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An Evidence-Based
Approach to Longevity

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author of *The Emperor of All Maladies*

'A tour de force'

VENKI RAMAKRISHNAN,

author of *Why We Die*

AGERS

'Gripping and vitally important'

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Eric Topol



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‘Fascinating . . . expertly surveys the latest approaches to managing the diseases and decline associated with ageing.’

Financial Times

‘*Super Agers* cuts through the hype and the bogus claims. In a real tour de force, Topol has illuminated a path forward to make aging a less challenging prospect for all of us.’

Lancet

‘In a discipline as dynamic as the science of aging – with our longevity on the line, billions of dollars at stake and extraordinary claims flying around – it’s essential to establish ground truths of the sort that Dr Topol sturdily delivers.’

Wall Street Journal

‘An extraordinary book . . . Topol manages to navigate the science of aging, to distinguish it from the pseudoscience, and to provide readers an honest and measured sense of what we do and don’t know. The result is a beautifully written journey into a world that is bound to change our lives.’

Siddhartha Mukherjee, Pulitzer Prize-winning and *New York Times* bestselling author of *The Emperor of All Maladies*

‘In this highly readable and engaging tour de force, Eric Topol takes on a field full of overblown or premature claims, using his personal expertise as a physician to wade through the mass of conflicting evidence to separate fact from hype and pseudoscience, and show us a path to healthy aging. People contemplating how to make the most of their lives will benefit from reading this book.’

Venki Ramakrishnan, Nobel Laureate and author of *Why We Die*

‘Imagine a world where diseases once thought incurable are treated, where we are healthier for longer. This future is getting close thanks to a radical convergence of AI and bioscience. In this gripping, vitally important and meticulously researched account, Eric Topol reveals the extraordinary breakthroughs that are transforming medicine – and our lives.’

Mustafa Suleyman, *New York Times* bestselling author of *The Coming Wave*

‘In *Super Agers*, Eric Topol offers detailed insight into the factors that affect aging – and proof of AI’s incredible potential to advance biomedical science, promote health and extend longevity.’

Demis Hassabis, Nobel Laureate and CEO of Google DeepMind

‘Eric Topol is not only a distinguished geneticist, cardiologist, and scientist: he is the most widely read and credible health “futurist” I know. *Super Agers* is a highly readable and evidence-based digest of those astonishing advances in medicine, science, and technology that directly affect our lifespans. A landmark book.’

Abraham Verghese, author of *The Covenant of Water*

‘*Super Agers* captures the extraordinary potential of today’s biomedical revolution. With breakthroughs like CRISPR genome editing and AI intersecting accelerating at a remarkable pace, we stand at the threshold of preventing age-related diseases and unlocking new possibilities for longevity. Eric Topol’s optimistic and inspiring vision makes this book an essential guide to the future of health.’

Jennifer Doudna, Nobel prize-winning author of *A Crack In Creation*

ABOUT THE AUTHOR

Eric Topol is the executive vice president and a professor of molecular medicine at Scripps Research, the largest non-profit biomedical institute in the United States. He is also a founder and director of the Scripps Research Translational Institute and a practising cardiologist. He is one of the top ten most-cited researchers in medicine, known for his groundbreaking studies on AI in medicine, genomics, and digitised clinical trials. He was named on *Time*’s 100 Health list of the most influential people in health in 2024. Dr Topol writes the Substack newsletter *Ground Truths* and is the author of *The Creative Destruction of Medicine*, *The Patient Will See You Now* and *Deep Medicine*.

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SUPER AGERS

**An Evidence-Based
Approach to Longevity**

ERIC TOPOL



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*To my inspirational force, my family: my wife, Susan;
our children, Sarah and Evan; and our grandchildren,
Julian, Isabella, and Seneca; and to all my patients over
many decades who've given me the privilege of caring
for and learning from them, and the impetus to make
medicine better.*

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“Every man desires to live long; but no man would be old.”

—Jonathan Swift

“It is not enough for a great nation merely to have added new years to life—our objective must also be to add new life to those years.”

—John F. Kennedy

“For the first time in the evolution of life on this planet, a species has developed the capacity to edit its own genetic makeup. That offers the potential of wondrous benefits.”

—Walter Isaacson, *The Code Breaker*

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Contents

PART I THE AGE OF HEALTH SPAN	1
1. A Tale of Two Patients	3
2. It's in Your Genes?	9
3. Lifestyle+	18
PART II CHRONIC KILLERS	71
4. Obesity and Diabetes	73
5. Cardiovascular Disease	104
6. Cancer	125
7. Neurodegeneration	157
PART III GREAT IMPLICATIONS	187
8. Curing Rare Diseases	189
9. Controlling Our Immune System	208
10. Defeating Infectious Agents	229
11. Promoting Mental Health	256
PART IV THINKING AHEAD	275
12. Changing Aging	277
13. The Path Forward	318
<i>Acknowledgments</i>	331
<i>Notes</i>	335
<i>Index</i>	429

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PART I

The Age of Health Span

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A Tale of Two Patients

Mmeet my patient Mrs. L. R. She's ninety-eight years young and has never suffered a day of serious illness in her long life. She was referred to me by her primary care physician to assess her heart condition because she had developed swelling in her legs, known as edema. When we first met in the clinic, I noted there was no accompanying family member, so I asked how she got to the medical center. She'd driven herself. I soon learned much more about this exceptionally vibrant, healthy lady who lives alone, has an extensive social network, and enjoys her solitude.

Her remarkable health span isn't shared by her family members. Her mother died at age fifty-nine; her father at sixty-four. Her two brothers died at ages forty-three and seventy-five. Three years prior to our meeting, her husband had died at age ninety-seven. He had also been quite healthy, with a similar health span profile in contrast to his parents and siblings, who all had chronic diseases and died decades younger. Following her husband's death, Mrs. L. R. got depressed and dropped thirty pounds. She lost her interest in her hobbies of painting and doing one-thousand-piece jigsaw puzzles. She did continue to play cards and Rummikub every week with a circle of eight women. One of these friends suggested she move from the house she'd lived in for decades to a senior residence apartment. The move led her

to artists, new friends, and an extended social network. This all brought her back to her “old” self, fully restoring her passion for her award-winning oil painting, and doing puzzles too. I met a woman brimming with optimism with a sunny disposition and an easy laugh.

The consultation needed to determine why she had some leg edema. Although she had no history of high blood pressure, her heart was thickened on my smartphone echocardiogram and her heart muscle function was well beyond the normal range. Her ejection fraction, the proportion of blood squeezed out of the main pumping chamber with each beat, was abnormally high. I diagnosed hypertrophic cardiomyopathy of the elderly, coincidentally a condition that I had described years before in the *New England Journal of Medicine*. Her heart had become stiffened and had difficulty relaxing. This accounted for the leg edema, the treating of which was straightforward. The leg edema cleared, and she has remained without symptoms.

Mrs. L. R. exemplifies healthy aging. She is the unusual individual who has escaped all the common age-related diseases, a resilience that defies what most of us expect from the human aging process. Her extreme health span and longevity, as well as her husband's, do not appear to be related to genetic makeup. Medical scientists don't understand it, but they would conclude, from all we know about the biology of aging and process of elimination, that it's stochastic, a random stroke of good fortune.

In marked contrast, let me briefly introduce another patient of mine whom I have followed for over thirty years, who is now also ninety-eight. At age seventy-five, following coronary artery bypass surgery at age sixty-two, Mr. R. P. presented with angina. At the time, I placed two stents in one of his bypass grafts that had developed blockages, which stem from buildup of atherosclerosis that limits blood flow. He later developed rapid atrial fibrillation resistant to medications and underwent two ablation procedures to maintain a normal heart rhythm. Many years subsequently, he had a shoulder replacement and sustained a small heart attack postoperatively. At age ninety-six, he was hospitalized with COVID pneumonia and, despite a prolonged hospitalization, did not develop respiratory failure and fully recovered. Mr. R. P. represents the triumphs of modern medicine. He had severe atherosclerotic cardiovascular disease, but with repeated restoration

of blood supply to his heart and aggressive secondary prevention treatment, all was well. He embodies the medical progress we've made with age-related diseases. What's exciting now is that we can accurately forecast heart disease as well as the other major diseases of aging in high-risk individuals many decades earlier and achieve primary prevention, or, at the very least, a marked delay in their appearance. Doctors can't promise to reverse or halt aging itself, but we can promise the second half of our lives can be much healthier than our forebears'. This is the type of health span extension that we will be seeing far more commonly in the future owing to the phenomenal advances in the five dimensions I highlight throughout this book.

THE DIMENSIONS

1. Lifestyle+

Allow me to explain. We've known for a long time that lifestyle factors—diet, exercise, and sleep—play an important role in health span. But that knowledge has greatly expanded to what I call the dimension of “lifestyle+” because it now includes broadly defined environmental exposures. Being outdoors in nature, pollution, social determinants of health including loneliness, specifics of physical activity including strength, and precision dieting including time-restricted eating are all aspects of lifestyle+. The cliché “the devil is in the details” is particularly fitting.

2. Cells

The latest understanding of the nearly thirty-seven trillion cells in our body offers an entirely new range of insights. Each week researchers are publishing new work involving molecular sequencing, determining the genetic material of hundreds of thousands to millions of single cells. We understand not only their workings across time and space but also how we can manipulate and rebuild them. This changes everything. T cells can be taken out of our body and engineered to substantially rev up our immune response to cancer, or alternatively to suppress a self-directed immune response. We are

making that process faster, cheaper, and simpler by transforming a person's own immune cells inside their body. We can take an organ from another species, a heart, say, edit the genes that provoke an immune response, and potentially solve the dearth of human donor organs. We can change a person's white blood cells into stem cells and then make, for instance, pancreatic cells that produce insulin. We can even grow cells in a dish into beating, multichamber hearts—or even brains. These organoids can preview how a person's brain will respond to a treatment for cancer or neurologic conditions.

3. Omics

Within our cells and body tissue there are many layers of biologic information that have become known collectively as omics. This term originated with the study of our genome, comprised of three billion DNA letters. The other principal layers include our RNA, proteins, epigenetics (the packaging of our genome), and microbiome. In aggregate, this rich set of biological data is critical to defining our uniqueness as individuals and lays the foundation for individualized medicine.

The advances in omic science are stunning. By sequencing our DNA, we can identify common and rare gene variants that tell us about risks of major diseases well beyond our family history. Detecting tumor DNA in the plasma portion of the blood, known as a “liquid biopsy,” can enable early diagnosis and treatment of cancer; abnormal proteins or RNA can indicate the beginning of a neurodegenerative disease or the earliest sign of preeclampsia. A cluster of proteins in our plasma can tell us about the aging clock for each of our organs. The microbiome of our gut is busy sending signals to our brain and shaping our immune response.

4. Artificial Intelligence

Artificial intelligence (AI) is starting to play a pivotal role in preventing age-related diseases. We're seeing how—across all dimensions—it can precisely determine a person's risk for specific conditions and provide actionable

steps and interactive coaching. Multimodal AI integrates layers of data—electronic health records, labs, images, omics, exposure to pollution, social determinants of health, and state-of-the-art medical knowledge—to build personal medical forecasts. Virtual medical coaches have been a fantasy of primary disease prevention for decades, though it is still not yet a reality. However, Thrive AI Health, a joint initiative between Open AI and Thrive Global, may be on the way to making that dream come true.

5. Drugs/Vaccines

New drugs and vaccines are being rapidly developed because we can now predict the atomic shape of more than two hundred million proteins. You're probably familiar with generative AI's propensity to hallucinate. But that's a good thing when you exploit this bug/feature to discover new proteins that don't exist in nature and may fulfill big unmet needs in medicine. Guess where Ozempic and Wegovy came from. AI didn't invent these man-made peptides out of thin air; their discovery was based on the naturally occurring ones that circulate at low levels in our bloodstream. These and other glucagon-like peptide-1 (GLP-1) drugs have far exceeded all expectations beyond the treatment of obesity and diabetes, improving the outcomes of heart attacks, strokes, heart failure, liver, and kidney disease—and more to come. New technology developed for COVID vaccines is now being successfully applied to a broad range of diseases, including cardiovascular and cancer. We now have drugs that take immune therapy against cancer to a new level, combining highly targeted chemotherapy to avoid noxious side effects. Vaccines to supercharge our immune response against cancer are taking hold, and the flip side, to block the immune system in autoimmune diseases. For the first time, after failing for many decades, we are seeing drugs for neurodegenerative diseases.

As shown in the graph below; all five dimensions interact with one another. Our lifestyle factors influence our microbiome and cells. Our response to drugs and vaccines is modulated by our genomics and cells, and discovery of new drugs has been enhanced by gene variants and by AI. We've learned how to engineer our cells to become living drugs (fig. 1.1).

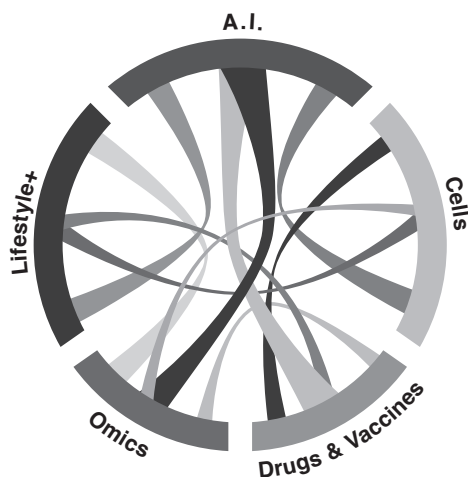


Figure 1.1. The five dimensions and their interactions

THE DRIVING FORCE

This multidimensional revolution in health span has been powered by a convergence of breakthroughs in life science and information technology. It has taken more than twenty years from the sequencing of the human genome, ten years from discovery of CRISPR genome editing, thirty years for mRNA and nanoparticle development, and many decades to get to large language AI models. Cumulatively, hundreds of years of dogged perseverance have put us in an enviable position of being able to reset our human health span expectations.

I ask you to bear with me. This book is evidence based. In some chapters the technical information is quite dense on the page. We are talking about life and death, and I know many readers feel an urgent need for the level of detail I offer. If nothing else, it will help families discuss options with their doctors. But it's my belief that these biomedical details build deep insights into our human potential.

It's in Your Genes?

For many years, my colleagues and I have been fascinated by individuals like Mrs. L. R. who are so lucky to be so resilient to diseases. In 2008, we set up a research project called “Wellderly,” to study people who were at least eighty years old and had never been sick or had a chronic illness. It took almost six years for us at Scripps Research to find fourteen hundred people who fit this extreme definition of healthy aging and consented to be participants, which meant they would provide a blood sample to have all three billion letters of their genome sequenced. We hypothesized that something in their genes would account for how these folks had such exceptional health span. I don't mean lifespan or longevity. Those measure the total number of years a person lives, whereas health span is the number of years lived in optimal health, without impairment due to disease or disability.

It turned out we were wrong. Despite the arduous and expensive task of sequencing and interpreting whole genomes several years ago, there wasn't much in their DNA to illuminate the basis for healthy aging. Their genetic risk markers for Alzheimer's and heart disease were only marginally smaller than they are for the rest of us. In contrast with the lack of novel genomic findings, this group of people, with an average age of eighty-four years, were obviously thinner, by almost thirty pounds, exercised more, and had more

education than the general population of advanced-aged Americans. The research nurse who enrolled and interviewed the participants* found the Wellderly to be remarkably upbeat people. Many had social interactions such as bridge clubs, dance, and a circle of friends; many were community volunteers. Well into their nineties, some were so busy it was hard to get an appointment to get them enrolled. Each had their own notion for why they were so healthy, despite that some were still smoking cigarettes—up to two packs a day. While our multiyear study failed to demystify the role of our DNA in attaining the most long-lived health span, it opened our minds to other factors.

Distinct from our Wellderly group of healthy aging outliers are most people; let's call them the Illlderly. In the United States, 60 percent of adults (all ages eighteen and older) have at least one chronic disease, and 40 percent have two or more. Among those age sixty-five and older, 80 percent have two or more chronic diseases, 23 percent have three or more, and about 7 percent have five or more. If you or someone you know has a chronic condition, it is probably one of the big four: diabetes, heart disease, cancer, or some kind of neurodegeneration. Beyond these, chronic lung and kidney disease are high on the list.

Who wouldn't want to live a long life? Achieving longevity obsesses many of us. But living longer with chronic conditions such as Alzheimer's, a disabling stroke, or marked frailty doesn't seem all that ideal. What we really want is for the additional years of life to be essentially free from disease. The good news is that maximizing the years of living with intact health is becoming easier. This book is about how we can achieve our maximal health span, the shift from becoming Illlderly to staying on the Wellderly path.

It can occur through two very different paths: by preventing or delaying age-related diseases or by slowing the aging process. The former is building on where we are now and for which we'll be making considerable headway in the near term. The latter, changing aging per se, is a more formidable challenge. Mrs. L. R. escaped the major chronic diseases, which only 19 percent of over four hundred centenarians (aged 97–119 years) managed to

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*The research nurse happened to be my daughter, Sarah Topol.

do in the New England Centenarian Study. The majority in that study, 81 percent, developed comorbidities, and were classified as either “survivors,” having a diagnosis of age-related illness before age eighty years, or “delayers,” diagnosed at age eighty and beyond. Preventing or markedly delaying age-related diseases, thereby extending health span, is what this book is (nearly all) about.

A Historic Convergence of Breakthroughs

The recognition of the immune system as a common mechanistic underpinning for chronic diseases, whether it be related to why they occur or to the untoward sequelae that they induce, is a historic turning point (fig. 2.1). These diseases—heart, cancer, neurodegenerative—take two or more decades to develop, giving us a longtime window of opportunity to prevent them. Atherosclerosis, which leads to heart attacks and strokes, endures, despite progress, as the number one cause of death and disability globally. It is due to inflammation in blood vessel walls, and all inflammation is generated by our immune system. Cancer isn't usually a killer unless it spreads, and our immune system can stop that from happening. If there weren't inflammation in the brain, it would be difficult for conditions like Alzheimer's or Parkinson's to take hold. When our immune system engages in self-directed attack on our body tissue, be it the nervous system in multiple sclerosis, or joints in rheumatoid arthritis, it becomes the foundation for autoimmune conditions. Dysfunctionality in our immune response is a principal driver of accelerated aging. Only in recent years have we begun to develop tools to handle the delicate modulating of our immune and inflammatory response. It's like a Goldilocks story whereby too little is not good and too much is bad, so we must get it just right—and target the precise tissue in the specific patient under care. Happily, the science of fine-tuning this pathway is rapidly advancing.

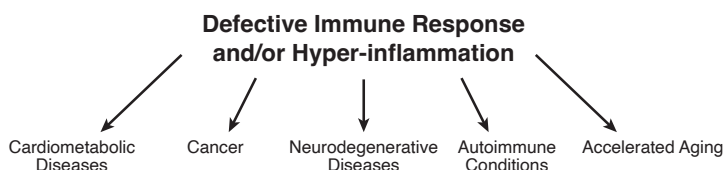


Figure 2.1. The common thread underlying major diseases and accelerating aging

There are other pathways. Transplanting feces between people started to be pursued as a treatment in the 1950s, but only in recent years has there been unequivocal proof of its lifesaving capacity, leading to its FDA approval in 2023 to prevent recurrent *Clostridium difficile* infection, which can result from antibiotics changing the balance of bacterial species on the gastrointestinal tract. Fecal microbial transplant has a “yuck factor,” obviously. It hasn’t been easy either. But now “crapsule” pills have been produced and are in clinical trials, not only to make it easier but also to extend its use for managing various conditions such as cancer, gastrointestinal diseases, and diabetes. The idea of “CRISPR-ing” or editing the gut microbiome is being explored too.

Our immune white blood cells designated as T, which derive their name from our thymus gland’s role in training them, are fundamental for fighting infections, differentiating between our own proteins and foreign proteins, and protecting us from diseases, such as cancer. T cell engineering, with or without genome editing, is emerging as a treatment for “liquid” tumors, blood diseases like leukemia, and is in early testing for hard-to-treat solid tumors, like pancreatic cancer. While it was previously considered far too expensive and impractical, the “off the shelf” potential has altered that perception.

The reversal of scarring (fibrosis) that occurs in many organs, previously considered as irrevocable, is being actively pursued in clinical trials with engineered T cells, known as chimeric antigen receptor (CAR-T) treatment, and new drugs, one of which was discovered using generative AI. CAR-T directed against fibrosis was used in mice to restore heart function. It was also used to achieve long-term remission of asthma and in the experimental

model of multiple sclerosis to deplete a specific type of T cell population that attacks the body's cells. This groundbreaking work is not just in animal models: a single shot of engineered T cells has achieved remissions, without the need for immunosuppression therapy, in patients with lupus and other autoimmune conditions.

In the short term, we're going to get much smarter about individualized, optimal diets, with a \$189 million investment by the National Institutes of Health (NIH), building on prior knowledge that each of us responds to food quite differently. Here the use of AI to help develop algorithms for what I call Diet 2.0 is likely to represent a challenge to the old food pyramids and one-size-fits-all food recommendations—as if all human beings are the same.

With the astounding effectiveness of human papilloma virus vaccines to prevent cervical cancer, and COVID vaccines for preventing hospitalizations and deaths during the pandemic, there is keen interest to build on these successes. When it comes to empowering the immune response against cancer, there have been multiple reports that a vaccine directed to a person's cancer cell proteins, known as neoantigens, can increase successful treatment beyond the existing drugs known as checkpoint inhibitors. Ultimately, there will be cancer vaccines produced to prevent specific cancers in people at high risk or show the earliest molecular signs of onset (such as via a liquid biopsy), but these will require a jump from current efforts that are directed at augmenting the immune response in people who have already developed cancer.

Well before we get cancer vaccines, we will see a shakeup in how we do cancer screening. Today, this is largely based on age as the dominant factor, which means if you are in *this* age group, get *that* screening. But only 14 percent of cancers in the United States are detected via mass screening, an expensive and inefficient method, which also induces considerable anxiety due to a preponderance of false positives. We're also seeing a significant rise in cancer among young people, such as colon cancer in people in their twenties, which is well below the age threshold for screening. With the help of AI analysis of multiple layers of data from a person's health records, we can identify people at increased risk, irrespective of age. There is

no need to screen people who have no—or extremely low—risk of cancer. Accurate prediction of high-risk status for major conditions like cancer and Alzheimer's that we can act on means we can live longer, healthy lives. Just integrating the information from our genes with our gut microbiome has substantially increased our medical forecasting capability across common chronic diseases.

We're already seeing preclinical evidence of vaccines putting the immune system in a kind of low gear that will likely be very useful for preventing or controlling autoimmune diseases. This approach applies to a wide range across type 1 diabetes, multiple sclerosis, and inflammatory bowel disease. Creating drugs and finding vaccines for prevention of Alzheimer's disease and other neurodegenerative conditions have been the most vexing challenges, supplying a graveyard of hundreds of failed attempts. Even the ones that have recently garnered FDA approval have modest efficacy, at best. The relentless pursuit of this vital objective, especially with accelerated AI drug discovery, will someday lead to powerful interventions to block neuroinflammation and destruction of brain tissue. CRISPR genome editing, which has been approved for conditions that were previously untreatable but can now be cured, may help. CRISPR stands for clustered regularly interspaced short palindromic repeats, a certain pattern in our genetic code we hadn't noticed at all until 1987. The CRISPR pioneer and Nobel Laureate Jennifer Doudna posed this intriguing question: "Could we protect people who have a genetic susceptibility to Alzheimer's from getting it by using CRISPR to alter the genes that might be causing that predisposition, and doing it early, before somebody is already kind of in the throes of dementia?"

Over the decades, I've had the opportunity to do patient-oriented research for advances in biotechnology in large randomized trials, novel monoclonal antibodies, biosensors, genome sequencing, and genome editing of stem cells. While I've long been a skeptic that we'd *ever* see antiaging drugs, as opposed to drugs that treat specific diseases that mostly afflict those in later life, I've changed my mind. From the billions of dollars of investment in advancing the science of aging and start-up companies with top-flight scientists, I've become convinced that we're in the early stages of

realizing that big audacious goal. It's an important reason I thought writing this book was warranted. Unfortunately, a lot of the hype right now is misplaced, not aligned with evidence in people, and can put the progress and the field at risk. Well before such systemic interventions against aging itself kick in, we'll be making major advances chipping away at the prevention of age-related diseases. That's the realistic and attainable counter to aging that is starting to blossom.

Let me emphasize up front that certain points of progress I mention in the chapters ahead may seem far off, as much as fifteen years away. However, keep in mind that I'm referring to the time when these changes will likely be incorporated into medical practice. That doesn't mean you wouldn't have the opportunity to take advantage of some of these now, which I'll identify, such as upending your cancer screening plan, using AI to help make a diagnosis or as a second opinion, or manipulating your gut microbiome. Furthermore, your knowledge about many of the potential health span expanders now will raise awareness when they can be available to you or your family, even when they are in research protocols, well before their general acceptance.

OBSTACLES

Health inequities across society are a profound problem in the United States, no less globally. If health span expanders are only accessible to the wealthy, then all they will do is make those inequalities worse. The lack of universal health care in the United States, unique among high-income countries, is holding us back. Genome editing for sickle cell anemia or GLP-1 drugs for obesity come at a high cost, making them less available to the people who can benefit the most. Efforts to improve health span for everyone must prioritize reducing and ultimately eradicating these gaps. We're beginning to see dedicated efforts to deliver these technologies to the underrepresented, such as mental health apps, AI diagnosis of retina disease in diabetics, or accelerated AI adoption for smartphone ultrasound imaging in low- and middle-income countries. Addressing narrow cultural biases that are embedded in AI models requires far more attention.

I reference results from the UK Biobank study of 502,000 participants many times in this book. With the participants' genome sequence, electronic health records, medical scans, and extended follow-up now approaching twenty years, the study has yielded seminal new insights for promoting health span. However, it is not a diverse population, with 94 percent of the participants of white ethnicity. We must have such resources that are multiancestry, and the All of Us initiative in the United States, the largest investment for a medical research program in our history, is pulling that together. I'm pleased to be a significant contributor to that effort.

Medical researchers face unnecessary delays in getting protocols approved and fulfilling enrollment targets, which adds up to great expense. There has been much effort to foster open science and broad collaboration, but we still have far to go. Generative AI firms protect their most important and valuable models, which is understandable, but this is a serious obstacle to health care developments.

We saw how Operation Warp Speed, with a nominal investment of \$12 billion in 2020, markedly accelerated the mass production and validation of COVID vaccines within ten months from the time the SARS-CoV-2 virus genome was first genetically sequenced. That investment was small compared with the increase of morbidity and loss of lives that would have occurred were highly effective vaccines not rapidly available. This was unprecedented in two ways: first, how fast a vaccine was produced and shown to be highly effective, which on average takes eight to ten years; and second, that the government invested to such an extent in a public-private industry partnership. Surely expanding the human health span is as worthwhile as halting the growth of one killer virus?

Compelling proof from medical research is difficult to come by without substantial dedicated funding. That validation is essential for acceptance in the medical community—doctors themselves must trust the evidence and be willing to change medical practice. Historically, the medical community has been resistant to change, especially when it involves ceding more responsibility to patients. The resistance to change is amplified by the need for regulatory approvals and the challenge of coming up with new

reimbursement paths. These barriers add up to years lost in contradistinction to the number of years of health span that we could gain.

We have preliminary data to get us to some of the most far-reaching objectives of preventing serious age-related diseases. You may have felt, like I have, that you were dealt “bad genes” from your parents. For me, it was a father who went blind from autoimmune diabetes by age forty-nine and a mother who died of cancer in her early fifties. How can we be optimistic with such family histories? We now have more accurate ways to assess a person’s risk for nearly all the major, common diseases, and these assessments will keep getting better. So too will our ability to prevent a dreaded condition from ever showing up or squashing it once it does. With the confluence of so many extraordinary biomedical and tech advances at once we are poised to move the needle and extract many more high-quality, healthy life years. To transform health span as we know it. I’m eager to share with you my excitement, along with notes of concern, for how we’ll augment the second half of our lives and come to be counted among the Wellderly. Soon, there will be many more people like Mrs. L. R. and Mr. R. P.

Lifestyle+

Biomedical technologies and new expertise are transforming how we think about the second half of our lives, but we need to look first at the category of new knowledge that might sound a little old-fashioned. In part to dispel that impression, I've added "+" to the word lifestyle.

When we get into discussions of "healthy lifestyle," it usually refers to diet, exercise, sleep, and intake of alcohol, coffee, and tobacco. My much broader definition, lifestyle+, adds environmental conditions such as exposure to toxins including air pollution, microplastics, forever chemicals, socioeconomic status, loneliness, and social isolation. Thinking about diet must now include consideration of ultra-processed food, time-restricted eating, and the optimum amount of daily protein for you specifically. Exercise means more than aerobic fitness; it includes good posture, resistance weight training, and that which maintains your sense of balance along with more standard notions. The reason to address this dimension first is that many more healthy years can be added to our lives without fancy, expensive technology.

The studies that have been done on diet, exercise, and sleep are predominantly observational studies from large cohorts. Why? It is extremely difficult to randomly assign a lifestyle to a person and expect compliance

for many years going forward. Instead, we observe “real-life” statistics in the wild rather than contrived experimentally focused studies. But these large real-life cohorts rely on imprecise data, such as food diaries or self-reported memory for nutritional intake, physical activity, or sleep. Nonetheless, collectively they comprise an enormous body of evidence that can illuminate an “association” when there is a consistent pattern of benefit or harm, often with respect to magnitude of effect, across multiple reports. This does not establish a cause-and-effect relationship but merely a link that is supported by analytics adjusting for any confounding factors. The problem with such adjustments is that even the cumulative, small effects of confounding factors can be important, and some factors are simply overlooked. Many such studies suggest there is an effect on “all-cause mortality,” meaning it doesn’t matter what exactly a person died of—their heart condition, cancer, or some other disease. Nevertheless, all-cause mortality numbers are meaningful because they suggest there are real negative health effects via yet undiscovered pathways. Evidence from randomized trials, which are typically much smaller with more limited follow-up, deserve extra credence because they can provide a causal relationship about the intervention.

DIET

The aphorisms “You are what you eat,” which dates to 1826, and “Let food be thy medicine and medicine be thy food,” misattributed to Hippocrates, reflect the long-standing belief in the vital importance of diet. A systematic assessment across 195 countries concluded that a poor diet is linked to 22 percent of all deaths, which accounts for more deaths around the world than tobacco, cancer, hypertension, or any other medical condition or health risk. So, what is a healthy diet? There are over sixty thousand diet books on Amazon, yet the evidence remains thin for what constitutes the best healthy diet, no less the presumption that it should be the same for all people. The global diabetes epidemic has been fueled, at least in part, by our diet, but the often-overlooked heavy influence of Big Food, an oligopoly of multinational corporations, must be recognized.

Ultra-Processed Foods

Big Food makes a lot of these. Of course, it is not just how much you eat but what you eat. Ultra-processed foods (UPFs) are like UFOs; they are alien, industrially produced, unnatural substances; they're not even food. I'm not going to name brands of foods, but they are not what you'd find in a standard home kitchen to make meals from. There are basically two major dimensions—chemical and physical—by which industrial processing does its damage. First, these foods and beverages contain additives and industrial ingredients. It's a long list, but here are some of the chemicals you should avoid or limit: coloring agents, sweeteners such as maltodextrin, high-fructose corn syrup, fruit juice concentrates, dextrose, lactose, artificial sweeteners, hydrogenated oils, palm oil, calcium propionate, soy protein isolate, modified starches such as maltitol, calcium caseinate, hydrolyzed beef gelatin, and emulsifiers such as soy lecithin, xanthan gum, guar gum, and diacetyl tartaric acid esters of mono- and diglycerides.

Second, the manufacture of these foods involves physical changes in texture and form—molding, extrusion, prefrying—to maximize digestibility and accelerate digestive tract absorption, which in turn produces spikes in blood glucose and insulin. That's the opposite of dietary fiber, which slows digestion, reduces glucose spikes, and does us a lot of good.

Extrusion cooking requires temperatures above 100°C and shear forces that “melt” or “extrude” food that is then molded into chips, snack bars, cookies, breakfast cereals, packaged pizzas, chicken nuggets, and doughnuts. Contaminants from packaging with such substances as bisphenols, mineral oils, and phthalates are not recognized in an otherwise helpful classification system known as NOVA: Group 1-unprocessed, Group 2-processed culinary ingredients, Group 3-processed foods, and Group 4-ultra-processed.

NOVA Food Classification			
Unprocessed or Minimally Processed Foods	Processed Culinary Ingredients	Processed Foods	Ultra-Processed Foods
Foods that did not undergo processing or underwent minimal processing techniques, such as fractioning, grinding, pasteurization, and others	Obtained from minimally processed foods and used to season, cook, and create culinary dishes	Unprocessed or minimally processed foods or culinary dishes that have added processed culinary ingredients; necessarily industrialized	Food products derived from foods or parts of foods, being added cosmetic food additives not used in culinary

Adapted from <https://www.theurbanco-op.ie/blogs/nova-food-classification>

In a much-referenced randomized trial by Kevin Hall and colleagues at the inpatient NIH Clinical Center, two groups were given either unprocessed foods or ultra-processed foods for fourteen days (fig. 3.1). Participants could eat as much as they desired. It is no surprise which group ate an extra five hundred calories a day, mostly of carbohydrate and fat, with a significant change in weight gain. The explanation for this overeating of ultra-processed food likely involves the disruption of gut-brain signals that unprocessed food conveys to the brain.

Eating ultra-processed food is associated with a markedly heightened risk of cardiovascular and metabolic diseases. These foods induce abnormal lipid levels, insulin resistance, and systemic inflammation. Furthermore, a diet rich in these foods is linked to 80 percent elevated risk of metabolic syndrome, 40 percent higher risk of type 2 diabetes, 23 percent increased risk of hypertension, 55 percent risk of obesity, and 66 percent risk of cardiovascular death. Increasing UPF in the diet leads to higher risk of cardiovascular, coronary artery, and cerebrovascular disease. Among older adults, a mere 10 percent increase of UPF intake is associated with a 16 percent increased risk of cognitive impairment. Regular consumption of ultra-processed red meat, such as bologna, bacon, sausage, and hot dogs, has been associated with a 14 percent higher risk of dementia. There is a remarkable dose-response curve.

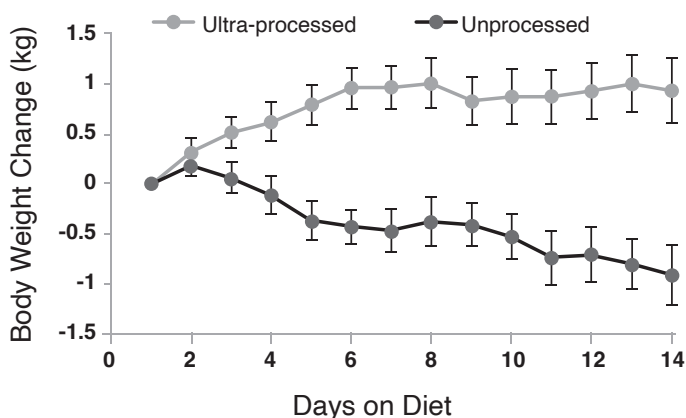


Figure 3.1. A randomized trial showed that participants who ate an ultra-processed food diet gained weight compared with those who consumed an unprocessed food diet and lost weight. Adapted from Kevin Hall et al., “Ultra-processed diets cause excess calorie intake and weight gain: An inpatient randomized controlled trial of ad libitum food intake,” *Cell Metabolism* 30, no. 1 (July 2019): 67–77 e3, <https://doi.org/10.1016/j.cmet.2019.05.008>.

It’s not just a matter of cardiovascular or metabolic or cognitive disruption. UPFs are associated with fatty liver disease, most types of cancer, sleep disorders, inflammatory bowel disease, depression, and dementia. A 62 percent increase in all-cause mortality is linked to more than four servings per day of UPF. This was echoed by a comprehensive review of forty-five studies involving a thirty-year follow-up of about seventy-five thousand women and nearly forty thousand men.

My friend Chris van Tulleken, a British physician-scientist who wrote the outstanding book *Ultra-Processed People*, conducted an experiment on himself. He increased his diet from 20 percent to 80 percent ultra-processed food for a month, with extensive baseline and follow-up assessments, including MRI brain scan and lab tests for lipids and inflammation. He gained fifteen pounds. As he put it to me, “There were enormous changes in connectivity between the habit, automatic behavior bits at the back in the

cerebellum and the reward addiction bits in the middle of the limbic system and associated brain regions.” Chris’s hunger hormones went sky high, such as a fivefold rise in leptin, and there was a doubling of his C-reactive protein that tracks with body-wide inflammation. Being hungry and swollen doesn’t sound fun.

Chris and his identical twin have had whole genome sequencing that indicated they have many genomic variants that predispose them to obesity. However, when his twin brother, Xand, followed the same diet of ultra-processed foods, he got forty-four pounds heavier than Chris. That represented the biggest weight difference in the very large twin study conducted in the United Kingdom. Once again, it’s not all in the genes.

For healthy aging, UPFs must be restricted in your diet to the lowest level possible.

That’s why it’s so important to read labels and select items without additives, without added or fake sugars, with as few ingredients as possible. If there’s a health claim, beware. High UPFs are usually found in the middle aisles of grocery stores, which explains the helpful tip to do most shopping in the perimeter for fresh foods. When there’s a question, consider using the Open Food Facts app, developed in France with the help of tens of thousands of volunteers providing information for about three million substances.

Why hasn’t the United States joined other countries like Brazil, Israel, Belgium, Chile, and Uruguay in publishing guidelines for people not to eat UPFs? There could be demands to reformulate UPFs, but that’s not happening. In the United States, the multinational corporations behind Big Food have a supersized chokehold influence on the Department of Agriculture. Big Food spends twice as much lobbying the government as the tobacco and alcohol industries combined. The *F* in FDA stands for Food, but there is little evidence that our regulatory body has true oversight and authority about potentially toxic constituents that we’re eating. There’s not even heightened UPF awareness led by the FDA or other public health agencies. In late 2023, the FDA proposed banning brominated vegetable oil, a food additive found in beverages for a century that was previously banned in Japan and Europe. Likewise, Red Dye No. 5 (found in candy), propylparaben (found in baked goods), and potassium bromate (found in packaged breads) have been

banned by the European Union because they are all linked to serious health problems. In the United States, only California approved such a ban for all four of these additives, but that won't take effect until 2027. Recall how it took the United States multiple decades after Europe to ban trans-fat foods, despite unequivocal evidence of cardiovascular harm.

Over time, it is quite likely that ultra-processed foods will be regarded as akin to cigarettes; public awareness of their dangers were suppressed for decades. Realistically, UPFs will not be banned, but there could be regulations enacted to reduce their toxicity and to enforce conspicuous labeling on all foods and beverages that spotlight their risks. Such labeling worked well in terms of public health for cigarettes.

Sweeteners

While sugar activates our dopaminergic reward circuits and provides hedonic value, too much of a good thing is clearly bad. The biggest source of added sugar in diet is from sugar-sweetened beverages. There are fifty grams of simple sugar in a can of Coca-Cola, and forty-four grams in a Starbucks Frappuccino. As seen in a large cohort of more than thirteen thousand people age forty-five and older, followed for six years, consumption of high sugary beverages, including fruit juices, was associated with a 24 percent increased all-cause mortality. This finding was independently replicated and extended by several other studies, in much larger cohorts and with longer follow-up, for both increased cardiovascular and cancer-related mortality. Notably, atrial fibrillation increased more than threefold during a ten-year follow-up among the two hundred thousand participants who drank more than two liters per week. The consistency of all the reports indicate that consumption of sugary beverages should be limited, and this includes moderating the intake of fruit juices for children. The evidence for fueling the burden of oral diseases including cancers and dental caries is also clear.

The story of nonnutritive, artificial sweeteners is a bit more complicated, with conflicting reports regarding the many nonsugar substances. A comprehensive review of all the available data from randomized and

observational studies found a lack of compelling evidence for associated risk. In contrast, another large cohort of more than one hundred thousand people found a direct association between consuming such sweeteners, particularly aspartame, acesulfame potassium, and sucralose, with cardiovascular and cerebrovascular disease risk. But that was not the case when different artificial sweeteners were examined separately through a randomized trial. In 120 healthy adults given saccharin, sucralose, aspartame, and stevia, versus controls for two weeks, the first two sweeteners induced impaired glucose regulation (also known as glycemic response), and all four were associated with changes in the oral and gut microbiome. Previous work has shown that such alteration of the gut microbiome is tied to the abnormal glycemic response. Overall, the data for artificial sweeteners is unfavorable, although it is not nearly as worrisome as high sugar consumption. Certain sweeteners, such as stevia, appear to be less concerning than others.

Salt

While the magnitude of the effect is debated, the link of sodium intake to hypertension is clear. A review from the Cochrane Library of all available data from 195 interventions studies that compared low- versus high-sodium diets concluded the effect of restriction was small, with a decrease in mean blood pressure of only 0.4 mm Hg, slightly greater among Black and Asian participants. In treating innumerable patients for hypertension over a few decades, I've seen that reduction of dietary sodium can help reduce blood pressure, as confirmed in many studies, but the impact varies considerably and may be small in many. An extensive analysis of sodium intake suggested moderate consumption (1–2 teaspoons of salt; 2 g of sodium = 5 g of salt) was not a problem. But increased cardiovascular risk became obvious at levels of more than 5 grams of sodium per day. Recommendations from the American Heart Association, World Health Organization, and European Society of Cardiology vary considerably, from 1.5 grams to 2.25 grams per day. By the same metric, the average American's intake is about 3.5 grams!

The risks from dietary sodium are not confined to high blood pressure. Multiple experimental model studies support high salt diet's reduction of

blood flow to the brain through dysfunction of the blood vessel wall (endothelium) and potential risk of cognitive impairment. The finding that people who consume the least amount of sodium have the lowest risk of cardiovascular disease has been backed up by other studies.

The best general advice for people with hypertension is to avoid or limit adding salt to foods, to keep an eye on overall intake by paying attention to food labels, and, when no kidney disease is present, to consider using a potassium chloride salt substitute. The evidence for salt substitute from a randomized trial of more than six hundred participants with normal blood pressure, average over seventy years of age, is encouraging—there was a 40 percent reduction of hypertension. A systematic analysis of the evidence for long-term salt substitution supported reduction of all-cause and cardiovascular mortality. The lower, the better is easy to say. I acknowledge Sir George Pickering's perspective from 1961: "The rigid low-sodium diet is insipid, unappetizing, monotonous, unacceptable, and intolerable. To stay on it requires the asceticism of a religious zealot."

Carbs, Protein, and Fat

The emergence of the term *carbotoxicity* conveys the multiplicity of risks associated with excessive intake of carbohydrates. As with everything, moderation is the ticket: both low, less than 40 percent, and high, greater than 70 percent, daily caloric intake are associated with increased all-cause mortality. Much of the relationship can be affected by the type of carb, with good comprising resistant starch and other high-quality carbs in the form of dietary fiber. From 185 prospective studies, 58 randomized clinical trials, assessing dietary fiber of 25–30 grams per day, there was an association with a 15–30 percent reduced all-cause and cardiovascular mortality, type 2 diabetes, and colon cancer.

In contrast, low-quality carbs are fast-digesting, like the sugars we've covered. They also include potato products, or refined grains, which are a high glycemic load, raising insulin levels and predisposing to weight gain. A high glycemic index diet among more than 157,000 people ages thirty-five to seventy years on five continents was associated with more than a

25 percent increase in cardiovascular deaths. Good, unprocessed carbs of nonstarchy vegetables, legumes, fruits, and whole grains are the ones to give priority.

Much of the current guidance via the National Academies' Recommended Dietary Allowance (RDA) for protein intake is based on relatively scant evidence, mostly from short-term nitrogen balance studies in young adults, underestimating what is needed in older individuals and longer term. The recommended daily intake of protein is 0.8 gram per kilogram of weight, 11 percent of total energy. You can get your somewhat personalized Dietary Reference Intakes calculated; my US Department of Agriculture recommendations are shown in the table below (vitamins and minerals are not listed). When I put in parameters for a much younger man, the output didn't change very much, and the estimated daily caloric needs is highly influenced by your input of "active" or "very active." The protein RDA is remarkably low, and that will not help prevent loss of muscle mass with age—by age eighty, the average person will lose eight kilograms of muscle from their peak. The evidence suggests that for older adults, higher protein intake is needed, but the optimal amount is unknown.

My US Department of Agriculture Recommendations	
Body Mass Index (BMI)	23.6
Estimated Daily Caloric Needs	3,544 kcal/day

MACRONUTRIENTS:

Macronutrients	Recommended Intake Per Day
Carbohydrate	399–576 g
Total Fiber	30 g
Protein	69 g
Fat	79–138 g
Saturated Fatty Acids	As low as possible while consuming a nutritionally adequate diet
Trans Fatty Acids	As low as possible while consuming a nutritionally adequate diet
a-Linolenic Acid	1.6 g

Macronutrients	Recommended Intake Per Day
Linoleic Acid	14 g
Dietary Cholesterol	As low as possible while consuming a nutritionally adequate diet
Total Water	3.7 L (about 16 cups)

(<https://www.nal.usda.gov/human-nutrition-and-food-safety/dri-calculator>)

Some doctors, like Peter Attia, have advocated for intake of one gram per body weight in pounds (not per kg), which has not been substantiated by evidence. Indeed, a study of high-protein diets in people and mice warned of the danger of promoting atherosclerosis through an increase in plasma leucine, an essential amino acid building block of proteins, and impaired cellular waste disposal (autophagy). The gut microbiome of people who consume a high-protein diet (more than 1.5 g/kg) has been shown to produce pro-inflammatory metabolites. While increasing your diet up to 1.2 gram/kilograms of protein is reasonable, it's the leucine-rich animal proteins that should be avoided. High-protein diets are intended to reduce the risk of sarcopenia—age-related loss of muscle mass and strength—which has been unequivocally demonstrated (in many studies, such as quantifying handgrip) is a well-established risk factor for reduced health span. We don't know that increasing protein in the diet with age titrates or negates that risk, which would require a randomized trial with multiyear follow-up that will likely never get done. (That's because randomized trials of diets are extremely hard to do at scale; also, it's difficult to rely on participants' long-term adherence and difficult to obtain financial support.) Furthermore, there's no information on food labels about the specific amino acids (nine of the twenty) in our diet that we require because we can't synthesize them—such as leucine, lysine, and methionine. Note that the recommendations above break down fats but not proteins. The hard truth is that we could be doing so much more to upgrade our knowledge of dietary protein intake that's not being done.

Like sugar, there is a dedicated gut-brain reward circuit for fat intake conveyed through the vagus nerve. Separately, the fat circuit encourages more caloric intake, but it is synergistic with the sugar reward circuit for

promoting dopamine release and overeating. Single-cell studies identified that the vagal neurons involved in the circuit, when silenced, abolished fat intake preference. Just as we've seen with salt, carbs, and proteins, there's no shortage of uncertainty. Take dairy products, a source of saturated fat, for example. The guidance to steer us to low-fat milk and yogurt dates back to 1980 and has never been updated. A 2018 report in more than 130,000 people from twenty-one countries followed for nine years found that consumption of two or more servings of dairy daily was associated with 22 percent less cardiovascular disease and 17 percent less all-cause mortality, with a greater reduction in those with greater whole fat dairy consumption. That same year a report from more than sixty thousand adults tracked for an average of nine years found a 29 percent reduction in type 2 diabetes related to greater dairy intake. Particularly yogurt (without sweeteners) and cheese (harder like cheddar or parmesan for slower absorption) have been most associated with better outcomes, which coincides with some current recommendations for three servings of dairy per day, with one or two made up of yogurt or cheese.

A running theme here is that the subtype of each macronutrient—carbs, protein, or fat—matters. The relationship to all-cause mortality demonstrated among more than 125,000 adults followed for up to thirty-two years is shown in figure 3.2. Note that the shift to unsaturated mono- or polyunsaturated fats is accompanied by more favorable longevity data. The shift from saturated fats to plant-based unsaturated fats was associated with substantial reduction of risk of cardiovascular and type 2 diabetes in four clinical trials.

In the influential *Science* magazine paper “Dietary Fat: From Foe to Friend?” by David Ludwig and colleagues, the answer depends on the quality of the fat, not so much the content level. The ketogenic diet, which relies on high fat, less than 10 percent carbs, and less than 20 percent protein, has been popular for weight loss. But it is also associated with higher cholesterol and cardiovascular risk, brain fog, flu-like illness (keto-flu), and promoting fatty liver disease. A randomized trial at the NIH Clinical Center compared a ketogenic diet (76 percent fat, mostly animal based) with a plant-based, low-fat diet with no limit on the amount of food eaten. Although it presented

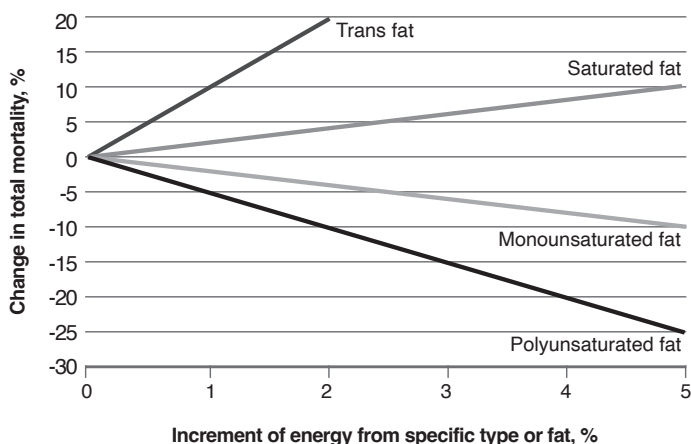


Figure 3.2. Relationship of dietary fat sources and total mortality. Adapted from Dong Wang et al., “Association of specific dietary fats with total and cause-specific mortality,” *JAMA Internal Medicine* 176, no. 8 (August 2016): 1134–45, <https://doi.org/10.1001/jamainternmed.2016.2417>.

less glycemic load to the participants, the ketogenic diet led to about seven hundred calories more ingested per day over two weeks. So it is not surprising that the low-fat diet group lost more weight. This small, rigorous trial defied the expectation for the carbohydrate-insulin model, which shows higher insulin driving more hunger and food intake. A fascinating study in mice showed a high-fat-diet-induced mitochondrial dysfunction, and through mitochondrial RNA, this was transmitted via sperm to male offspring. That is a particularly unnerving reason to be concerned about the impact of high-fat diets.

Caffeine

Coffee lovers enthusiastically received reports of up to a 30 percent reduced mortality, such as from more than 170,000 participants in the UK Biobank and another UK Biobank study supporting a dose response: the more

coffee, the longer the person lived. However, most of the studies converge on about four cups per day linked with maximal benefit. A study of more than 520,000 people in ten countries in Europe followed for over sixteen years found a 12 percent reduction in all-cause mortality and 22 percent reduction for cardiovascular mortality. In three large cardiovascular cohort studies, increasing coffee intake was consistently associated with less heart failure. In well over two hundred meta-analyses of coffee and caffeine consumption, there was an association with less risk of breast, colon, endometrial, and prostate cancer; cardiovascular disease; Parkinson's disease; and type 2 diabetes. These are all observational studies that have a major caveat that the benefit could be linked to other factors, such as lifestyle, diet, and exercise, that might be contributing. We don't have a cause-and-effect relationship or unequivocal *proof* that coffee improves health outcomes.

Nonetheless, the overall good news on coffee and caffeine is complemented by studies looking at effects on the heart, particularly inducing rhythm disturbances like premature ventricular contractions (PVCs), premature atrial contractions (PACs), or atrial fibrillation. For decades patients have been warned against coffee for fear of just this kind of heightened risk to heartbeat. A randomized trial showed no increase in PACs but did show some increase in PVCs. Nearly 450,000 participants in the UK Biobank did not show a higher risk of arrhythmias among coffee drinkers. In fact, among another large study of UK Biobank participants, for every cup of coffee increase, there was a 3 percent lower risk of a heart rhythm disturbance, including atrial fibrillation and ventricular tachycardia. This study also looked at genetic markers that affect caffeine metabolism, such that slower metabolism might be linked with more arrhythmias—but that wasn't the case.

The totality of the data support lack of hazard for coffee and caffeine, and the potential, albeit with some uncertainty, for some health benefits, even seen in some studies with decaffeinated coffee. If true, we don't know how coffee promotes health. Many hypotheses have been offered, such as promoting brown adipose tissue, and one based on the insulin sensitivity of coffee's polyphenol chlorogenic acid. Perhaps coffee works as an antioxidant, favorably modulates the gut microbiome, reduces inflammation, or

facilitates DNA repair. This level of uncertainty about the causal connection is unsettling.

Alcohol

The profile we see in the evidence surrounding alcohol consumption is less blurry than for coffee and caffeine. Both moderate and heavy drinking does one no good. The long-standing myth about the benefits of red wine and the French connection was never adequately substantiated; instead, it's been refuted in an analysis of almost six hundred thousand people in eighty-three prospective studies. The International Agency for Research on Cancer classifies alcoholic beverages as carcinogenic, with a strong link to oral cavity and esophageal cancers established in multiple cohort and case-control studies. Ireland is mandating labels on alcohol products: "There is a direct link between alcohol and fatal cancers." Other countries, such as Canada, Norway, and Thailand, are beginning to follow suit. Most studies support a J-curve, with potential small benefit, both for cardiovascular and cancer, with light intake (such as two drinks per week), which varies by age, but significant risk beyond this level of consumption. A dose-response relationship between alcohol intake and high blood pressure has also been noted. This was reinforced by a UK Biobank study that also factored in genetic predisposition (known as Mendelian randomization) to alcohol consumption. The evidence supports a causal relationship between alcohol consumption and two different types of cardiovascular disease (fig. 3.3). One study showed a small added risk at less than seven drinks per week, but an exponential rise with higher intake levels. Perhaps the best summary from the mixed data is that light alcohol intake is not a problem, but the risks quickly increase.

Red Meat and Plant-Based Diets

I've grouped these together because they are at opposite ends of the spectrum for reduced versus increased risk of mortality and relative environmental impact. At one end is processed meats like hot dogs, bacon, and

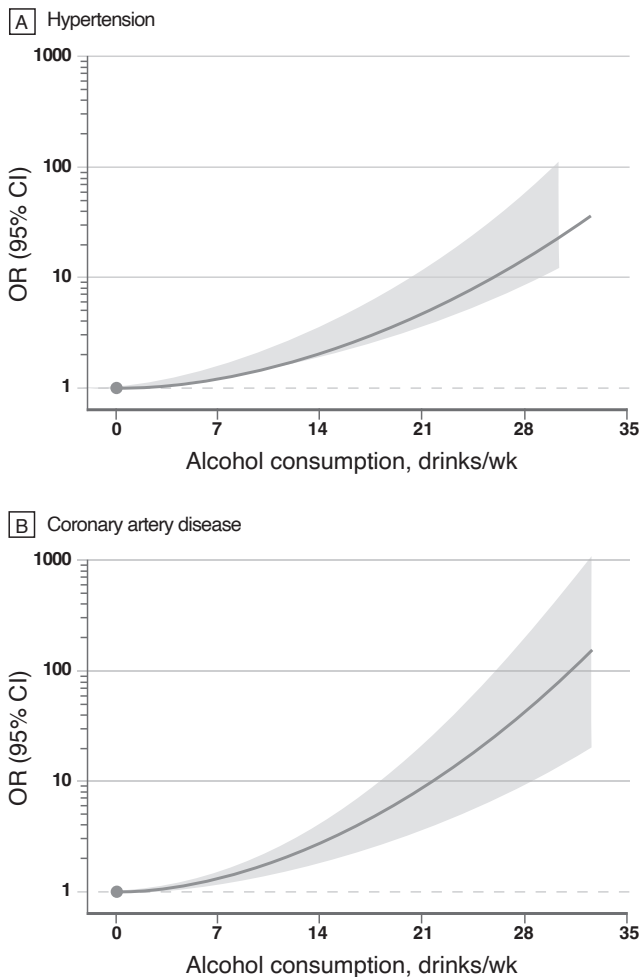
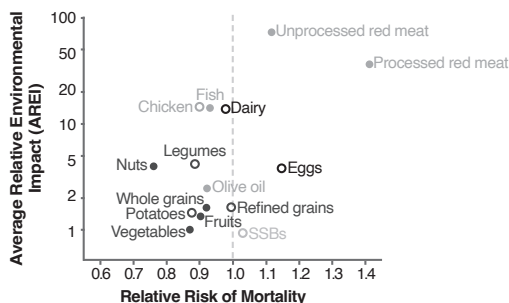


Figure 3.3. Association of alcohol intake and cardiovascular conditions. Adapted from Kiran Biddinger et al. “Association of habitual alcohol intake with risk of cardiovascular disease,” *JAMA Network Open* 5, no. 3 (March 2022): e223849, <https://doi.org/10.1001/jamanetworkopen.2022.3849>.

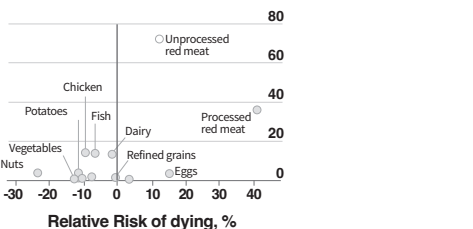
sausages that are linked to the highest risk, deemed carcinogenic by the World Health Organization, and their production leads to large amounts of greenhouse gas emissions. Not far away for increased associated mortality risk are unprocessed meats, pork and beef, which have been labeled “probably carcinogenic.”

In prospective studies of more than fifty-three thousand women and twenty-seven thousand men, with an eight-year follow-up, there was a clear association with increased mortality (fig. 3.4). The environmental impact of the opposite poles represents a marked difference: a switch from high meat to a vegetarian diet would reduce greenhouse gases by 47 percent. But this twofold of putative benefit for health and the environment is not clear-cut. A systematic review of all the studies (nearly 120) did corroborate the increased risk of cancer for processed and unprocessed red meat, but concluded it was small and with low certainty. A similar study made the same point for cardiometabolic outcomes. It certainly isn't settled. A more recent study of nearly thirty thousand Americans followed for nineteen years concluded that both processed and unprocessed meat, but not poultry or fish, were linked to a small increased risk of all-cause mortality. There was a twist with respect to poultry: two or more servings of unprocessed or processed meat or poultry was associated with a 4 to 7 percent increased risk of developing cardiovascular disease.

In contrast, plant-based foods are plainly healthier. A summary of nine studies in more than three hundred thousand participants linked plant-based diets with 23 percent lowered risk of type 2 diabetes. A meta-analysis of thirty-two studies indicated substantial protection from all-cause mortality, cardiovascular deaths, and type 2 diabetes when processed meat diets were substituted by plant-based foods. Among more than seventy-two thousand participants in Japan, the intake of plant protein was linked to an 11 percent reduced risk of total and cardiovascular-related mortality. Compared with a ketogenic diet, a vegan diet enhanced the immune system responsiveness. Substitution of plant for animal protein for 3 percent of caloric intake was associated with 40 percent less cancer-related mortality. A systematic review added to the reduction of cancer risk linked to plant-based diets. Using DNA methylation markers, a way to assess epigenetic



Health and environmental impact of one extra serving per day
Average relative environmental impact



United States, greenhouse-gas footprint
kg of CO₂ equivalent per person per year

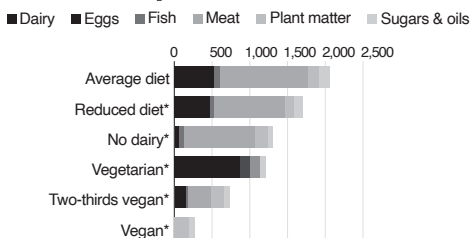


Figure 3.4. Relationship between red meat consumption, mortality, and environmental impact. Risk of mortality (upper panel) and risk of dying and relative environmental impact (middle panel). Adapted from Michael Clark et al., “Multiple health and environmental impacts of foods,” *Proceedings of the National Academy of Sciences of the USA* 116, no. 46 (November 2019): 23357–62, <https://doi.org/10.1073/pnas.1906908116> (lower panel); and “How much would giving up meat help the environment?” *Economist*, November 15, 2019: <https://www.economist.com/graphic-detail/2019/11/15/how-much-would-giving-up-meat-help-the-environment?> (middle and lower panels).