ballestros K, et al. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA.* 2018;319(14):1444.
8330. King ML Jr. *Stride Toward Freedom: The Montgomery Story*. Harper; 1958.
8331. Mathers JC. Obesity and mortality: is childhood obesity shortening life expectancy? *Maturitas*. 2015;81(1):1–2.

8332. Ludwig DS. Lifespan weighed down by diet. *JAMA*. 2016;315(21):2269–70.
8333. Mathers JC. Obesity and mortality: is childhood obesity shortening life expectancy? *Maturitas*. 2015;81(1):1–2.
8334. Xu J, Murphy SL, Kochanek KD, Arias E. Mortality in the United States, 2015. *NCHS Data Brief.* 2016;(267):1–8.
8335. Olshansky SJ, Passaro DJ, Hershow RC, et al. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med*. 2005;352(11):1138–45.
8336. Masters RK, Aron LY, Woolf SH. Changes in Life Expectancy between 2019 and 2021 in the United States and 21 Peer Countries. Public and Global Health; 2022.
8337. Walker BR, Colledge NR. *Davidson's Principles and Practices of Medicine E-Book*. Elsevier Health Sciences; 2013:169, 170, 194, 648.
8338. Shay CM, Ning H, Allen NB, et al. Status of cardiovascular health in US adults: prevalence estimates from the National Health and Nutrition Examination Surveys (NHANES) 2003–2008. Circulation. 2012;125(1):45–56.
8339. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. 2012;125(1):e2–220.
8340. Murray CJ, Atkinson C, Bhalla K, et al. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. *JAMA*. 2013;310(6):591–608.
8341. Villines TC. Risks of the American lifestyle: insights from a trans-Pacific comparison of coronary artery calcium progression. *Circ: Cardiovasc Imaging*. 2019;12(2):e008810.
8342. Mokdad AH, Ballestros K, Echko J, et al. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319(14):1444–72.
8343. Mayo Clinic News Network. Nearly 7 in 10 Americans take prescription drugs, Mayo Clinic, Olmsted Medical Center find. MayoClinic.org. http://newsnetwork.mayoclinic.org/discussion/nearly-7-in-10-americans-take-prescription-drugs-mayo-clinic-olmsted-medical-center-find/. Published June 19, 2013. Accessed January 29, 2023.

8344. Mokdad AH, Ballestros K, Echko J, et al. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319(14):1444–72.
8345. Wansink B, Kniffin KM, Shimizu M. Death row nutrition. Curious conclusions of last meals. *Appetite*. 2012;59(3):837–43.
8346. Ezzati M, Riboli E. Can noncommunicable diseases be prevented? Lessons from studies of populations and individuals. *Science*. 2012;337(6101):1482–7.
8347. Katz DL, Frates EP, Bonnet JP, Gupta SK, Vartiainen E, Carmona RH. Lifestyle as medicine: the case for a True Health Initiative. *Am J Health Promot*. 2018;32(6):1452–8.
8348. Goldberg JP, Hellwig JP. Nutrition research in the media: the challenge facing scientists. *J Am Coll Nutr*. 1997;16(6):544–50.
8349. Keys A. Nutrition and capacity for work. *Occup Med*. 1946;2(6):536–45.
8350. Bodai BI, Nakata TE, Wong WT, et al. Lifestyle medicine: a brief review of its dramatic impact on health and survival. *Perm J*. 2018;22:17–025.
8351. Katz DL, Frates EP, Bonnet JP, Gupta SK, Vartiainen E, Carmona RH. Lifestyle as medicine: the case for a True Health Initiative. *Am J Health Promot*. 2018;32(6):1452–8.
8352. THI_About Us. True Health Initiative. https://www.truehealthinitiative.org/about_us/. Accessed January 29, 2023.
8353. Pledge of support for core principles. True Health Initiative. https://www.truehealthinitiative.org/wp-content/uploads/2021/02/THI_Pledge_2021–02–23.pdf. Published February 23, 2021. Accessed January 29, 2023.
8354. Milton K. Hunter-gatherer diets—a different perspective. *Am J Clin Nutr*. 2000;71(3):665–7.
8355. Tutin CEG, Fernandez M. Composition of the diet of chimpanzees and comparisons with that of sympatric lowland gorillas in the Lopé Reserve, Gabon. *Am J Primatol*. 1993;30(3):195–211.
8356. Beitz DC, Bauer JE, Behnke KC, et al. *Nutrient Requirements of Dogs and Cats*. National Academies Press; 2006.

8357. Roberts WC. We think we are one, we act as if we are one, but we are not one. *Am J Cardiol*. 1990;66(10):896.
8358. Nestle M. Paleolithic diets: a sceptical view. *Nutr Bull*. 2000;25(1):43–7.
8359. Walker AR. Are health and ill-health lessons from hunter-gatherers currently relevant? *Am J Clin Nutr*. 2001;73(2):353–6.
8360. Kahleova H, Levin S, Barnard ND. Vegetarian dietary patterns and cardiovascular disease. *Prog Cardiovasc Dis*. 2018;61(1):54–61.

References

For a full list of searchable citations, point your phone camera at the QR code below or go to nutritionfacts.org/book/how-not-to-age/citations. Each cited source is hyperlinked so you can read the original studies themselves.

Scan for cited sources:

Or visit:
nutritionfacts.org/book/how-not-to-age/citations

Acknowledgments

Primary appreciation goes to the researchers whose enlightenment of the natural world forms the foundation of all my work. There is no evidence-based nutrition without evidence.

Then, first and foremost, I want to thank editing extraordinaire Miyun Park, who expertly coordinated this whole massive project, with sweet potato dreams to her precious Ollie. Then gratitude for everyone every step of the way. We're so fortunate to have a veritable army of volunteer article retrievers, but standout source sleuths include Jolene Bowers, Gregory Butler, Devra O'Gara, Laura McClanathan, Julie Van Horn, and Kevin Wise. Thanks to Marie Townsley and Chrissy Liptrot for annotation compilation, Dawn Chang for citation formatting, Caroline Garriott for the figures, editors Lee Oglesby and Laura Greger (the latter of whom also did the favor of birthing the author), Christi Richards for wrangling all the citations online, Abie Rohrig for helping with promotion, and, finally, fearless fact-checking savant Alissa Finley, who regularly reminds me just how remarkably wrong I can be. (What's five orders of magnitude between friends?) Also deep appreciation to Katie Schloer for keeping NutritionFacts.org running so smoothly, Richard Pine and Bob Miller for negotiating such a great book deal in the midst of pandemic uncertainty, and the amazing charities to which that money is going to help make the world a healthier place.

Index

The index that appeared in the print version of this title does not match the pages in your e-book. Please use the search function on your e-reading device to search for terms of interest. For your reference, the terms that appear in the print index are listed below.

AARP
abdominal fat
Academy of Nutrition and Dietetics
açai berries
acarbose
acetaldehyde
acetaminophen (Tylenol)
acetic acid
acetone
acetylcholine
acid-base balance
acid reflux
AcipHex
acne
acromegaly
acrylamide
acupuncture
acute myeloid lymphoma (AML)
adrenal hormones
aducanumab (Aduhelm)
aerobic exercise
Africa
African Americans
Age-Related Eye Disease Study (AREDS)
AGEs (advanced glycation end products, or glycotoxins)
age spots

Ah receptor
air pollution
Akkermansia muciniphila
alaria (*Alaria esculenta*)
alcohol
algae
alkaline-forming foods
alkylamines
allergies
allicin
almond milk
almonds
alopecia areata
alpha-carotene
alpha hydroxy acids
alpha-lipoic acid
ALS Parkinsonism dementia complex
alternate-day fasting
aluminum
Alzheimer's
Alzheimer's Disease Cooperative Study
Alzheimer's Foundation of America
Ambien
American Academy of Anti-Aging Medicine
American Academy of Dermatology
American Academy of Family Physicians
American Academy of Orthopaedic Surgeons
American Academy of Pediatric Dentistry
American Academy of Sleep Medicine
American Association of Clinical Endocrinology
American Association of Retired Persons
American Cancer Society
American College of Cardiology
American College of Family Physicians
American College of Lifestyle Medicine
American College of Obstetricians and Gynecologists
American College of Physicians
American College of Preventive Medicine
American College of Rheumatology
American Egg Board
American Geriatrics Society
American Heart Association
American Indians
American Institute for Cancer Research
American Medical Association
American Psychological Association
American Urological Association
Ames, Bruce

amino acids
aminoglycoside antibiotics
amla
ammonia
AMPK (AMP-activated protein kinase)
amyloid beta
amyloid cascade hypothesis
anal fissure
androgenic alopecia
andropause
anemia
anesthesia
angiogenesis
angiogram
angioplasty
animal fats
animal foods
animal microRNAs
animal protein
animal-to-plant protein swap
ankle-brachial index
anorexia
antagonistic pleiotropy
anthocyanins
anti-aging industry
antibiotics
antidepressants
antifungal drugs
anti-glycation foods
anti-inflammaging
anti-inflammatories
antioxidants
antiperspirants
anxiety
apigenin
APOE ε4
appetite suppression
apple juice
apples
APPROACH (Animal and Plant PROtein And Cardiovascular Health) trial
arachidonic acid
arame
arginine
Aristotle
aromatherapy
artemisinin
arteries
arthritis

arthroscopic surgery
artichokes
artificial sweeteners
arugula
ashwagandha
Asians
asparagus
aspartame
aspirin
asthma
astragalus
atherosclerosis
athletes
athlete’s foot
Atkins diet
atrial fibrillation
Australia
autism
autoimmune diseases
autoimmune inflammation
autologous platelet-rich plasma therapy
autophagy
avocado
Ayurvedic medicine

Bacillus licheniformis
Bacillus subtilis
bacon
bacteria. *See also* microbiome
Bacteroides
baking powder
baking soda
balance
balding
Baltimore Longitudinal Study of Aging
Bama County
bananas
barberries
bariatric surgery
barley
basal cell carcinoma
basil
bathing
BCAA supplements
B cells
BDNF
beans

beef
beer
beets
bell peppers
benign prostatic hyperplasia (BPH)
berberine supplements
berries
beta-carboline alkaloids
beta-carotene
beta-glucans
beverages
bicycle helmets
Bifidobacteria
bilberries
Bilophila wadsworthia
bioflavonoids
biogerontology
bioidentical hormones
biological age
biological clock
biotin
birth defects
blackberries
Blackburn, Elizabeth
black cohosh
black cumin
black currants
black-eyed peas
black pepper
black rice
black salve
black tea
bladder
bladder cancer
blood, young vs. old
blood-brain barrier
blood clots
blood orange juice
blood pressure. *See also* high blood pressure; low blood pressure
blood rheology
blood sugar
blood tests
blood thinning
blood vessels. *See also* arteries; veins
blueberries
blue-green algae supplements
Blue Mountains Hearing Study
blue zones

BMAA
BMPEA
body fat
body mass index (BMI), ideal
body odor
Bogalusa Heart Study
Bolivia
bone density
bone fractures
bone loss
bones
Boseman, Chadwick
Botox
bovine microRNAs
bovine spongiform encephalopathy (mad cow disease)
bowel movements
BPA
brain
brain-derived neurotrophic factor (BDNF)
branched-chain amino acids (BCAA)
Brazil nuts
BRCA mutation
bread
breakfast cereals
breast cancer
breast milk
breast self-exams
breastfeeding
broccoli
Broccoli Osteoarthritis (BRIO) study
broccoli sprouts
bronchitis
brown adipose tissue (BAT)
brown rice
Brown-Séquard, Charles-Édouard
brussels sprouts
Buchinger fasting
Buck v. Bell
buckwheat
Buettner, Dan
burgers
Burkitt, Denis
butter
butyrate
B vitamins. *See also specific types*

cabbage

cadmium
caffeine
calcified aortic valve disease
calcium
CALERIE (Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy) trial
California Dried Plum Board
California Teachers Study
caloric density
caloric dilution
caloric restriction
Calorie Restriction Society
Campbell, T. Colin
Canada
cancer
cannabidiol (CBD) oil
cannabis
canola oil
capers
capsaicin
caramelization
carbohydrates
carboxymethyl-cellulose
cardamom
cardiovascular disease
carnitine
carob powder
carotenoids
carotid arteries
carpal tunnel syndrome
carrot juice
carrots
cartilage
casein
cashews
Castelli, Bill
castration
catalase
cataracts
cauliflower
caviar tongue
cavities
cayenne pepper
CD38
celecoxib (Celebrex)
celery
celery seed
cell growth
cell phone radiation

cellular senescence
Centella asiatica
centenarians
Center for Alzheimer's Disease Research
Center for Menopause, Hormonal Disorders and Women's Health
Center for Science in the Public Interest
Centers for Disease Control and Prevention (CDC)
Central America
Centrum Silver
cereals
cervical cancer
chamomile tea
cheese
chemical peel
chemotherapy
cherries
cherry juice
chia seeds
chicken
chicken pox
chickpeas
childbirth
children
chili peppers
China
China-Cornell-Oxford Project (China Study)
Chinese medicine
chlorella
chlorination
chlorogenic acid
chlorophyll
chocolate
cholesterol. *See also* HDL cholesterol; LDL cholesterol
cholesterol-lowering drugs
cholesterol oxidation products (COPs)
choline
cholinesterase inhibitors
chondroitin
choriocapillaris
Christensenellaceae
ChromaDex
chromosomes
chronic diseases
Cialis
cilantro
cinnamon
cinnamon tea
circadian rhythm

circulation
citrinin
citrulline
citrus
Cleveland Clinic
clitoris
clones
Clostridium difficile
cloves
Coca-Cola
Cochrane review
cocoa
coconut milk
coconut oil
coenzyme Q10 (CoQ10)
coffee
cognition
cognitive decline or impairment
cognitive stimulation
colds
cold sensitivity
colectomies
collagen
collard greens
colon
colon cancer
colonoscopies
colorectal cancer
colorectal polyps
Complete Health Improvement Program (CHIP)
compression stockings
constipation
Consumer Product Safety Commission
cooking
COPD (chronic obstructive pulmonary disease). *See also* emphysema
copper
corn
coronary artery disease
coronary calcium scores
Coronary Drug Project
corticosteroids
cortisol levels
cosmetic surgery
Costa Rica
Coumadin (warfarin)
COVID-19
CPAP machines
cranberries

cranberry juice
cranberry powder
C-reactive protein (CRP)
cream
creatine
Crete
Crohn’s disease
CRONies
CrossFit
cruciferous vegetables
cryostimulation
CT scans
cucumber
cumin
curcumin
Curie, Marie
cuticles
cyanide
cyanocobalamin
cycling
cycloastragenol (TA-65)
cycloheximide
cyclosporin
cysteine
cytokine storm
cytomegalovirus (CMV)

DAF-16 suppressor gene
dairy
dandelion tea
dark green leafy vegetables
DASH diet
dates
Dawkins, Richard
DDE
DDT
death, good
deferoxamine
dehydration
dementia
Denmark
dental cavities
dental enamel erosion
dental plaque
dental X-rays
dentition
dentures

depression
dermatosis papulosa nigra
desserts
detoxification
DHA
DHEA (dehydroepiandrosterone)
diabetes
  type 1
  type 2
Diabetes Prevention Program
diabetic retinopathy
dialysis
diarrhea
diclofenac sodium gel (Voltaren)
diet, optimal. *See also specific types*
dietary fiber hypothesis
Dietary Guidelines for Americans
Dietary Inflammatory Index
dietary quality index
dietary restriction mimetics
Dietary Supplement Health and Education Act (DSHEA)
diet soda
dignity
dill
DIM
dioxins
DIRECT trial
diuretic drugs
diverticulosis
DNA
DNA damage
DNA methylation
DNA repair
Dog Aging Project
dogs, as pets
Dolly (cloned sheep)
donepezil (Aricept)
Dramamine
Dr. Greger's Daily Dozen app
DrugAge database
drusen
dry eye syndrome
dulse
durian fruit
DXA (DEXA) scanning
dypepsia
dysbiosis
dysphoria

earwax
Easter Island
echinacea
E. coli
edamame
EGCG (epigallocatechin gallate)
egg cell, human
eggs
egg whites
ejaculatory disorders
elastin
elderberry
electrolytes
ellagitannins
emphysema. *See also* COPD
emulsifiers
endocarditis
Endocrine Society
endometrial cancer
endophthalmitis
endorphins
endothelial function
endothelial progenitor cells (EPCs)
endotoxins
endurance training
Enfamil
Ensure
enterotypes
EPA
Epic of Gilgamesh
epigenetics
epilepsy
Epsom salts
Epstein-Barr virus
equol producers
erectile dysfunction (ED)
ergothioneine
esophageal cancer
Esselstyn, Caldwell
essential amino acids
essential tremor
estrogen-dependent disease
estrogenic products
estrogen-like chemicals
estrogens
estrogen therapy
ethylamine
eugenics

eunuchs
European ancestry
European Association of Urology
European Food Safety Authority
European Prospective Investigation into Cancer and Nutrition (EPIC) study
exercise
exercise-induced oxidative stress paradox
exopolysaccharides
exosomes
eye color. *See also* vision

face-lifts
facial masks
facial moisturizers
facial youth serum
falls
fasting
fasting blood sugar
fasting-mimicking diet
fat, dietary. *See also* body fat; saturated fats; *and specific types*
fat cells
fat oxidation
fat storage
fecal impaction
fecal incontinence
fecal transplants
female androgen deficiency
female sexual function
femur fractures
fennel creams
fennel seeds
fenugreek
fermented foods
fertility
fetal ductus arteriosus
FGF21 (fibroblast growth factor 21)
fiber
fibrocystic lumps
50-food challenge
figitumumab
figs
fillers
finasteride (Propecia, Proscar)
FINGER (Finnish Geriatric Intervention Study)
fingernails, artificial
Finland
Finnish Mental Hospital Study

fisetin
fish
fish oil
5:2 fasting
flatulence
flavones
flavonoids
flavonols
flaxseed
flexitarians
flibanserin (Addyi)
Flomax
flossing
flour
flu
fluid restriction
fluoride
flu vaccine
FODMAP
folate
folic acid
follicular unit transplanting
Fontana, Luigi
Food and Drug Administration (FDA)
food chain, eating low on
food color
foods, best and worst
footbaths
forest bathing
FOXO gene
frailty
Framingham Heart Study
Framingham Risk Score
Franklin, Rosalind
Freedom of Information Act
free radicals
french fries
French paradox
fruit and vegetable dose-response longevity study
fruit juice
fruits
fucoxanthin
Fugh-Berman, Adriane
Fuhrman, Joel
fungal infections
fungal meningitis
fungi
furocoumarins

furosemide (Lasix)

galactagogue
galactokinase
galactose
gallbladder disease
Game Changers (documentary)
gamma-delta T cells
gargling
garlic
garlic powder
garlic supplements
gastritis
gastrocolic reflex
gastrointestinal system
gelatin
GEMINAL study
gene expression
genetics
genistein
genitourinary syndrome of menopause (GSM)
genotoxic chemotherapy
Germany
germ theory of disease
Gerontological Society of America
gerontology
gerontotoxins
geroprotectors
ghee
ginger
ginger tea
gingivitis
gingko
ginseng
glaucoma
Global BMI Mortality Collaboration
Global Burden of Disease Study
GLP-1
glucosamine
glutamine
glutathione
glycation
glycemic index
glycemic load
glycine
GNC
goji berries

gonorrhea
Good Manufacturing Practices
gooseberry
gotu kola
gout
grains. *See also* whole grains
grapefruit
grape juice
grape polyphenols
grapes
grape seed extract supplements
grape skins
graying hair
great apes
Great Protein Fiasco
Greece
green beans
green leafy vegetables
green peas
greens. *See also* dark green leafy vegetables; green leafy vegetables
green tea
green tea lotion
grip strength
groats
guava
Guillain-Barré syndrome
Guinness Book of World Records, The
gums
gut
gut leakiness
gut permeability
gynecomastia

Hadza tribe
hair
hair dyes
hair loss
hair plugs
haloalkanes
ham
hand pain
Harvard Health Professionals Follow-Up Study
Harvard Medical School Center of Excellence in Women's Health
Harvard Nurses' Health Study
Harvard Nurses' Health Study II
Harvard Physicians' Health Study II
Harvard School of Public Health

Harvard University
Harvard Women's Health Study
Hashimoto's thyroiditis
Hayflick limit
hazelnuts
HbA1c
HDL cholesterol
headaches, chronic
head injuries
healthspan
Healthy Lifestyle and Preventable Death study
Healthy Man Study
hearing
hearing aids
heart
heart attacks
heartburn
heart disease
heart failure
heart fibrosis
heart rate
heavy metals
Hegsted, Mark
height
Helicobacter pylori
hematocrit
hemoglobin
hemorrhagic colitis
hemorrhagic stroke
hemorrhoids
hemp seeds
hepatitis A vaccine
hepatitis B vaccine
hepatitis C
herbal hair loss treatments
herbal medicines
herbal sleep aids
herbal supplements
herbal teas
herbs
herniated discs
herniation
herpes (HSV)
heterocyclic amines
hiatal hernias
hibiscus
hidradenitis suppurativa
high blood pressure (hypertension)

high botanical diversity diet
high-fat diet
high-intensity interval training (HIIT)
high-nutrient density
high-protein diet
hip fractures
hip or spine T-scores
hip pain
Hippocrates
hip protectors
Hispanics
HIV
HMB
Hoffman effect
homeopathy
homocysteine
honeybees
honeybush
honeysuckle
hops
hormesis
hormone replacement therapy
hormones
hospice care
hospitals
hot dogs
hot flashes
How Not to Age Cookbook, The (Greger)
How Not to Die (Greger)
How Not to Diet (Greger)
How to Survive a Pandemic (Greger)
HPV (human papilloma virus)
human ancestors
Human Genome Project
human growth hormone (HGH)
Hunza Valley
hyaluronic acid
hydration
hydrogen sulfide
hyperfiltration
hypertension. *See* high blood pressure
hyperthyroidism
hypogonadism
hypomethylation
hypothyroidism
hysterectomies

ibuprofen (Advil)
IGF-1 (insulin-like growth factor 1)
Ikaria, Greece
illicit drugs
Imitrex
immune cells
immune suppression
immune system
immune thrombocytopenic purpura
immunoglobulin A (IgA)
immunosenescence
India
indole-3-carbinol
Indo-Mediterranean Trial
indoxyl sulfate
infant formula
infections
infertility
inflammaging
inflammation
inflammatory bowel disease
inflammatory microRNAs
insomnia
Institute for Biomedical Aging Research
Institute for Science in Medicine
Institute for the Medical Humanities
Institute of Medicine
insulin
insulin resistance
insulin secretion
insulin sensitivity
interleukin 6 (IL-6)
interleukin 10 (IL-10)
interleukin 18
intermittent fasting
intermittent vegan diet
International Osteoporosis Foundation
International Society of Sports Nutrition
interval training
intraocular pressure
in vitro fertilization
iodine
Iowa Women's Health Study
Iran
iron
irradiation of food
irritable bowel syndrome
isoflavones

isoleucine
Italy

Japan
jaundice
J curve
Jenkins, David
Jews
joints
Jumpstart program
Junctional adhesion molecule-A
junk food
JUST Egg
Justice Department

Kaiser Permanente
kale
Kame Project
kanamycin
Kaposi sarcoma
kefir
Kegel exercises
Kenyon, Cynthia
ketogenic diet
Keys, Ancel
kidney cancer
kidney disease
kidney failure
kidney fibrosis
kidneys
kidney stones
kimchi
King, Martin Luther, Jr.
kiwifruit
knees
Kraft Foods
Kremezin
Kyolic aged garlic extract

lactic acid
Lactobacillus
lactose
lactucin
lactulose
lacunar infarcts
lamb
Laron syndrome

L-ascorbic acid
laser skin resurfacing
lavender
laxatives
L cells
LDL cholesterol
lead
lecanemab (Lequembi)
lecithin supplements
Leeuwenhoek, Antonie van
legumes
lemon balm
lemon-infused water
lemon juice
lemons
lemon verbena tea
lentils
lettuce
leucine
leukemia
Levitra
libido
licorice
LIFE (Low Inflammatory Foods Every Day) Diet
lifestyle
light therapy
lignans
lima beans
Lipitor
lipofuscin
lipoid pneumonia
lipoprotein(a) [Lp(a)]
liposuction
liver
liver cancer
liver disease
liver failure
lobster
Loma Linda University
Longo, Valter
Lotrimin (clotrimazole)
lovastatin
low back pain
low blood pressure
low-carb diet
low-fat diet
low-glycemic diet
low-level laser therapy (LLLT)

low-protein diet. *See also* protein restriction
low T syndrome
lumbar disc
lung cancer
lungs
lupus
lutein
lycium berries
lycopene
lymphocytes
Lyon Diet Heart Study

Mabaan tribe
maca
MacArthur Study of Successful Aging
macrophages
macula
macular degeneration
magnesium
Maillard reaction
malaria
male hormones
male sexual function
malondialdehyde (MDA)
mammograms
MAMPs (microbe-associated molecular patterns)
mangos
manicures
manual labor
marathon runners
marjoram
Mars520 space flight
matcha
Mayo Clinic
meat. *See also specific types*
Medicare
medications. *See also* prescription drugs; *and specific types*
meditation
Mediterranean diet
melanoma
melasma
melatonin
memantine (Namenda)
memory
MeNAM
meningitis
meniscus damage

menopause
menstruation
mental health
Merck
mercury
messenger RNA
meta-analysis, defined
metabolic acidosis
metabolic disease
metabolic syndrome
metabolism
metalloestrogen
Metamucil
metastases
Metchnikoff, Élie
metformin
methionine
methionine restriction
methionine sulfoxide reductase
methylation
methylglyoxal
Mexican Americans
microbiome
microbiome and
microlife
microRNAs
migraine
milk
millet
Million Women Study
MIND diet
ministrokes
Minnesota Green Tea Trial
Minnesota Starvation Study
minoxidil (Rogaine)
mint
Miocene era
misfolded proteins
miso soup
mitochondria
mitochondrial myopathy
MMR vaccine
model organisms
Moderate Alcohol and Cardiovascular Health Trial
moles, suspicious
monk fruit
monounsaturated oils
Mormons

morphine
mosquitos
mouthwash
MRSA
MTHFR
mTOR (mechanistic target of rapamycin)
Multidomain Alzheimer Preventive Trial
multidrug-resistant bacteria
multiple sclerosis
multivitamins
Munroe, Randall
muscles
mushrooms
music
mussels
MyPlate campaign

N-acetylcysteine (NAc)
NADH
NAD+ (nicotinamide adenine dinucleotide)
nails
NAMPT enzyme
naproxen (Aleve)
National Academy of Medicine
National Cancer Institute
National Cattlemen's Beef Association
National Chicken Council
National Dairy Council
National Football League
National Geographic
National Institute on Aging
National Institutes of Health
National Osteoporosis Foundation
National Sleep Foundation
National Toxicology Program
natto
natural killer cells
Natural Science Foundation of China
naturopaths
neomycin
neroli oil (bitter orange)
nerves
Nestle, Marion
neu5Gc
neuridine
Neurobiology of Aging
neurodegeneration

neurons
neurotransmitters
neurotrophins
New Zealand
Nexium
NF-κB
niacin (nicotinic acid, NA). *See also* Vitamin B3
nicotinamide (niacinamide, NAM)
nicotinamide cream
nicotine
Nicoya Peninsula
Nigerian paradox
night sweats
NIH-AARP Diet and Health Study
nitrates
nitric oxide
nitrites
nitrosamines
NMDA blockers
NMN (nicotinamide mononucleotides)
nocturia
noise exposure
non-arteritic ischemic optic neuropathy (NAION)
noncoding RNA
non-Hodgkin's lymphoma
nonmitochondiral DNA
nori
normal pressure hydrocephalus
North American Menopause Society
Norway
NR (nicotinamide riboside)
Nrf2
NSAIDS (nonsteroidal anti-inflammatory drugs)
nutritional yeast
NutritionFacts.org
nuts

oatmeal
oat milk
oats
obesity
Okinawan diet
oleic acid
oligosaccharides
olive oil
olives
omega-3 fatty acids

omega-6 fats
omega-7 fats
oncogenes
onions
ONTRAC (Oral Nicotinamide to Reduce Actinic Cancer)
onychomycosis
opioids
optic nerve
oral cancer
oral contraceptives
orange juice
oranges
oregano
organic foods
organ transplants
orgasm
Ornish, Dean
orthopedic surgery
oseltamivir (Tamiflu)
Osler, Sir William
ospemifene
osteoarthritis
osteonecrosis of the jaw
osteoporosis
ovarian cancer
ovarian hormones
ovaries
overdentures
Over-the-Counter Hearing Aid Act
overweight. *See also* obesity
oxalates
Oxford Vegetarian Study
oxidation
oxidative stress
oxidized cholesterol
oxygen
oxylipins
oxysterols
oysters

PAHs (polycyclic aromatic hydrocarbons)
Paleo diet
palliative care
palmitic acid
palm kernel oil
palm oil
PAMPs (pathogen-associated molecular patterns)

pancreas
pancreatic cancer
pancreatitis
paprika
parabiotic studies
Parkinson’s disease
PARP-1
parsley
parsnips
pasta
Pasteur, Louis
pasteurization
Pauling, Linus
Paxil
PCBs
PCSK9 gene
peaches
peanut butter
peanuts
pears
pecans
pectin
pellagra
pelvic arteries
pelvic floor exercises
penicillin
penile arteries
penile implants
perimenopause
periodontal bone
periodontitis
peripheral artery disease
permethrin clothing treatments
persimmons
pesticides
pesto
pets
Pew Charitable Trusts
pharmaceutical industry
pH balance
Philip, Prince, Duke of Edinburgh
Philip Morris
PhIP
phloridzin
photosynthesis
phototherapy
phthalates
physical activity

physician-assisted dying
phytochemicals
phytoestrogens
phytoncides
phytonutrients
pickled vegetables
pinene
pine nuts
pippali (piperlongumine)
pistachios
pituitary gland
placebo effect
plantains
plant-based diet
plant protein
plasmids
plastics
platelet count
Plato
plums
pneumococcal disease
pneumonia
pneumonia vaccine
polio vaccine
pollutants and toxins. *See also* air pollution
polycystic ovary syndrome (PCOS)
polyethylene glycol
polygonum multiflorum
polyphenol chlorogenic acid
polyphenols
polysorbate
polyunsaturated fat
pomegranate juice
pomegranates
popcorn
pork
porphyran
porphyria
postbiotics
postherpetic neuralgia
potassium
potassium bicarbonate supplements
potassium chloride
potato chips
potatoes
poultry
prebiotics
prediabetes

PREDIMED study
prednisolone
pregnancy
Premarin
premenstrual syndrome
PremPro
prescription drugs. *See also* medications; *and specific types*
Prevacid
Prevagen
Prevotella
Prilosec
Pritikin, Nathan
probiotics
processed foods
processed meats
progeria
progesterone cream
progesterone therapy
Program to Reduce Incontinence by Diet and Exercise (PRIDE)
ProLon diet
pro-oxidants
Proscar
prostate cancer
prostate enlargement
prostate surgery
protein. *See also* animal protein; plant protein
protein restriction
Protonix
proton pump inhibitor (PPI) drugs
Prozac
PRP (platelet-rich plasma)
prunes
PSA screening
psoriasis
psoriatic arthritis
psyllium
pterostilbene
puberty
pull test
pumpkin pie spice
pumpkin seeds
P value
PVC plastics
pyrithione zinc shampoo

Q-tips
quack remedies

quadriceps muscles
quercetin

radiation
radiation therapy
radioactive products
RAGE
RAND Corporation
rapamycin
raspberries
red blood cells
red clover
red meat
red rice
red sage
red tea (rooibos)
red wine
red yeast rice supplements
refined foods
religion
Replens
reproduction
resistance exercise
resistant starch
respiratory disease
respiratory syncytial virus
resveratrol
retina
Retin-A
retinoids
retirement
Reynolds Risk Score
rheumatoid arthritis
rhubarb
riboflavin
rice
rice milk
RNA
Roberts, William Clifford
Rochester Lifestyle Medicine Institute
Rockefeller Foundation
rooibos (red tea)
roots
rose hips
rosemary
rosemary oil
rotator cuff surgery

royal jelly
Ruminococcus
running
Rush Memory and Aging Project
Rush University Medical Center
rye bread
rye groats

Sachs, Oliver
saffron
sage
salad
salad dressing
salami
salicylic acid
salmon
Salt Institute
salt (sodium)
salt substitutes
Sanofi
San Quentin State Penitentiary
sarcopenia
Sardinia
SASP (senescence-associate secretory phenotype)
saturated fat
sauerkraut
sausage
saw palmetto berry
scallops
Scarborough Fair Diet
schizophrenics
sciatica
Scripps Clinic Sleep Center
scurvy
sea buckthorn berries
seaweed
secondhand smoke
seeds
selenium
semen
senescent cells
senility
senna
senolytics
sepsis
serotonin
sesame seeds

Seven Countries Study
Seventh-day Adventists (Loma Linda)
sex life
sex toys
sexual performance supplements
sexually transmitted disease
Shakespeare, William
shark fins
shingles
shingles vaccine
shoes
short-chain fatty acids (SCFAs)
shredded wheat
shrimp
sigmoidoscopies
silent infarcts
Sinclair, David
sirtuins (silencing information regulators)
skin
skin cancer
Skin Cancer Foundation
skin lotion
skin treatments
sleep
sleep apnea
sleeping pills
smell, sense of
smoking and tobacco
smoothies
snoring
social ties
Society on Sarcopenia, Cachexia and Wasting Disease
soda
sodium. *See* salt
sodium phosphate enemas (Fleet)
sorghum
souvenaid (Fortasyn Connect)
Soviet Union
soy
soybean oil
soybeans
soy lecithin
soymilk
soy nuts
soy protein
Spanish fly
spearmint tea
Spence, J. David

sperm
spermidine
spices
spinach
spinach powder
spine
spine fractures
spirulina
Splenda
split peas
sports drinks
SPRINT MIND study
SPRINT (Systolic Blood Pressure Intervention Trial)
SSRI drugs
STACs (sirtuin-activating compounds)
Stadtman, Earl
Stamler, Jeremiah
Standard American Diet (SAD)
staph infections
starch
STAT
statins
stem cells
stents
steps, daily
sterilization
steroids
stevia
stomach cancer
stomach ulcers
Stone Age
stool softeners
stool tests
strawberries
Strehler, Bernard
strength training
strep infections
streptomycin
stress
stress hormones
stress incontinence
stress management
Stroke Prevention and Atherosclerosis Research Centre
strokes
subcutaneous fat
Successful Aging Index
sugar
sulfide

sulforaphane
sulfur
sun
sunburn
sunflower oil
sunscreen
superoxide dismutase
supplements. *See also specific types*
surgery
sweat glands
Sweden
Swedish Obese Subjects (SOS) trial
sweet potatoes
swiss chard
synergy
syphilis
Szent-Györgyi, Albert

Tabasco sauce
Tai Chi
Taiwan
TAME (Targeting Aging with Metformin) trial
tanning beds
tannins
taste
T cells
tea. *See also specific types*
tea tree oil
teeth
teff
telogen effluvium
telomerase
telomeres
tempeh
tendons
tequila
Terbinafine (Lamisil)
testicles
testicular hormones
testicular implantations
testosterone
Testosterone in Older Men (TOM) trial
testosterone therapy
tetanus vaccine
theanine
thiamin
3-MCPD

thyme
thyroid
thyroid hormone replacement
ticks
tilapia
time-restricted eating
TMAO (trimethylamine oxide)
TNF-α; (tumor necrosis factor alpha)
toenails
tofu
tolterodine (Detrol)
tomatoes
tomato juice
tomato paste
tongue
toothbrushing
tooth loss
tooth surgery
toxins. *See* pollutants and toxins
trade-off theory of aging
transcription factor 7
trans fat
trees
tretinoin
triglycerides
tropical oils
True Health Initiative
Tru Niagen
tryptophan
T-scores
Tsimane men
tuberculosis
tumor necrosis factor (TNF)
tumors
tumor suppressor gene
TUMT (transurethral microwave thermotherapy)
tuna
TUNA (transurethral needle ablation)
turkey
turmeric
TURP (transurethral resection of the prostate)
TVP (textured vegetable protein)
Twain, Mark
twenty-five-diets mega-study
27-hydroxycholesterol
twin studies
2-nonenal
Tyson, Neil deGrasse

Uganda
ulcerative colitis
ultraviolet light
United Kingdom
University of Zurich
unsaturated fats
urinary incontinence. *See also* bladder; prostate enlargement
urinary incontinence and
urine
urolithins
U.S. Army Rangers
USC Longevity Institute
U.S. Department of Agriculture (USDA)
U.S. Dietary Guidelines
U.S. Preventive Services Task Force (USPSTF)
U.S. Supreme Court
U.S. Tobacco Institute
uterine cancer
UV rays

V8 juice
vaccines
vaginal atrophy
vaginal dryness
vaginal fennel cream
vaginal hormones
vaginal lubrication
vagus nerve
valine
vanillin
varicose veins
vascular dementia
vascular disease
vascular inflammation
vegans
vegetable oils
vegetables
vegetarians
veggie Viagra effect
venison
Veterans Affairs
Viagra
Vilcabamba, Ecuador
vinegar
viruses
visceral fat
vision

VITACOG study
VITAL study
vitamin A
vitamin B3 (niacin). *See also* nicotinic acid
vitamin B6
vitamin B12
vitamin B12 deficiency
vitamin C
vitamin D
vitamin E
vitamin K
vitamin “P”
Voluntarily Stopping Eating and Drinking (VSED)
vulvovaginal atrophy

wakame
Walford, Roy
walking
walnuts
warfarin (Coumadin)
water
watercress
water filters
watermelon
Waterpiks
Wegovy
weight, ideal
weight-bearing exercise
weight control
weight loss
weight-loss diet, best
weight-loss drugs
weight-loss surgery
Wermer syndrome
wheat, purple
wheat germ
wheat grass juice
whey protein
white blood cells
white matter
white meat
white noise
white tea
white wine
whole food, plant-based diet
whole grains
whole wheat

wild game
Wilkins, Maurice
Willett, Walter
Wilson, Robert
wine
wineberries
Women's Health Initiative
World Anti-Doping Agency
World Health Organization
World Heart Federation
World Sleep Society
World War I
World War II
wormwood
wounds
wrinkles

xenohormesis
xeno-microRNAs
X-rays

Yamanaka factors
Yanomami tribe
yeast
yoga
yogurt
Yohimbine

zeaxanthin
zinc
Zoloft
zombie cells
Zostavax
zoster

Also by Michael Greger, M.D.

How Not to Die
The How Not to Die Cookbook
How Not to Diet
The How Not to Diet Cookbook
How to Survive a Pandemic

About the Author

Caroline Garriott

A founding member and fellow of the American College of Lifestyle Medicine, DR. MICHAEL GREGER is a physician, *New York Times* bestselling author, and internationally recognized speaker on nutrition. He is a graduate of the Cornell University School of Agriculture and Life Sciences and Tufts University School of Medicine. All of the proceeds he receives from his books and speaking engagements are donated to charity. You can sign up for email updates here.

www.flatironbooks.com

Cover design by Jason Gabbert
Cover images: grapes, blueberries, and spinach © Shutterstock;
nuts © iStock / Getty Images
Graphs and charts by Caroline Garriott, NutritionFacts.org

The Library of Congress has cataloged the print edition as follows:

Names: Greger, Michael, author.
Title: How not to age: the scientific approach to getting healthier as you get older / Michael Greger, M.D., FACLM.
Description: First edition. | New York: Flatiron Books, 2023. | Includes index.
Identifiers: LCCN 2023026352 | ISBN 9781250796332 (hardcover) | ISBN 9781250796325 (ebook)
Subjects: LCSH: Longevity—Nutritional aspects. | Aging—Nutritional aspects. | Aging—Prevention.
Classification: LCC RA776.75 .G744 2023 | DDC 612.6/8—dc23/eng/20230830
LC record available at https://lccn.loc.gov/2023026352

eISBN 9781250796325

Our ebooks may be purchased in bulk for promotional, educational, or business use. Please contact the Macmillan Corporate and Premium Sales Department at 1-800-221-7945, extension 5442, or by email at MacmillanSpecialMarkets@macmillan.com.

First Edition: 2023

Contents

Title Page
Copyright Notice
Dedication

Preface
Introduction
I. SLOWING ELEVEN PATHWAYS OF AGING
Introduction
AMPK
Autophagy
Cellular Senescence
Epigenetics
Glycation
IGF-1
Inflammation
mTOR
Oxidation
Sirtuins
Telomeres
Conclusion
II. THE OPTIMAL ANTI-AGING REGIMEN

Diet
Beverages
What Do Centenarians Eat?
The Mediterranean Diet
The Okinawan Diet
The Red, White, and Blue Zone
Plant-Based Eating
Lifestyle
Exercise
Weight Control
Sleep
Stress Management
Social Ties
III. PRESERVING FUNCTION
Preserving Your Bones
Preserving Your Bowel and Bladder Function
Preserving Your Circulation
Preserving Your Hair
Preserving Your Hearing
Preserving Your Hormones
Preserving Your Immune System
Preserving Your Joints
Preserving Your Mind
Preserving Your Muscles
Preserving Your Sex Life
Preserving Your Skin
Preserving Your Teeth
Preserving Your Vision
Preserving Your Dignity
IV. DR. GREGER'S ANTI-AGING EIGHT
Introduction

Nuts
Greens
Berries
Xenohormesis and microRNA Manipulation
Prebiotics and Postbiotics
Caloric Restriction
Protein Restriction
NAD+

Conclusion

Noets
References
Acknowledgments
Index
Also by Michael Greger M.D.
About the Author
Copyright