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Extending Healthspan in an Aging World

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Extending Healthspan in an Aging World

Extensions in human longevity are prompting policymakers, the medical profession, and employers to find new ways to maximize health span, or the number of years people live unencumbered by the chronic diseases of old age. This chapter reviews recent research on healthy life extension, including several measures and determinants of longer healthspans. We also provide an overview of recent efforts by medical and business enterprises to enhance both longevity and health span, followed by a discussion of policy and workplace options to foster healthier lives. Such efforts hold the promise of improving quality of life, expanding labor supply, and lowering the cost of health care costs associated with population aging.

Keywords: Longevity, healthspan, chronic diseases, life extension, workplace health

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Global life expectancy has more than doubled over the past two centuries, with continued improvements in recent decades: life expectancy rose from an average of 65.5 years in 1990, to 73.3 years in 2019, a gain of nearly eight years.[1] Whether these longevity increases will continue indefinitely or reach a natural biological limit is unknown, although recently improvements in life expectancy have begun to slow in richer and older nations. Nevertheless, these long-term lifespan gains, paired with tumbling fertility rates, have made a reality the well-documented phenomenon of global aging, driving concern about labor shortages, fiscal pressures from rising pension, medical, and long-term care expenditures, and the negative effects of dissaving on macroeconomic growth (Bloom et al., 2015).

In parallel, the medical profession, policymakers, and members of the business community have extended their locus of concern beyond extending the *absolute* number of years lived, to enhancing the *quality* of those years. In this context, the term 'healthspan' refers to the number of years humans can live unencumbered by age-related disease and disability.[2] It has long been known that aging brings a constellation of health concerns including medical diseases such as cardiovascular and other heart disease; hypertension and stroke; obesity, metabolic disorder, and type 2 diabetes; chronic obstructive pulmonary disease (COPD); neoplasms or cancer; and neurodegenerative diseases such as Parkinson's, dementia, and Alzheimer's. Quality of life in old age can also be impaired by physical deficits arising from osteoarthritis (degeneration of cartilage tissue), osteoporosis (bone density loss), sarcopenia (muscle loss), and sensory impairments

[1] Authors' calculations from the Global Burden of Disease (2021). See also Table 1.

[2] Although estimates of the years of disabled life date back to an approach defined by Sullivan (1971), and references to 'health span' date back to the 1980s, the term 'healthspan' has come into wider use in the past decade (Merriam-Webster 2018).

(hearing and vision loss). The accumulation of such illnesses and impairments in later life contributes to the distinct medical condition known "frailty," particularly among persons age 85+.[3] As we detail below, efforts to avert or shorten the period of old-age frailty, or 'compress morbidity' in later life, are costly and often yield uncertain results, yet the payoffs to society and the global economy offer substantial promise.

In this chapter, we provide an overview of recent research that defines and measures the human healthspan. After briefly reviewing longevity trends, we describe population-level healthspan metrics including healthy life expectancy (HALE) and disability-adjusted life year (DALYs) measures. In addition, we touch on individual healthy life measures such as biological (versus chronological) age. Next, we summarize the known determinants of healthspan including demographic and socio-economic measures such as sex, income, and education; in addition, we discuss behavioral determinants such as diet, exercise, and social interactions, as well as environmental factors such as the impact of workplace and physical environments. Of additional interest is the research on centenarians and the factors believed to explain why some people live exceptionally long, including the notable delay in the initial onset of chronic illnesses of aging among this group. We then briefly discuss the new biological science of aging, called geoscience, and the remarkable rise of the longevity marketplace.

In a final section, we touch on the implications of these developments, including how health policy could further extend humans' healthspan, thereby enhancing our quality of life and reducing expenditures for late-life medical care. We acknowledge that behavioral interventions to improve healthspan will not be easy to implement, as they go well beyond the scale of previous

[3]Frailty is a condition characterized by three or more of the following five conditions: low grip strength, low energy (or self-reported exhaustion), slow walking speed, low physical activity, and unintentional weight loss (Fried et al., 2001).

public health attempts to eliminate smoking. Recent research suggests that massive efforts would be required to improve the quality and amount of food consumed; levels of activity and exercise undertaken by much of the population, along with reducing alcohol, tobacco, and drug consumption. Potential levers could include new dietary standards reducing the role of sugar and ultra-processed foods, new food and menu labeling, and so-called “sin” taxes (e.g., on sugar-sweetened beverages) in the service of reducing the diseases of aging. Other levers would involve nutritional and fitness education for health care professionals, and new policies for adults and children including in the schools, workplaces, and the community. Such efforts face enormous challenges, due to the difficulty of altering behavior in the face of peoples’ self-control problems. An additional channel useful for enhancing the human healthspan is likely to involve pharmaceutical interventions, though again, results have not been uniformly positive in this sphere. Moreover, pharmaceuticals also present challenges in terms of efficacy, negative side effects, and cost. For instance, even an inexpensive drug (for example, metformin, used for diabetes treatment), if found to offer longevity benefits, would be very expensive if offered on a universal basis and with lifetime dosing.

Extensions of Human Longevity

Human longevity in the developed world has risen markedly over the last century, with average lifespans rising by 30 years, as illustrated in Figure 1. Cutler et al. (2006) have outlined the determinants of this phenomenon, pointing first to declines in mortality due to better nutrition (in terms of calories per capita consumed), and next to the widespread adoption of public health measures in the 19th century including clean water and sewage, as well as personal health practices such as handwashing and food safety. Longevity improvements continued through the 20th century due to vaccinations and antibiotics, and later with the public health campaign against smoking. From the middle of the 20th century, longevity gains have increasingly resulted from intensive and expensive medical interventions at older ages, including substantial mortality reductions in cardiovascular disease.

Figure 1 here

Debate continues as to whether past improvements in lifespan will continue, cease, or even reverse in the future. Olshansky and co-authors (c.f., Olshansky et al. 2001; Olshansky and Carnes, 2019) have long proposed that there is a natural, biologically-determined limit to maximum life expectancy. This set of researchers holds that prospects for altering the biology of aging are unlikely, and that while marginal improvements in longevity could continue with costly medical treatments, the costs may not be worth the benefits. A second team led by Vaupel and colleagues (c.f., Oeppen and Vaupel, 2002; Vaupel et al. 2021) posits that the long-term record offers no proof of a binding constraint on lifespans. Accordingly, this second group expects meaningful and ongoing gains in life expectancy among persons age 80+, anticipating technological breakthroughs in the treatment of age-related illnesses such as obesity, metabolic disease, and dementia.[4]

Regardless of which group of researchers proves correct, it appears that life expectancy gains have slowed of late, especially in the developed world. Raleigh (2019) examined data from the European Union and other OECD countries since 2011 and reported slowing lifespan gains across the board. Olshansky et al. (2024) documented a similar result in the eight longest-lived countries (Australia, France, Italy, Japan, South Korea, Spain, Sweden and Switzerland), along with Hong Kong and the United States. They also showed a deceleration in life expectancy gains

[4] In this vein, Scott (2024) argues for major changes in health systems, the economy and financial sector to support a rapidly aging society.

over 1990-2019, and they estimated the chance of living to age 100 at only 15 percent for females and 5 percent for males.

The United States offers what could be a cautionary tale in terms of forecasting ever-rising life expectancy, since in the past half century, this nation has not been a leader in life expectancy, and its global ranking has fallen. In 1960, it ranked 20th in the world, on par with Ireland and Germany at the time; by 2015, the US ranked 40th, on par with Lebanon and Chile, even as U.S. life expectancy rose from 70.1 to 78.9 years over the period (Medina et al., 2020). In addition, beginning in the 1990s, US mortality rates began to rise among middle-aged nonHispanic Whites, due to a surge in deaths from drug and alcohol overdose, suicide, chronic liver disease, and cirrhosis (Case and Deaton, 2017). These "deaths of despair" created a significant headwind for U.S. life expectancy in comparison to other nations.[5] Meanwhile, chronic illnesses among the US working-age population, such as heart and liver disease, have also failed to improve at prior rates or at rates comparable to those in other countries (National Academies of Sciences, Engineering and Medicine, 2021). As a consequence, US life expectancy actually fell between 2014 and 2019 (even before Covid-19) for only the third time in its history, the prior times being during the U.S. Civil War and the flu pandemic of 1918.

Although the opioid crisis has taken a toll unique to the U.S., some experts worry that obesity-related longevity effects, manifesting themselves first in the U.S., also threaten life expectancy gains. Swiss Re Institute (2023) noted that nearly 70% of the U.S. population was either overweight (body mass index or BMI > 25 kg/m^2) or obese (BMI > 30 kg/m^2), explained by ultra-processed fast food diets and added sugar in foods. Using a wide range of data sources, the GBD 2021 US Obesity Forecasting Collaborators (2024) estimated the rate of overweight or obese

[5] For a discussion of whether "deaths of despair" were an inevitable feature of American capitalism, or whether they were a particular aftermath of the opioid and obesity crises, see Case and Deaton (2020) and Ruhm (2022).

U.S. adults at nearly three-quarters, and a doubling in obesity from 1990-2021. Boutari and Mantzoros (2002) contended that obesity already has reached global pandemic proportions, with far-reaching effects in terms of illness and longevity. Moreover, global obesity levels have nearly tripled since 1975, with the American and European areas having the highest rates: 60% of Europeans are now either overweight or obese. They also noted that a BMI of 30-40 kg/m^2 was associated with a nearly 50% increase in healthcare expenses due to obesity comorbidities (disease and illness associated with obesity), and a BMI exceeding 40 kg/m^2 was associated with a doubling of such costs.

In addition to obesity, other trends adversely affecting longevity include the threat from climate change (e.g., due to a rise in heat-related deaths), pandemics from zoonotic disease (where, as in Covid-19, a disease jumps from another species to humans), the rise of antibiotic-resistant infectious disease, and the negative effects of vaping (Swiss Re Institute 2023). Meanwhile, although statin therapies for cardiovascular disease have substantially boosted life expectancy, the rate of improvement has slowed more recently, and life extension gains from reducing smoking are believed to be largely complete. On the positive side, advances in cancer and neurodegenerative disease treatments, the rise of autonomous vehicles (potentially curtailing accidental deaths), and pharmaceutical interventions to tackle the aging process itself may still mitigate or offset these negative life expectancy developments.

Measures of Healthspan

Against the backdrop of longer life expectancy, experts have also questioned whether and how disease (morbidity) has shaped the quality of the additional years gained due to longer lifespans. To understand this evidence, we next discuss both population-level metrics and individual-level measures of the quality of longer lives.

Health average life expectancy. The conventional measure of population healthspan defined by the World Health Organization (WHO Nd.) is termed 'healthy life expectancy' (HALE). This metric, calculated using a method introduced by Sullivan (1971), subtracts from life expectancy any years marred by disability from injury or illness. In these calculations, each disease or injury is assessed as to both its prevalence and the severity of disability.

HALE statistics reported by the WHO are drawn from the Global Burden of Disease Study (GBD21, 2024a and 2024b; WHO, 2020a and 2020b).[6] The study relies on an extraordinary global dataset of administrative and survey health data covering 204 countries and territories and encompassing over 607 billion data measures of 459 health outcomes and risks. Launched in 1990 by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, the GBD is now published on a bi-annual schedule; the latest available GBD for 2021 was published in 2024 and is referred to as GBD21. More than 12,000 individuals in 160 countries support the data collection and analysis effort.

In Panel A of Table 1, we present global mean life expectancy statistics at birth (LE) and HALE taken from GBD21. Prior to the Covid pandemic, global life expectancy had risen from 65.5 years in 1990, to 73.3 years in 2019, for a gain of 7.8 years. The pandemic then depressed global life expectancy by about two years through 2021. Similarly, from 1990-2019, HALE rose from 57.1 years to 63.5 years, or by 6.5 years, but this gain was cut by 1.4 years due to the pandemic

[6] A link to current WHO tables of HALE using GBD2019 can be found at WHO (2020a). A summary of WHO methods can be found at WHO (2020b). Stibich (2022) provides an overview and discusses an alternative formulation of HALE known as the multistate life table method. Top-level findings from the 2021 study can be found in GBD21 (2024a), with data on the most recent HALE statistics in GBD21 (2024b). See also Institute for Health Metrics and Evaluation (IHME, 2024).

through 2021. The fact that HALE fell less than LE due to the pandemic may be due to the fact that less healthy older individuals were more likely to die from Covid-19 than their healthier counterparts. In 2019, the difference between LE and HALE figures stood at around 10 years, in line with the view that the typical number of unhealthy years was around a decade. Naturally this global population average hides substantial variation at individual, regional, and national levels.

Table 1 here

Panel B of Table 1 presents LE and HALE statistics by sex, and it shows that both male and female metrics improved over both the 1990-2019 (pre-pandemic) and 1990-2021 (pandemic-influenced) periods. In 2021, women's mean LE exceeded mean men's LE by about 6 years (74.8 v. 69.0), while the comparable difference for HALE was only 2.7 years. In other words, women do live longer than men, but less than half of that advantage is free of disabling illness or injury. Women experience somewhat longer periods of health-related disability than do men. Calculated another way, 88% of the average male's (shorter) life is healthy, versus 85% of the average woman's (longer) life.

Calculations of LE and HALE means also differ by country. Younger and typically lower-income nations are characterized by higher illness and death rates due to maternal and childhood illness, communicable infectious diseases, accidents, and working-age disabilities. Table 2 summarizes LE and HALE statistics according to a four-level country income classification provided by the World Bank, which divides the world into upper, upper-middle, lower-middle, and lower income groupings.[7] The upper income category provides a view of LE and HALE where the diseases of aging predominate. In 2021, upper income LE was 80.2 years and HALE was 68.5

[7] The World Bank evaluates gross national income per capita in U.S. dollars for each country; the standards for the four groups are fixed, so that over time, as economic conditions improve, fewer countries are included in the lower categories. For example, in 2021, 37% of 217 rated countries were upper income; 25% upper-middle income; 25% lower-middle income; and 13% lower income (Hamadeh et al. 2002).

years, for a difference of 11.7 years. In other words, in the richest countries, people could anticipate spending nearly a dozen years in an unhealthy state. LE and HALE levels are considerably lower in lower-income categories, particularly for the bottom income group. Also notable is that both LE and HALE improvements occurred more rapidly in the lowest income group, as efforts gained ground to eradicate maternal, childhood, and infectious diseases. For example, over the 1990-2021 pandemic-influenced period, LE rose 9.5 years and HALE by 8.6 years in the poorer countries, from much lower initial levels versus richer countries. Over the same 1990-2021 period, LE rose only 4.6 years and HALE by 3.0 years in the richer nations.

Table 2 here

Other healthspan measures. In addition to HALE, experts have also devised other measures for understanding how disease and death shapes the quality of later life. The 'Years of Life Lost' (YLL) metric estimates the number of years lost to premature death attributable to a specific cause such as cardiovascular disease or lung cancer; this is calculated compared to a life expectancy frontier for a given population. For example, if an individual dies of heart disease at the age of 75 but the population life expectancy for 75-year-olds is 80, that person's YLL is 5 years due to heart disease. A second statistic, 'Years of healthy life Lost to Disability' (YLD), is based on the prevalence (and severity) of disability arising from a specific cause. For instance, someone with a stroke who is disabled for 1.5 years would have YLD of 1.5 years for that condition.

These two statistics, one measuring years lost to premature death and the other measuring years lost to disability, are sometimes added together to produce a new, population-level measure called 'Disability-Adjusted Life Years' (DALYs). One DALY represents the loss of one year of full health, either to premature death or disability. Accordingly, the DALY metric is best interpreted as a summary of the disease burden of a given population, useful for understanding the aggregate impact of any specific disease on population health. For instance, it permits analysts to examine how cancer compares to neurodegenerative diseases, in terms of total healthy years of life lost. It also can be used to compare disease burdens across populations, such as to compute how many DALYs are lost to cancer in Europe versus Asia. Additionally, the measure indicates the burden of disease when one condition results in premature death (e.g., an early heart attack), while another results in chronic disability (e.g., disabling arthritis).[8]

Table 3 reports DALYs for a set of developed countries, where DALY is expressed as the total number of years lost per 100,000 inhabitants. Interestingly, the burden of disease proves to be quite varied, even among affluent countries, ranging from a DALY of 26,047 years lost per 100,000 inhabitants of Australia, to 38,079 years lost per 100,000 U.S. inhabitants. Once again, the U.S. has the highest disease burden, a finding echoing the lower U.S. life expectancy versus other rich countries. Nevertheless, even among long-lived and healthier European countries, there is substantial variation from, say, Norway (26,072 DALYs lost) to Germany (34,571 DALYs lost).

Table 3 here

Figure 2 illustrates the relative impact of different types of disease and disability in older, richer societies using GBD21 data. These data record the incidence of diseases and disabilities across all age groups, rather than focusing only on the older population. Each square represents the fraction of total DALYs lost to a given condition due to premature death or disability. Clearly, high-income country DALYs are dominated by non-communicable diseases, with the three largest categories being neoplasms or cancer (15.9% of the total), cardiovascular disease (15.2%), and musculoskeletal disorders (9.6%). Other notable diseases of aging are diabetes and chronic kidney disease, neurogenerative disease, and sensory loss disorders (e.g., loss of sight or hearing). In the

[8] The World Health Organization (WHO, nd) provides basic definitions for the most commonly used terms.

communicable category, a total of 6.7% of DALYs were due to deaths and disability specifically related to Covid-19 during that period (and a separate 0.9% for other Covid-19-related illnesses).

Figure 2 here

The Global Burden of Disease project has also used these data to forecast the effect of disease and disability by the year 2050, along with estimated rates of change (GBD21 Forecasting Collaborators, 2024). Figure 3 indicates that DALYs due to non-communicable diseases of aging are predicted to surge globally in the next 25 years, while DALYS due to infectious and maternal and neonatal causes are anticipated to decline. Interestingly, these effects are more marked in richer countries with older populations, versus poorer nations.

Figure 3 here

Healthspan versus health status indicators. The healthspan measures just described refer to population statistics generated from health data gathered from surveys or administrative sources. In addition, health researchers often use additional data elements and models to categorize and predict individual-level health status information. One widely-used survey metric is peoples' self-reported health status (SRHS), where respondents describe their own health as 'excellent,' 'very good,' 'good,' 'fair' or 'poor.' The SRHS measure can also be augmented by survey respondents' self-assessments of their levels of disability, including their ability to complete activities of daily living (ADLs such as dressing or bathing), or independent activities of daily living (IADLs including managing prescriptions or doing laundry). Other self-assessed survey measures include respondent mentions of medical conditions, psychological or cognitive health problems, prescription drug use, and physical and mental health indicators. Administrative records can include information provided by health providers on specific disabilities, medical conditions, and treatments, including prescription drug data, and lab or diagnostic reports.

With these data sources, experts can then combine and synthesize the health data elements into more complex indicators of health status. The "intrinsic capacity" measure from WHO (2015) captures physical and mental characteristics associated with healthy aging, rather than focusing on the incidence of disability or disease. It includes cognitive, locomotor, psychological and sensory elements. Using this measure, Beard et al. (2024) reported marked improvements in intrinsic capacity for successive generational cohorts in the UK and China. In the UK sample, for example, a 68-year-old born in 1950 had the same intrinsic capacity as a 62-year-old born a decade earlier. Gains in lifespan appear to be accompanied by gains in healthspan. Put colloquially, "70 really may be the new 60" (Nature Aging 2025).

More complex measures can also be used to evaluate specific aspects of disability or health. For example, a 'healthy working life expectancy' metric focuses on peoples' ability to remain employed at older ages. Such a measure can inform policymakers seeking to encourage longer working careers by delaying retirement payments. In the OECD, Boissonneault and Rios (2021) concluded that unhealthy working life expectancy generally rose over the period 2002-2017. Quinby and Wettstein (2021) drilled into the data more deeply and reported that working life expectancy improved for highly-educated individuals, but not for less-educated persons.

Another measure, 'cognitively healthy life expectancy,' evaluates how many years of life are unimpaired by dementia and other types of neurocognitive disorders. Crimmins et al. (2016) used the U.S. Health and Retirement Study from 2000-2010 to assess changes in this outcome, and the authors reported a 'compression of cognitive morbidity,' meaning that most of the life expectancy increases during the period occurred in years associated with good cognitive health. In other words, they concluded that a declining fraction of the overall lifespan was spent being cognitively impaired over the period they studied.

Additional examples of more complex measures of healthspans include the ‘frailty index’ of Hosseini et al. (2022), and the ‘chronic disease index’ proposed by Danesh et al. (2024). We turn to these in the next section.

Biological versus chronological age. New measures of healthspan come from the emerging field of ‘geroscience,’ or the medical science of aging, which seeks to estimate the effects of aging at the cellular level. One approach is to measure an individual’s distinct ‘biological’ age versus the individual’s chronological age. The aim is to determine whether a particular individual exhibits faster or slower signs of aging than the norm. For example, a 70-year-old person (measured in chronological terms) may have a biological age of 75, suggesting more rapid aging than the norm, or a biological age of 65, suggesting slower than average aging. This measure has also been extended to individual organs or systems. Thus a 70-year-old may be assessed as having the heart of a 60-year-old and the knees of an 80-year-old. An appeal of measuring biological age is that it can offer individuals (and their clinicians) a single number for summarizing the current effects of aging and predicting future concerns. This is particularly useful when a single statistic like biological age can be easier to comprehend than the myriad results of numerous medical tests. It can also serve as a useful guide for measuring the impact of alternative interventions to improve health such as changes in diet, exercise, sleep, and medication.

The measurement of biological aging has become increasingly sophisticated in recent years. For example, Rutledge et al. (2022) noted that biological aging was traditionally assessed visually by physicians observing patients’ gross physical and mental changes including greying of hair, loss of mobility, muscular atrophy, skin wrinkling, and cognitive decline. Over the past century, medical tests were added to evaluate deterioration of various organs and systems (e.g., blood glucose, blood pressure, and lipid, kidney, and liver function tests). More recently, aging has been assessed at the cellular level (discussed further below). And, as the authors observed, with molecular level data generated from new technologies—generally described as 'omics,' as in genomics, proteomics, metabolomics, etc.—combined with machine learning techniques, scientists can now design biological 'aging clocks' at the human or organ scale.

As one recent example of the "omics" technology, Oh et al. (2023) used blood plasma proteins to assess aging across 11 organs in a sample of more than 5,600 adults of varying chronological ages. Nearly one-fifth of the group proved to have advanced aging in one organ, and nearly 2 percent were 'multi-organ agers.' Faster organ aging was generally associated with a 20-50 percent increase in mortality. Figure 4 summarizes the increased mortality effects of a one-standard deviation increase in organ age. For the heart, increased mortality over 15 years exceeded 50 percent, while for the kidneys it was below 10 percent. In another "multi-omics" study combining blood, saliva, skin, and other body samples from 108 patients ranging from age 25 to 75, Shen et al. (2024) discovered profound changes in molecular markers of aging at two critical points: ages 44 and 60. This remarkable finding has suggested to some that aging is likely to be a highly non-linear process.

Figure 4 here

A related population-level measure of aging is phenotype age, which is a measure based on chronological age and nine additional blood test biomarkers (such as albumin, creatine, glucose and C-reactive protein). This metric uses only data from whole blood, but it is widely correlated with aging in tissues and cells across the body and is predictive of health span, physical function, Alzheimer's, and all-cause mortality (Levine et al. 2018). In U.S. panel data, Liu et al. (2019) studied the relationship between phenotype age and a range of individual characteristics. Those authors reported that 30 percent of the variation of phenotype age could be attributed to childhood environmental measures (socioeconomic status and a measure of adversity), adult environmental measures (socioeconomic status and adversity), behaviors (obesity, smoking, alcohol consumption and physical activity), and a variety of genetic measures.

Determinants of the Human Healthspan

Next we summarize recent research on the determinants of human healthspan. The list of factors plausibly influencing the outcome is quite large. At the outset, there is the individual's genetic endowment and early-life upbringing, along with sociodemographic factors such as age, sex, income, education attainment, marital status, wealth, and race and ethnicity. Health is also influenced by an individual's behavior in terms of diet, exercise, sleep, smoking, alcohol and drug use, and accident risk. It also includes psychosocial factors including social connections, social isolation, and loneliness. Naturally, a person's medical and psychological conditions play a critical role, along with access to health care, in terms of assessing illness, prescribing treatments, and sustaining good health throughout life. Analysts also emphasize the key role played by the physical and social environment in which a person lives, with factors as diverse as workplace risks, environmental pollution, economic and social stress, and even climate change playing a role. The WHO (2008) and Sadana et al. (2016) analyses of the social determinants of health inequalities set forth a useful framework capturing these and other factors. In what follows, we focus on recent research examining genetic, sociodemographic, behavioral, environmental, and social determinants, followed by a discussion of insights from centenarians.

Genetic determinants. Studies of twins have established that 20-25% of the variation in human lifespans appear to be genetically determined. For example, Herskind et al. (1996) estimated that the heritability of longevity was 0.26 for males and 0.23 for females in a Danish study of persons born 1870-1900. Moreover, they found no evidence of any longevity effect from living in a common family environment. Skytthe et al. (2003) extended that dataset to include the 1901-1910 period and estimated longevity heritability at 0.20 for males and 0.23 for females. [9]

It is worth noting that these estimates applied to individuals born over a century ago, after which virtually all (>99%) of the sample had died, and where all resided in one specific Nordic country. As a result, it is unknown whether genes exert a greater or smaller effect than environment for current cohorts living in different settings. Using an observational study with about 400,000 individuals in the UK Biobank, Argentieri et al. (2025) estimated that they could explain 67 percent of the variation in total all-cause mortality by three factors: age and sex (47 percent), environmental and lifestyle exposures (17 percent) and genetic measures (3 percent). Of the explainable variation, in other words, genetics accounted for less than 5 percent of the total (3 percent out of 67 percent). In part this much lower estimate than in the Nordic twin studies could be due to partial measures of genetic variation in the dataset.

Argentieri et al. (2025) also estimated weightings of age and sex, environmental and lifestyle and genetic factors for many diseases of aging. The associations were quite varied depending on the disease. For example, whereas genetics was the predominant determinant of breast disease, accounting for 90 percent of variation, whereas environmental and lifestyle factors accounted for nearly three-quarters of explained variation in incidence of lung and liver cancer. Genetics explained half of the variation in diseases like type 2 diabetes, ovarian cancer, Alzheimer's and prostate cancer. But for other diseases, like heart disease, stroke and Parkinson's, the very aging process, as represented by age and sex, was the predominant source of variation.

[9] In a study of Swedish twins, Ljungquist et al. (1998) estimated that up to one-third of longevity was genetically determined.

Sociodemographic variation. When it comes to longevity, it is a clear that lifespan and socio-economic status (SES) are positively correlated. Table 2, cited earlier, shows an 18-year difference in life expectancy in 2021 between lower- and higher-income countries, and similar variation has also been demonstrated within-countries. In the U.S., Chetty et al. (2016) found the difference in life expectancy between the richest and poorest 1% of persons by income was 14.6 years for men and 10.1 years for women. In Norway, a country with universal health insurance and less income inequality than the U.S., Kinge et al. (2019) found the top and bottom 1% differences in life expectancy were smaller, yet were still 13.8 years for men and 8.4 years for women.[10] In a study of four Nordic countries, namely Denmark, Finland, Norway and Sweden, Mortensen et al. (2016) showed that a non-linear gradient of mortality by income was evident in all four countries. Moreover, the mortality-income gap widened during a period of rising income inequality. Additional evidence on a widening over time of the longevity gap by SES has been reported by Auerbach et al. (2017), who compared the 1960 with the 1930 birth cohort. That analysis determined that those in the top two US income quintiles would experience a life expectancy advantage over the lowest income quintile by 7-8 years. Furthermore, the difference in lifetime Social Security and Medicare benefits (public pension and health) was estimated to increase by an additional $130,000 (in $2009) between the highest and lowest income quintile.

To assess the factors driving good versus poor health, researchers have begun to construct more complex measures of lifetime health status. Gerontologists' measures are based on the accumulation of deficits or frailties associated with aging (Mitnitski et al. 2001), where the deficits can include specific medical problems or diagnoses (e.g., cancer or heart disease), or problems associated with ADLs or IADLs. Following this approach, Hosseini et al. (2022) constructed their

[10] While the difference in longevity between the richest and poorest in the two countries is similar, U.S. life expectancy, at 76 years, is still much lower than Norway's life expectancy, at 83 years.

own ‘frailty index’ using U.S. longitudinal data. They demonstrated, first, that frailty increases with age, as it does in the cross-section. Second, many young and middle-aged individuals have no indication of frailty, but this group shrinks steadily with age, while frailty increases. Third, frailty is lower for the better-educated, and it is higher for women than men. Fourth, at all ages, the frailty distribution is skewed to the right.

Using data from the Netherlands, Danesh et al. (2024) constructed a ‘chronic disease index’ and demonstrated, first, that the gap in mortality by socio-economic status (SES) as measured by income was largely explained by higher prevalence of chronic diseases among low-income households, rather than due to a ‘treatment effect’ whereby low-income households were less likely to obtain medical care. Second, they found striking age and income differences, indicating that much of the disease burden occurred early in life. For example, those in the bottom half of the income distribution at age 35 had the health profile of the top half of the income distribution at age 50. Moreover, 60 percent of the cross-group difference was attributable to those in the low-income groups experiencing chronic illness at a faster rate, and not from sicker individuals self-selecting into lower income quintiles. Case and Deaton (2005) also demonstrated that those in the lowest income quartile reported worse health at age 20 than those in the top income quartile at age 50. Health was also systematically worse for men and women in the lowest quartile, at all ages, and it deteriorated faster with age among low-income men.

In terms of other determinants of healthspan, Zaninotto et al. (2020a) studied a sample of persons age 50+ in England and the US, focusing on the relationship between disability-free health status and household wealth. The researchers reported that persons in the bottom tercile of household wealth could expect seven to nine years fewer healthy lives, compared to persons in the top tercile. Chen et al. (2020) using data from the Netherlands, evaluated the relationship between multimorbidity—having multiple poor health conditions—and peoples' physical and mental health and education level, both of which served as a proxy for socio-economic status. Compared to the highest educated group, the least-educated had three times the prevalence of disability and four times the mental health problems.

Even more broadly, education appears to play a role not just in boosting longevity and healthspan, but also in reducing the incidence of chronic illness, particularly dementia. Reuser et al. (2011) found in US data that highly-educated men and women lived longer, and had fewer years of cognitive impairment (1.6 years for men and 1.9 years for women), compared to their less-educated counterparts. As a rule, they concluded that the longer that people live, the greater their risk of dementia—with the exception of those with the most education. It is also possible that a multi-pronged program consisting of diet changes, exercise, and cognitive training, could be beneficial in warding off dementia. But, as Kivipelto et al. (2018) noted, few interventions of this sort have been subject to rigorous randomized control trials. Of those that have, the authors observed, programs targeting behavioral change among those at high risk of dementia (with risk measured by certain clinical assessment tools) showed some potential to slow advance of the disease.

Similar disparities exist when the measurement variables are race and ethnicity. Using the U.S. Health and Retirement Study, Russo et al. (2024) discovered that Black men and women had frailty levels at age 55 comparable to White men and women 13 and 20 years older, respectively. For Hispanic men and women, frailty rates were comparable to White men and women 5 and 6 years older.

Behavioral determinants. The health and medical literature has found a strong positive link between healthy behaviors, increased longevity, and healthspan. In U.S. data, Mehta and Myrskyla

(2017) found that people over age 50 who never smoked, were not obese, and who consumed alcohol moderately, lived 7 years longer on average, and delayed disability onset by up to six years. In other words, those three behaviors were associated with more years lived and a marked reduction in disability. Sadly, the researchers also found that nearly 80 percent of Americans reached age 50 having smoked, been obese, or both. Only 7 percent of older adults were in the lowest-risk category: non-obese non-smokers with moderate alcohol consumption.

To assess the relationship between healthy behaviors and longevity, Li et al. (2018) used data on over 120,00 health professionals, including females tracked in the US Nurses' Health Study and males in the Health Professionals Follow-up Study. The study team defined five low-risk lifestyle risk factors in their study: (1) never having smoked; (2) having a body mass index in a 'normal' range (18.5 to 24.9 kg/m^2); (3) doing 30 or more minutes of exercise per day; (4) having moderate alcohol intake; and (5) following a healthy diet (defined as being in the top 40% of diets classified). Women adopting all five low-risk behaviors were projected to live about 14 years longer than women having none (43.1 years versus 29.0 years as of age 50). Men adopting all five low-risk factors were likely to live about 12 years longer than men with none (37.6 years versus 25.5 years as of age 50). Figure 5 reports their estimates of life expectancy as of age 50 for men and women based on their number of low-risk behaviors, illustrating a consistent dose-response relationship, meaning that each additional low-risk factor increased life expectancy.[11]

Figure 5 here

It is also worth underscoring the fact that very few individuals demonstrated all five low-risk behaviors in Li at al. (2018) study. At baseline, only 1.2% of nurses (in 1980) and 1.5% of male health professionals (in 1986) exhibited all five low-risk behaviors. Only 10% of respondents

[11] Fadnes et al. (2023) modeled the effects of a shift to a healthier diet for the United Kingdom and estimated a life expectancy gain of up to 10 years from dietary changes along.

exhibited either four or five low-risk behaviors, and more than 80% of respondents reported following only one, two, or three low-risk behaviors (the remainder exhibited none of the low-risk behaviors).

Li et al. (2020) extended the effort to study healthspan measuring the incidence of diabetes, cardiovascular disease, and cancer, again based on the number of five low-risk behaviors observed, with results summarized in Figure 6. At age 50, women who adopted four or five low-risk behaviors had an average of 34 years free of these diseases, versus 24 years for women following none of the behaviors; this represents a striking difference of a decade of good health. Among men, the effect was smaller, with the difference averaging 7 years. Men at age 50 adopting four or five low-risk behaviors had 31 years free of these three chronic illnesses, versus 24 years among men observing none.

Figure 6 here

Another study, by Zaninotto et al. (2020b), used data from the U.S. and U.K. in a cross-national comparison of the effects of high-risk behaviors on healthy life outcomes. This team focused on four risk factors: alcohol consumption, obesity, smoking, and physical inactivity. People exhibiting none of these factors were likely to live more than 11 additional years free of disability, and up to a dozen years without chronic illness. In England, 18% of men and 15% of women reported none of the risky behaviors; by contrast, in the U.S., 27% of men and 22% of women had none. Nevertheless, the U.S. sample overall could anticipate a shorter period of chronic-disease-free healthy life expectancy compared to their U.K. counterparts.[12]

As part of a broader study on the evolutionary nature of exercise, Lieberman (2024) reviewed and summarized the specific impact of exercise on longevity and health outcomes. Citing

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[12] The earlier incidence of chronic illnesses in the U.S. versus England and Europe has also been reported by others; c.f., Avendano et al. (2011).

a US study of over a million individuals, he reported that those with higher activity levels had lower mortality rates, although with a declining marginal benefit. Mortality dropped 30 percent for those exercising 60 minutes a week at a moderate or vigorous level,[13] versus sedentary individuals, and more hours of exercise led to smaller improvements. Those data are also the basis of the current US standard for exercise, namely a minimum of 150 minutes of moderate or vigorous exercise per week (CDC 2024). Exercise is also a valuable way to combat the diseases of old age, whether in isolation or when combined with drugs and diet. It has been shown to improve outcomes for obesity, diabetes, heart disease, high blood pressure, and cholesterol, as well as sarcopenia, osteoarthritis and osteoporosis; it also appears to help reduce rates of cancer, Alzheimer's, mental health conditions (anxiety, depression), and respiratory infections. While there is evidence about the specific modalities of exercise in some instances—cardio training appears best for the heart system, while cardio and weight training combined are beneficial for diabetes—the type and recommended duration of exercise is less clear for other diseases. Lieberman's recommendation drawing on the evidence to date was to emphasize cardio exercise, with weight training a secondary activity.

A related body of research is exploring the psychosocial aspects of healthy behavior, including having a higher purpose or meaning in one's life, having deep social connections, and avoiding loneliness. It is unclear exactly what mechanism is at work, but Kim et al. (2020) demonstrated that older Americans in the top quartile of having a reason to live (life purpose) had a 24% lower chance of being inactive, a 33% lower chance of developing sleep problems, and a 22% lower change of developing an unhealthy body mass index, compared to those in the bottom quartile. Meanwhile, loneliness and social isolation are both associated with higher mortality and

[13] Moderate aerobic exercise is defined as raising one's heart rate to 50 percent to 70 percent of maximum heart rate; vigorous, 70 percent of 85 percent.

illness rates. Also using U.S. data, Crowe et al. (2021) observed that 18% of their age 50+ respondents met the criteria for being lonely at a given time, and 21% for social isolation. Further, they reported that 6% of the older population met the criteria for being persistently lonely two times or more over an eight-year study period, and 8% were socially isolated. In addition, persistent loneliness and social isolation were associated with higher mortality rates as well as greater difficulties with ADLs and IADLs. In a meta-analysis, Wang et al. (2023) found a similarly strong relationship between loneliness, social isolation, and mortality. That team also documented that both factors contributed to higher rates of cancer, and that social isolation (but not loneliness) contributed to an increased risk of cardiovascular disease.

Recent research is also showing that behavioral factors are critical determinants of various chronic diseases of aging. In the case of cognitive decline, Livingston et al. (2024) identified 14 factors, many of them behavioral, associated with higher incidence or advance of dementia. These included 12 features documented in earlier reports, including having less education, having hypertension or a hearing impairment, smoking, being obese or depressed, being physically inactive, having diabetes, consuming excessive alcohol, having traumatic brain jury, experiencing low social contact, and being exposed to air pollution. Two additional factors identified in the 2024 report included having untreated vision loss and high LDL cholesterol. Taken together, reductions in these 14 factors were predicted to curtail the probability of dementia by 45 percent, leaving 55 percent still unexplained.

In considering the findings of these behavioral studies, it is worth recalling that they rely on epidemiological or observational studies of respondents over a long period of time; obviously, in view of the research questions and lengthy time scales involved, randomized experimental trials are both impractical and costly. This reality leaves researchers associating outcomes of interest such as life expectancy and healthspan measures with other measures recorded in any given study. One concern is that observational studies tend to rely on self-reports of past behaviors, leading to the possibility of respondent error or bias in reporting. Another is that such studies are also subject to the problem of unobserved or omitted variables. For example, it could be that healthy behaviors are also associated with unobserved factors such as genetics, psychological or personality factors, or childhood, physical, or work environments, which might not have been recorded in the relevant study or at the proper time frames. Similarly, none of the longitudinal studies surveyed here have estimated the contribution of healthy behaviors to variations in lifespan and healthspan relative to other factors discussed in this section, such as the role of exercise versus education. Moreover, none of the studies has had sufficiently precise measures to be able to report marginal effects in detail, as for example, the effect of one additional hour of exercise or an additional kilogram of weight on healthspan, or the differential effects from one particular type of diet or exercise over another, during a specified time frame. Nevertheless, these longitudinal studies are obviously of enormous value compared to single point in time analysis where respondents' memories and ability to recall past behaviors and exposures are likely to be much less precise.

Environment and social determinants. Most research on environment and health has focused on health at all ages, or often only on the young, and not mainly on older populations and their chronic diseases, yet some progress is being made. Duncan and Kawachi (2018) reviewed recent research on the role of neighborhoods on local population health, linking peoples' locations to healthy and unhealthy behaviors (including obesity, food and dietary choices, propensity to engage in exercise, and alcohol, tobacco and drug use). As one example, they reported that urban areas known as 'food deserts' which lack access to fresh and high-quality food, can independently contribute to residents' poor health. At the same time, the authors acknowledged the ongoing challenge of disentangling the unique causal effects of a resident's physical environment compared to own behavioral choices and other factors.

Some research has also confirmed that so-called neighborhood effects may relate not just to the physical environment, but also to characteristics of other residents. Bor et al. (2024) report a strong neighborhood effect related to residents' education: every 10 percent point increase in the share of college-educated adults in an area was associated with a decline in all-cause mortality of 7 percent. Better-educated neighbors also contributed to lower disease prevalence and higher self-reported health. More than half the correlation between local human capital and health appears to be due to association with obesity and smoking: that is, better-educated neighbors insist on stronger anti-smoking restrictions and express more negative beliefs about obesity, thus contributing to better resident behaviors.

In addition, a great deal of work considers the role of exposure to environmental toxics on health. Using GBD19, Fuller et al. (2022) documented that environmental pollution accounted for approximately 9 million deaths per year globally, or one in six deaths worldwide. While deaths due to 'traditional' toxins such as household air and water pollution (including poor sanitation) have continued to fall, deaths due to 'modern' toxins including carcinogens, particulates in the workplace, and lead pollution, have jumped by two-thirds since 1990. In addition to pushing up mortality rates, environmental toxins also drive disease, and pollution has been linked to health concerns of the brain, liver, kidneys, and reproductive system. In a meta-analysis of 86 other studies, Yang et al. (2020) linked levels of air pollution to the incidence and prevalence of diabetes, and the authors also reported evidence of a relationship between these pollution levels and glucose markers in the blood. While a more detailed review of this research falls beyond the scope of this chapter, it is worth noting that an important area for future healthspan research is establishing the relationship between environmental toxins and diseases of aging.

In addition to toxic workplaces, workplace stress is also receiving increased attention from public health experts. In 2021, the WHO and ILO (International Labor Organization) issued a joint report assessing the impact of overwork, defined as long working hours, on health. Pega et al. (2021) found a sharp increase in cardiovascular disease and stroke among those who worked more than 55 hours per week, noting that around 9% of the global population labored at that level. Fairbank (2024) points out that the resulting disease burden falls heavily on workers over age 60 who had worked long hours at younger ages. Working long hours for a decade or more appears to be a critical factor determining health outcomes, versus occasional or episodic periods of overwork.

Exceptional aging. Another way to evaluate determinants of lifespan and healthspan is to consider cases of exceptional aging. Centenarians—namely, those individuals living to age 100 and beyond—are a case in point. According to Schaeffer (2024), the U.N. Population Division estimated that there were about 722,000 centenarians in 2024, representing 0.009% of the world population of 8 billion. Japan has the largest absolute numbers, with 146,000 centenarians in a population of 123 million in 2024, or 0.11% of the total Japanese population. The U.S. had the second largest number, with an estimated 108,000 centenarians in 2024, for an incidence of 0.03% of the total U.S. population. Other rich and long-lived countries had smaller absolute numbers but higher incidence levels than the U.S.[14] More importantly, centenarians are set to nearly quadruple in 30 years, by 2054, to nearly 4 million globally, and in the US, reaching 0.1% of nation's population.

[14] Individual county and global centenarian estimates can also be obtained from the International Data Base of the U.S. Census Bureau (US Census Bureau nd.)

Pignolo (2019) summarized a large body of research on this subpopulation. One distinguishing fact about the group is its delay in the onset of the traditional diseases of aging. Around 43% of centenarians reach age 80 with no chronic disease of aging, and 15% of male and 30% of female centenarians have no chronic illnesses at age 100. That said, many centenarians do encounter age-related illnesses prior to age 80, suggesting that, when they do experience diseases at an early age, they also manage to avoid succumbing to them. Eighty five percent of centenarians are women, and the greater longevity of women—both in general and among centenarians—remains a puzzle. Pignolo (2019) also noted that centenarians tend to be clustered in specific geographic regions ('blue zones'): in Japan, Italy, Costa Rica, Greece, and California. Several factors are common to these hot spots, including a low-calorie plant-based diet; healthy body weight; regular exercise like walking and gardening; social support and community connections, and spirituality. Beyond these behavioral factors are likely the common factor of a shared genetic heritage.[15]

Nevertheless, some authors have urged skepticism in interpreting the historic evidence on centenarians. Across several countries, Newman (2024) documented that age records were often inaccurate. Relatedly, he suggested that strongest predictors of centenarian status were being in area with a low-income or low average life expectancy. A number of blue zones also were associated with low income, low life expectancy, and high crime rates, suggesting fraud or error in centenarian age records.

Another aspect of exceptional aging has been found among older individuals who experience substantially delayed physical or cognitive deterioration. 'Super-agers' are defined as those age 80+ who exhibit cognitive skills on memory tests comparable to individuals 20-30 years

[15] Buettner (2023) also summarizes findings from global 'blue zones.'

younger; this group is estimated to account for less than 10 percent of the age 80+ population. Harrison et al. (2012) identified individuals age 80+ with memory skills equivalent to those of a 50-to-65-year-old comparison group, and established that these super-agers were notable for having none of the brain volume loss typically associated with aging. In fact, one part of their brains, the cerebral cortex, was thicker among super-agers compared to their younger comparison group. Similarly, Garo-Pascual et al. (2023) also found that super-agers avoided age-related shrinkage in brain volume. This may explain why super-agers resist the deleterious cognitive effects of aging such as memory decline, even though they had the same dementia biomarkers in their blood as average individuals of the same age. They also had certain behavioral markers, including better walking gait and finger-tapping speeds, despite not differing from their peers in terms of total exercise, and better mental health, with lower levels of anxiety and depression. Finally, super-agers were more likely to have had musical training earlier in life; accordingly, it is thought that musical training is associated with improved memory and larger brain volume.

The New Science of Aging: Geroscience

Geroscience, the science of aging, is seeking to understand the cellular and molecular processes that cause poor health and death, and if possible, to also slow or reverse them (US National Institutes of Health, nd). In an in-depth review of the field, Ramakrishnan (2024) discussed the underlying science, recent research, and potential interventions to extend health and life. At the heart of geroscience is the ‘disposable soma’ hypothesis from evolutionary biology, first proposed by Kirkwood (1997), where the ‘soma’ is defined as the non-reproductive portion of a living organism. According to this hypothesis, there is a tradeoff between investing in reproduction, that is, bearing offspring and helping them grow to reproductive age, versus investing in the maintenance of one's own soma. The soma can repair itself at the cellular and molecular level to sustain health and advance reproduction, but once reproduction is completed, there is little incentive to continue this investment. After that, the underlying biological processes that sustain life for reproduction can deteriorate and become increasingly error-prone. It is the accumulation of defects at the cellular level over time that leads to the well-known characteristics of aging, to age-related diseases, and to death. In short, after reproducing, the soma is seen to become dispensable, and the body's cellular processes are optimized around that reality.

Geroscientists have constructed several models of cellular deterioration flowing from this hypothesis. Lopez-Otin et al. (2023) summarized recent findings in one such model, which sets forth 12 distinct elements or hallmarks of aging, presented in Figure 7.

Figure 7 here

One example of an aging hallmark is mitochondrial dysfunction. Cellular mitochondria are responsible for the body's energy generation process, as well as regulation of inflammation and cell death. When mitochondria function incorrectly, they generate excessive inflammation and cell death. A second example is loss of proteostasis, or the process of creating, managing, and dissolving proteins in the body. In this process, proteins must be folded in specific ways to work effectively. When errors in protein-folding increase, proteostasis declines; in other words, proteins stop working as they should. A third example is telomere shortening. Human beings undergo an estimated 10 trillion cell divisions in a lifetime. With each cell division, DNA must replicate itself, yet there are often replication errors at the tips of the chromosomes. Telomeres are located at the ends of chromosomes to protect the important information in DNA; it is believed that they consist of non-critical genetic information that can be lost during the replication process with no detrimental effect. Unfortunately, as a cell continues to replicate, the telomeres become shorter, and when the telomeres become short enough or disappear, they trigger the cell to stop dividing, known as cell senescence. When senescent cells fail to die and exit the body, their accumulation contributes to many of the chronic diseases of aging. For a fourth example, as the body ages, chronic inflammation occurs systemically at the cellular level throughout the body. As inflammation increases, damage increases. Such damage can manifest itself in very visible ways, as with arthritis, cardiovascular disease, or disc degeneration in the back. With higher levels of inflammation, the function of the immune system declines, which further increases susceptibility to disease and malignancy (c.f. Smith 2024).

Scientists are working diligently to identify the direct biochemical linkages between healthy behaviors found in population studies and optimal cellular function. In a recent survey of research on the cellular basis of physical exercise, Conroy (2024) found that exercise directly increases cellular inflammation by producing interleukin-6, an inflammatory cytokine (an immune system molecule). At the same time, it spurs generation of anti-inflammatory versions of interleukin, thus boosting cellular repair and maintenance. In this way, exercise directly helps counteract the effects of aging.

In the case of diet, Pignatti et al. (2020) described recent research on how food influences the ‘nutrition-sensing pathways’ in human cells. Calorie restriction is a one strategy that reduces cellular inflammation and improves mitochondrial function. In addition, drugs used for other medical purposes, such as rapamycin and metformin (discussed further below), alter nutrition pathways and improve cellular function. Longo and Anderson (2022) explained how aging can be slowed by influencing these cellular nutrition pathways or by varying the amount, type or timing of food. After assessing the benefits and limitations of strategies such as calorie restriction and time-restricted eating (also known as intermittent fasting) for these nutrition pathways, they proposed a ‘longevity diet’ that consists of complex carbohydrates and plant- and fish-based proteins—a diet, they note, characteristic of at least one group of centenarians, those in Okinawa, Japan.

This new science of aging is also contributing to a new medical model of chronic disease. In the traditional organ- or system-based view of chronic illness, diseases like heart disease or diabetes have been thought of in terms of the affected body organs or systems: in the case of heart disease, inflammation and deterioration of the heart and blood circulatory system; or in the case of diabetes, a breakdown in the blood glucose and insulin regulation system and the pancreas. In the new cellular model, by contrast, deterioration in fundamental cell processes occurs throughout the body and is a common factor driving multiple diseases of aging. Depending on individual genetics, life history, and environment, this cellular deterioration may result in heart disease in one individual; in another person, diabetes; in a third, cancer; in a fourth, cognitive decline; and so on. This new model of the diseases of aging suggests that future treatments could focus less on an affected organ (e.g., heart, pancreas, brain), and more on common cellular processes contributing to such diseases across multiple systems or organs.[16]

Geroscience has also stimulated interest in medications to alter these fundamental cellular processes, thereby extending both health- and lifespans. The drugs rapamycin and metformin are cases in point. Ramakrishnan (2024) described the science behind these drugs, both of which are approved for specific clinical uses, yet both appear to have broader anti-aging properties. Rapamycin is an immune-suppressive agent used for transplant patients which reduces cellular inflammation by inhibiting the function of the immune system; hence its approved use. It is a compound discovered in the soil of Easter Island off the coast of South America. Metformin is a

[16] This approach has been cited by several commentators in the geroscience field; see Siera (2016) for an in-depth discussion.

front-line medical treatment for diabetes that improves blood sugar control, based on a plant extract dating back to medieval Europe where it was also used for diabetes patients. As Ramakrishnan (2024) noted, both medications have been shown to extend healthspan and longevity in mice. A study of metformin in humans showed that diabetes patients taking this medication lived longer than diabetics taking other medications, and indeed longer than nondiabetics. Rapamycin is currently being evaluated in middle-aged dogs in a major research project on canine aging; prior studies have already shown a longevity-boosting affect among older mice. Despite its potential, rapamycin poses a risk of serious side effects including cancer and infection. Metformin, a drug currently taken by millions around the world for diabetes, is now the subject of a major human clinical trial, Targeting Aging with Metformin (TAME), to understand its longevity effects. These are just two of the many medical interventions being tested for the potential effects on slowing or reversing the hallmarks of aging (Economist, 2023).

Developments in the Longevity Marketplace

Next, we provide a brief overview of recent developments in the marketplace for longevity- and healthspan-enhancing products and services. Before considering the longevity market, however, it is worth noting that this is, strictly speaking, distinct from the rapidly growing 'wellness' marketplace. A large segment of the wellness market is motivated by research on the importance of healthy behaviors, so the wellness market includes products and services in a wide variety of areas: supplements, nutrition and diet, exercise and training, mindfulness and therapy, and sleep.[17] McKinsey (2024) estimated the size of the US wellness market in 2024 at $480 billion, and $1.8 trillion globally.

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[17] McKinsey (2022) divided the wellness market into five categories: (1) health, including over-the-counter medicines, vitamins, supplements and hygiene; (2) fitness, such as gyms, at-home equipment and wearables; (3) nutrition, including diet programs, subscription food services, nutrition apps and juice cleanses; (4) appearance, including

In contrast, the longevity marketplace seeks to extend healthspan and lifespan. It has generally been venture-capital focused, where entrepreneurs seek to exploit the latest scientific research to defer the aging process. As with elements of the wellness marketplace, it is often based on speculative ideas not yet proven scientifically.[18] Newman and Belleza (2024) estimated the size of the venture-backed longevity marketplace (which, in their definition, excludes cancer treatments, given their distinct complexity): over the period 2014-2023, they concluded that longevity firms attracted more than $42 billion in venture capital, classified into the domains displayed in Figure 8.

Figure 8 here

Some of these investment domains can be tied to efforts to improve the defective cellular processes discussed above, including 'seno-therapeutics' as well as cellular 'rejuvenation,' 'regeneration,' and 're-programming.' For example, cellular senescence is a state when a cell is no longer able to grow and divide, but instead of dying off, remains in the body and causes localized inflammation. An increase in senescent cells is one of the hallmarks of aging, and the proliferation of these cells leads to diabetes, cancer, and neurodegenerative illnesses. Seno-therapeutics are therefore proposed pharmaceutical interventions to eliminate the senescent cells directly, active the immune system to remove them, or transform them into younger cells. Park and Shin (2022) summarize recent scientific developments in the field.

Key to the longevity marketplace is a rapidly growing 'longevity diagnostics' field, which aims to introduce novel measures such as biological age estimates, along with comprehensive body

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traditional skin and hair care; (5) mindfulness, including therapy and meditation programs and apps; and (6) sleep, including supplements, apps and other sleep aids.

[18] Janin et al. (2024) discuss a recent scientific controversy over claims by Harvard aging researcher David Sinclair and a related company to have reversed again in monkeys. Marcus et al. (2024) also note the failure to-date of Sinclair's start-ups in the aging field.

scans and tests, to assess the risks of aging. ‘Companion longevity’ includes efforts to extend the healthspan and lifespans of domestic pets like cats and dogs. The ‘repurposed drugs’ category represents evaluating existing medications (like rapamycin and metformin) for their potential anti-aging benefits, while the ‘longevity drugs’ category includes new compounds. The latter include medications from major pharmaceutical firms such as the revolutionary anti-obesity GLP-1 drugs, as well as compounds from newer start-ups.

‘Longevity clinics’ offering to deliver longevity medicine are also proliferating, usually involving in-office services that provide diagnostics (e.g., full body scans, body age estimates, and comprehensive medical testing), clinical recommendations (medical, pharmaceutical, and behavioral), patient coaching, and support. Yet as Hamzelou (2024) noted, longevity medicine is still in its infancy and suffers from inconsistent standards and weak scientific backing. For instance, estimates of individuals’ biological age are likely to be more speculative than scientific, given current data. Many such clinics offer safer services like all-body MRIs, while others provide stem-cell infusions that may pose safety risks. Janin and Pohle (2024) have noted that some traditional spa vacations have now been transformed into longevity clinic experiences. Services can include biologic age testing, vitamin IV drips, stem-cell infusions, and ozone therapy (in which blood is withdrawn, treated with ozone, and then returned to the body), along with more traditional sauna, cold plunge, and massage therapies. An education component can include health insights from the research on centenarians.

More broadly, publicity efforts have included best-selling books and social media content from aging scientists (e.g., Sinclair, 2019), medical doctors and YouTube influencers (e.g., Attia, 2023 or the ‘glucose goddess’ Inchauspé, 2022) and retirement and aging experts (e.g., Dychtwald, 2024). There is also a plethora of topic-specific publications and social media content on diet and nutrition, exercise, sleep, and social and psychological elements focusing on life purpose, connectedness, and loneliness.

Policy and Employer Implications

Now that scientific and medical evidence has suggested some possible paths to extend healthy lifetimes, what real-world steps could policymakers and employers undertake to do their part? This section offers some suggestions toward that end, along with a brief discussion of some potential costs and benefits of such approaches.

Shifting the policy objective: From lifespan to healthspan. The research summarized so far makes clear that, if the human healthspan is indeed to be extended, health and medical systems of the future will need to focus on extending years of health, more than they have in the past. One highly ambitious policy option would be to mount a major public and social effort to delay the onset of multiple age-related diseases (multi-morbidities) and frailty in the population (Garmany et al. 2021). The Global Roadmap for Health Longevity has called on governments to 'shift health care systems to focus on health longevity,' including realigning payments and financial incentives around that goal (National Academy of Medicine 2022: 4). At least part of the answer may be a 'Medicine 3.0' program designed to delay the onset of chronic illness (Attia, 2023), as opposed to 'Medicine 1.0,' focused in the past on the treatment of injury and infection, and today's 'Medicine 2.0,' which treats age-related illnesses after they occur.[19]

Of course, the potential scope for policy action – and its likely cost – in pursuit of this goal is vast. As noted above, genetic or early childhood factors are estimated to account for 20-25 percent of longevity differences; if the same is true of healthspan, this leaves 75 to 80 percent of

[19] See also Crimmins (2015) and Olshansky (2022). The National Academies of Sciences, Engineering and Medicine (2024) also underscored the importance of improved children's health care for better health outcomes among adults.

total variation to factors other than pre-determined genetics and early childhood exposures.[20] A comprehensive public health effort to reverse the fundamental cellular processes of aging, by enhancing diet, strengthening physical and cognitive capability, building social connections, and reducing environmental stresses and toxins, is a problem much larger in scope and complexity than was the public health effort against smoking. Since the scale of these issues is beyond the remit of this chapter, in what follows we focus instead on one very specific question—diet and food quality—to illustrate some of the policy tradeoffs in promoting healthspans. We discuss behavioral interventions in the form of nutrition standards and food labeling; tax policy; and pharmaceutical interventions in the form of the recent success of anti-obesity drugs.

The problem of diet and nutrition. Diet is one of the five key behavioral risk factors associated with chronic illness and premature death. At the heart of the problem is the global rapid rise of metabolic syndrome or disease, associated with overconsumption of food and rising rates of overweight or obesity, contributing to rising rates of Type 2 diabetes and other disorders of the liver, heart, and gut. It is a global pandemic of a man-made kind (Boutari and Mantzoros, 2022).

One explanation for the rising rates of obesity is ultra-processed foods (UPFs), as described by Lustig (2021), Van Tulleken (2023), and Swiss Re Institute (2023). UPFs are conventionally defined as manufactured foods in which some or all of the ingredients are industrial substances not found in the home kitchen; they are usually characterized by high levels of sugar, salt, and fat, and

[20] And as enumerated above, the sources of variation are numerous: (1) health behaviors including diet, nutrition, exercise, and sleep quality, but also smoking, alcohol, and drug use, as well as, in older populations, avoidance of muscle and bone loss and hearing and vision impairment; (2) the psychological and social states of individuals and families, including stress levels, interpersonal support, degrees of loneliness or social isolation, and sense of life purpose; (3) the design and structure of medical and health systems, including not only the care delivery system and drugs and therapies, but also the health insurance and payment side; (4) the food system in terms of its nutritive value and cost; (5) the workplace environment and occupational health risks, as well as work spillover effects in terms of activity, sleep and stress; and (6) the physical environment, ranging from issues like clean air and water, access to the outdoors, and exposure to toxins. Also on the list are (7) possible pharmaceutical interventions to stop or reverse the underlying cellular processes of aging. And of course, this list does not include factors as yet undiscovered or untried.

low levels of dietary fiber. UPFs are described as ‘hyper-palatable;’ since with their lack of fiber, they do not trigger the normal satiation hormones in the body on a timely basis, leading to overconsumption which then triggers an intense dopamine pleasure response in the brain. ‘Junk foods’ like sugary or salty snacks, desserts, or soft drinks clearly fall into the UPF category, as do many conventional foods (breads, breakfast cereals, yoghurts, processed frozen foods, etc.) with distinct UPF characteristics: mechanical processing, industrial ingredients, high levels of added sugar, salt, and fat, and minimal fiber (Lustig 2021). The repetitive surges people experience in blood sugar after each meal eventually produce insulin dysfunction and, over time, to pre-diabetes and diabetes. They also contribute to higher body weight and damage to the liver and heart. Moreover, the lack of fiber in UPFs not only contributes to overconsumption of food but also to an unhealthy biome in the gut.

Food nutrition and labeling standards. The problem presented by UPFs and poor nutrition differs broadly from the problem of smoking, one of the critical health policy issues of the second half of the 20th century. Smoking is a non-essential activity and ‘quitting’ has been established as a clear-cut public health objective. In contrast, eating and drinking are essential to life. Consequently, policy cannot focus not on the extensive margin of change (eat/don’t eat, drink/don’t drink), but rather on the intensive margin (change type, improve quality, reduce quantity).

A key policy lever toward that end is food labeling regulation, designed to educate consumers about nutritional content and, more recently, to design school lunches provided to children in the U.S. and elsewhere. The NOVA program in Brazil represents an effort to classify UPFs in national diet regulations into four food groups: unprocessed or minimally processed food (whole foods, fermented foods), processed culinary ingredients (oil, butter, sugar, salt), processed food, and ultra-processed food. Monteiro et al. (2018) described how the system was developed and its results. In a meta-analysis of programs using the NOVA classification scheme (and similar definitions of UPFs) to assess the relationship between UPF consumption and health, Lane et al. (2024) found a strong positive link between UPF consumption and the prevalence of heart disease, type 2 diabetes, and mood disorders. They also found a strong link of UPFs to all-cause mortality.[21]

Nevertheless, the question remains as to whether such a food-labeling program would be sufficient to change food consumption and reduce obesity, metabolic syndrome, and related diseases over peoples' remaining lifetimes.[22] Looking at behavioral modification programs using choice architecture changes, Mertens et al. (2021) found small to moderate effects over short periods; encouragingly, food choices showed some of the largest effects. In the case of specific dietary change, doing beyond food labeling, some limited evidence now suggests that intermittent fasting (also known as time-restricted eating, in which food consumption is limited to an eight-, ten- or twelve-hour period each day), can lead to weight reduction and potentially address obesity and metabolic disease (De Cabo and Mattson, 2019; Ezpelta et al., 2024). Additional trials are underway testing this and other nutrition-related techniques.

Sin taxes. A second policy channel that has been used to alter peoples' diets involves raising the relative prices of poor-quality food through penalty or 'sin' taxes, such as taxes on sugary soft drinks (Allcott et al. 2019). Beverage taxes have been imposed by several U.S. cities, more than 20 U.S. states, and over 30 countries including Mexico and Saudia Arabia. Although this policy falls outside the scope of our present discussion, there is some early evidence of possible

[21] Food processing is a problem even for plant-based diets. Rauber et al. (2024) found that plant-based non-UPF food was associated with a 7% lower risk of cardiovascular disease and a 13% lower risk of death from cardiovascular disease. But plant-based UPFs were associated with a 5% increased risk of disease and 12% increase in mortality.

[22] As one point of reference on the challenge of long-term behavioral change, it took nearly 60 years for the U.S. anti-smoking campaign to reduce smoking rates by 73 percent, with rates declining from 42.6 percent in 1965 to 11.6 percent in 2022 (American Lung Association, 2024).

effectiveness. For example, Petimar et al. (2024) found that such a tax imposed by the City of Philadelphia in 2017 curtailed the consumption of sugary sodas, and modestly reduced BMI and obesity three years after introduction of the tax. Moreover, as Allcott et al. (2019: 224) concluded after reviewing the literature, “sugar-sweetened beverage taxes are not a panacea—they will not, by themselves, solve the obesity epidemic in America or elsewhere. But sin taxes have proven to be a feasible and effective policy instrument in other domains, and the evidence suggests that the benefits of sugar-sweetened beverage taxes likely exceed the costs.”

Pharmaceutical interventions. Drug treatments are a third policy lever for influencing diet and food consumption. The lack of sustained progress through behavioral modification, such as with dieting programs, stands in sharp contrast to the recent success of the class of drugs known as GLP-1 agonists. The first generation of these drugs was approved in 2005 for the treatment of Type 2 diabetes. More recent generations not only improve diabetes outcomes but also contribute to a substantial reduction in appetite and food consumption, leading to sizeable weight loss. In addition, the drugs have been effective in treating related diseases of the liver and heart. In many ways, the GLP-1 agonists are an early example of a ‘new model’ medicine, in which multiple diseases of aging are treated through a single mechanism, namely a reduction in appetite and food intake.[23] The drugs’ success also demonstrate how central diet and metabolic disease are to the constellation of the diseases of aging. Currently, list prices for GLP-1 drugs in the U.S. are high, typically over $1,000 per month (McGrane and Ajmera, 2024). Complications, mostly gastrointestinal, are not uncommon, and others have raised concerns about long-term muscle loss (Shukla, 2025).

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[23] Some clinicians refer to this as an ‘obesity-first’ medicine, in which reducing excess body weight is seen as key to reducing the effects of other chronic illnesses such as diabetes (Wen, 2024).

Given the success of these drugs, J.P. Morgan (2023) forecasted a market of $100 billion, and coverage of some 30 million people or 9% of the U.S. population, by 2030. Because of the drugs' high costs, however, coverage remains uneven among private insurers and employers in the U.S. The US Medicare system (the public health insurance program for adults age 65+) does cover the new class of drugs for diabetes, but not for obesity—an example of treating the disease rather than the predecessor condition. At present, the expectation is that GLP-1 drugs will need to be taken indefinitely, although it remains to be seen whether patients who have eliminated Type 2 diabetes and achieved optimal weight can be weaned from them.[24] Patient compliance is also still in question. One pharmacy benefit manager in the U.S. reported that 85 percent of patients stopped using the drugs within two years, while an insurer study found that 58 percent of patients stopped the medication before achieving a clinically meaningful level of weight reduction (Cohen, 2024).

While the GLP-1 drugs promise the potential for pharmaceutical interventions in advancing healthspans, their success must be compared with recent results for new medications targeting another disease of old age, Alzheimer's. Lecanemab is a drug designed to reduce or eliminate the characteristic brain plaques associated with this neurodegenerative disease. Approved by U.S. regulators in 2023, it was expected to have 10,000 active patients in the first year, but it managed to achieve fewer than a fifth of that number. In the U.S., adoption by doctors and patients has been hindered by the drug's high costs and the need for frequent brain scan testing (to check for brain swelling and other complications). Another concern expressed by physicians was whether the drug yielded benefits that could be recognized by interacting with the patient. The drug approval tests yielded statistically significant results, yet the size of the effects was considered modest, and the UK National Health Service did not adopt the drug for this reason. Some physicians have also

[24] See Cleveland Clinic (2024) for an overview and J.P. Morgan (2023) for market forecasts and other insights.

cited ‘therapeutic nihilism’ as an explanation for low demand for the drug: a feeling that Alzheimer’s was so intractable that little could be done about it, especially if a drug offered small benefits.[25]

These case studies offer critical lessons about the impact of pharmaceutical interventions for age-related illnesses, and for future medical interventions intended to reverse cellular aging. The ideal anti-aging drug has metformin-like characteristics: low-cost and with few complications.[26] Yet many therapies successful in treating age-related illness are likely to be exceedingly difficult to pay for, given the scale of most age-related disease, the number of patients involved, the cost of the treatment, and its duration. In addition, despite meeting scientific effectiveness and regulatory standards, certain therapies may still have negligible real-world impacts due to safety, effectiveness, and cost concerns. Statistically significant but medically small marginal effects can be underpowered in the face of major chronic disease, like the just-described Alzheimer’s treatment. Moreover, patient compliance is a critical variable, and such compliance is likely to be lower in the face of medications that are more costly or require long periods of use. Finally, long-term impacts will depend on the pace of innovation. The original GLP-1 drugs were approved in 2005, but then surged in popularity after the recent generations offered dramatic weight reduction benefits. As of 2024, there were over 30 proposed treatments in stage 3 clinical trials for dementia and other neurodegenerative illness. One or more may follow the GLP-1 path in the treatment of dementia. All of these same constraints apply to the as-yet-to-be-introduced pharmaceuticals targeting the hallmarks of aging, whether they be already established medicines (such as metformin or rapamycin) or new compounds.

[25] For recent media coverage on the topic, see Steenhuysen (2024) and Walker, Loftus and Mosbergen (2024).

[26] Current generation GLP-1 drugs are quite cheap to manufacture, costing less than $1 per day (Barber et al., 2024) and will come off patent in the early 2030s.

Employer considerations. Employer concerns about workers' healthspans parallel those of policymakers, although many employers are likely to be more concerned with their active employees' rather than their retirees' welfare. To the extent that healthspan extension is successful and chronic diseases deferred to older ages, employers will benefit from greater worker productivity due to their lower disease burden. A related employer benefit, in a world of declining fertility and shrinking labor forces, will be a larger supply of healthier older workers. All things equal, healthier workers may be more willing to work longer before they retire. Working longer not only boosts employers' labor supply but can also enhance workers' retirement preparedness, as they will have longer to save and will spend less time in retirement.

Employers could also potentially benefit from lower health insurance costs. For example, widespread use of GLP-1 drugs may be expensive initially, but it could also reduce medical costs associated with workers' obesity, heart attacks, and diabetes. In the US, where employers generally provide workplace-based health insurance coverage, such savings could increase costs in the near term but reduce premiums in the longer run. This would be especially true for large U.S. firms which underwrite their own health insurance plans. Similar reasoning can apply to employers in countries where health insurance is a social responsibility; costs may be higher initially but lead to lower obesity-related costs in the health system and impose less pressure to increase social insurance taxes. For this reason, if healthspan efforts prove to be both successful and low-cost, both private and public health system costs could fall below current predictions.

In pursuit of healthspan benefits, some employers have also introduced a number of behavioral education programs targeting food, exercise, stress, and other health-related behaviors; these are often termed 'wellness programs.' Their goal has been to generate both cost savings and productivity increases from having a healthier workforce; they can also help employers attract and retain healthier workers. That said, one important study of a major employer wellness program found it had minimal effects after two years (Jones et al. 2019). Workers were randomly assigned to the program, allowing for the measurement of program effectiveness independent of participant self-selection. The researchers did see program participants enrolling and experiencing lower medical costs at the outset, yet most health and productivity metrics did not differ meaningfully between participants and nonparticipants within two years. It remains to be seen whether programs designed differently or with a different commitment of resources will produce better results.

In a more recent study, Bolnick et al. (2021) summarized evidence on behavioral interventions for improving healthspan. The team focused on key areas where there was reasonable evidence of success with behavioral methods: tobacco use; weight management; metabolic disease; other dietary risks (such as sarcopenia and osteoporosis from poor diet or nutrition); exercise; medical screenings and tests; immunizations; social engagement; and cognitive and mental health. The authors also noted the importance of other emerging areas, such as sleep or life purpose, where evidence from interventions was less clear. Of most interest was the range of possible tactics employers could consider implementing, including healthy foods in workplace lunchrooms and nutrition education; onsite gyms and work breaks for exercise during working hours; financial incentives to stop smoking or the introduction of smoking cessation programs; weight and stress management programs at work; and a comprehensive program focusing on mental health. The authors observed that the workplace, given its importance to peoples' lives, remains a critical setting for influencing adult health behaviors.

Discussion

Our aging global population faces a tsunami of chronic illness, and a critical strategy for mitigating this development is to focus on improving healthspans. Longer healthspans can inspire better life trajectories in an aging world, prompting better mental and physical capability for many years. In such a world, medical costs associated with debilitating disease could also be confined to a narrower window. Aging would then become more of a plateau, perhaps with occasional dips followed by recoveries. By analogy, death would then be seen as the reaching of the edge of the plateau, followed by a sudden drop. This perspective differs substantially from the current model of aging, with its steady or intermittent ratcheting downward in terms of physical and mental capability, starting earlier and extending longer, and bringing with it the threat of a substantial 'red zone' of frailty and disability at the end.

Potential benefits of extending healthspans would include higher individual and social welfare in the form of a healthier, more active, and more cognitively intact older population; better retirement preparation by workers due to potentially longer periods of work and saving; and better macroeconomic performance, in the form of both lower health care costs, a larger supply of older workers, and higher productivity resulting from a smaller burden of disease.[27] On the other side of the ledger are the potential costs and effectiveness of behavioral programs and pharmaceutical interventions needed to achieve these health enhancements. These will likely be concerning in the aggregate, given the need for near-universal participation and lifetime treatment in many cases.

Additionally, policymakers and employers still confront the question of what can be done to achieve a better trajectory. Certainly, heathy behaviors including diet and exercise (and non-smoking and limited alcohol consumption) are critical. Nutrition guidance is one possibility, although behavioral change programs are difficult to carry out, while behavioral conditions such as social connectivity and loneliness seem much less tractable to policy or employer interventions.

[27] For example, Ball et al. (2024) estimated that in the UK, a 20 percent reduction in the incidence of six major chronic illnesses would boost GDP 0.74 percent in 5 years and 0.98 percent in a decade. This, of course, would be in addition to the improved individual and social welfare from better health.

Drug interventions hold great promise, whether based on conventional pharmaceutical models like the GLP-1 anti-obesity drugs, or on as yet undiscovered therapies based on geroscience, targeting not a single disease but instead a defective cellular process.

Our review implies that, given the breadth of factors influencing human health, there is no single pathway for improving global healthspan. Instead, rhe effort will require major public health programs to alter fundamental behaviors around food, exercise, sleep, stress and social relationships. It will also require concerted efforts in the workplace and schools, as well as in the medical and health systems of the world. And it will also require one or more inexpensive, novel medications that can offer major health benefits, either at the disease or cellular process level. It remains to be seen how current interventions on the behavioral and pharmaceutical side will scale to the size of the healthspan problem—and what other strategies and approaches future research might yield.

References

Allcott, Hunt, Benjamin B. Lockwood, and Dmitry Taubinsky. (2019). 'Should We Tax Sugar-Sweetened Beverages? An Overview of Theory and Evidence.' *Journal of Economic Perspectives* 33(3): 202–227

American Lung Association. (2024). 'Trends in Cigarette Smoking Rates.' https://www.lung.org/research/trends-in-lung-disease/tobacco-trends-brief/overall-smoking-trends#:~:text=Long%20term%2C%20smoking%20rates%20have,1965%20to%2011.6%25%20in%202022.

Argentieri, M.A., Amin, N., Nevado-Holgado, A.J. *et al.* (2025) "Integrating the environmental and genetic architectures of aging and mortality." *Nature Medicine.* 31: 1016–1025. https://doi.org/10.1038/s41591-024-03483-9.

Attia, Peter with Bill Gifford. (2023). *Outlive: The Science & Art of Longevity*. New York: Harmony.

Auerbach, Alan J., Kerwin K. Charles, Courtney C. Coile, William Gale, Dana Goldman, Ronald Lee, Charles M. Lucas, Peter R. Orszag, Louise M. Scheiner, Bryan Tysinger, David N. Weil, Justin Wolfers, and Rebecca Wong. (2017). 'How the Growing Gap in Life Expectancy May Affect Retirement Benefits and Reforms.' *The Geneva Papers on Risk and Insurance: Issues and Practice.* 42(3):475-499. https://www.doi.org/10.1057/s41288-017-0057-0.

Avendano, Mauricio, M. Maria Glymour, James Banks and Johan P. Mackenbach. (2011). 'Health Disadvantage in US Adults Aged 50 to 74 Years: A Comparison of the Health of Rich and Poor Americans With That of Europeans.' *American Journal of Public Health.* 99: 540-548. https://doi.org/10.2105/AJPH.2008.139469.

Ball, Sir John, Tamsin Berry, John Deanfield, Ines Hassan, Rishni Joshi, Yannick Schindler and Andrew Scott. 2024. 'The Macroeconomic Case for Investing in Preventative Health Care in the U.K.' Tony Blair Institute for Global Change. https://institute.global/insights/economic-prosperity/the-macroeconomic-case-for-investing-in-preventative-health-care-UK

Barber, J., Dzintars Gotham, Helen Bygrave, and Christa Cepuch. (2024). "Estimated Sustainable Cost-Based Prices for Diabetes Medicines." *JAMA Network Open*. 7(3):e243474. https://doi.org/10.1001/jamanetworkopen.2024.3474.

Beard, J.R. et al. (2024). "Cohort trends in intrinsic capacity in England and China." *Nature Aging.* https://doi.org/10.1038/s43587-024-00741-w .

Bloom, David E., David Canning and Alyssa Lubet. (2015). 'Global Population Aging: Facts, Challenges, Solutions & Perspectives.' *Daedelus.* American Academy of Arts and Sciences. 144(2): 80-92.

Boissonneault, M. and Paola Rios. (2021). 'Changes in Healthy and Unhealthy Working-life Expectancy over the Period 2002-2017:A Population Based Study in People Aged 51-65 years in 14 OECD Countries.' *The Lancet: Health Longevity.* 2(10): October 2021. e629-38.

Bolnick, Howard, Lianne E. Jacobs, Daniel Kotzen, Francois Millard, and Martin Stepanek. (2021). 'Maximizing Health Span: A Literature Review on the Impact of a Healthy Lifestyle in Retirement.' *SOA Research Institute.* https://www.soa.org/49b23d/globalassets/assets/files/resources/research-report/2021/healthy-lifestyles-in-retirement.pdf

Bor, Jacob H., David M. Cutler, Edward L. Glaeser, and Ljubica Ristovska. (2024). 'Human Capital Spillovers and Health: Does Living Around College Graduates Lengthen Life?' NBER Working Paper No. 32346. https://www.nber.org/papers/w32346.

Boutari, Chrysoula and Christos S. Mantzoros. (2022). 'A 2022 Update on the Epidemiology of Obesity and a Call to Action: As its Twin COVID-19 Pandemic Appears to be Receding, the Obesity and Dysmetabolism Pandemic Continues to Rage on.' *Metabolism.* 133: 155217.

Buettner, Dan. 2023. *The Blue Zones, Second Edition: 9 Lessons for Living Longer.* Washington, D.C.: National Geographic, Disney Publishing Group.

Case, Anne and Angus Deaton. (2005). 'Broken Down by Work: How our Health Declines.' In David A. Wise, editor. *Analyses in the Economics of Aging.* Chicago: University of Chicago Press. 185-212.

Case, Anne, and Angus Deaton. (2020). *Deaths of Despair and the Future of Capitalism*. Princeton, NJ: Princeton University Press.

Case, Anne, and Angus Deaton. (2017). 'Mortality and Morbidity in the 21st Century.' *Brookings Papers on Economic Activity* 47 (1): 397–476.

CDC. (2024). "Physical Activity Guidelines for Americans." Centers for Disease Control, Office of Disease Prevention and Health Promotion. https://odphp.health.gov/our-work/nutrition-physical-activity/physical-activity-guidelines/current-guidelines

Chen, Yi Hsuan, Milad Karimi, and Maureen P.M.H. Rutten-van Molken. (2020). 'The disease burden of multimorbidity and its interaction with education level.' *PLoS One.* 15(12): e0243275. doi:10.1371/journal.pone.0243275.

Chetty, Raj, Michael Stepner, Sarah Abraham, Shelby Lin, Benjamin Scuderi, Nicholas Tuner, Augustin Bergeron, and David Culter. (2016). 'The Association Between Income and Life Expectancy in the United States, 2001-2014.' *JAMA.* 315(16): 1750-1766. https://doi.org/10.1001/jama.2016.4226

Cleveland Clinic. (2024). 'GLP-1 Agonists.' https://my.clevelandclinic.org/health/treatments/13901-glp-1-agonists

Cohen, John. (2024). "Study Shows 85% of Patients Discontinue GLP-1s for Weight Loss After 2 Years." *Forbes.* July 11. https://www.forbes.com/sites/joshuacohen/2024/07/11/study-shows-85-of-patients-discontinue-glp-1s-for-weight-loss-after-2-years/

Conroy, Gemma. (2024). 'Why is Exercise Good for You? Scientists are Finding Answers in Our Cells.' *Nature.* 629. 26-28. https://www.nature.com/articles/d41586-024-01200-7.

Crimmins, Eileen M. (2015). 'Lifespan and Healthspan: Past, Present and Promise.' *The Gerontologist*. 55(6): 901-911. https://doi.org/10.1093/geront/gnv130.

Crimmins, Eileen M., Yasuhiko Saito, and Jung Ki Kim. (2016). 'Change in Cognitively Healthy and Cognitively Impaired Life Expectancy in the United States: 2000-2010.' *SSM – Population Health.* Vol. 2, December. 793-797. https://www.sciencedirect.com/science/article/pii/S2352827316301148.

Crowe, Christopher, Benjamin W. Domingue, Gloria H. Graf, Katherine M. Keyes, Dayoon Kwon, and Daniel Belsky. (2021). 'Associations of Loneliness and Social Isolation With Health Span and Life Span in the U.S. Health and Retirement Study.' *The Journals of Gerontology: Series A*. 76 (11): 1997–2006. https://doi.org/10.1093/gerona/glab128.

Cutler, David M., Angus S. Deaton, and Adriana Lleras-Muney. (2006). 'The Determinants of Mortality.' *Journal of Economic Perspectives.* 20(3): 97-120. https://www.aeaweb.org/articles?id=10.1257/jep.20.3.97.

Danesh, Kaveh, Jonathan T. Kolstad, Johannes Spinnewijn, and William D. Parker. (2024). 'The Chronic Disease Index: Analyzing Health Inequalities Over the Lifecycle.' NBER Working Paper 32577. www.nber.org/papers/w32577.

De Cabo, Rafael and Mark P. Mattson. (2019). "Effects of Intermittent Fasting on Health, Aging and Disease." *New England Journal of Medicine.* 381(26): 2541-2441. https://doi.org/10.1056/NEJMra1905136.

Duncan, Dustin T., and Ichiro Kawachi. Editors. (2018). *Neighborhoods and Health*. 2nd edition. Oxford Academic, New York. https://doi.org/10.1093/oso/9780190843496.003.0001.

Dychtwald, Maddy, Kate Hanley. (2024). *Ageless Aging: A Woman's Guide to Increasing Healthspan, Brainspan and Lifespan.* Rochester MN: Mayo Clinic Press.

Economist. (2023). 'In Search of Forever.' *The Economist Technology Quarterly.* September 30. https://www.economist.com/technology-quarterly/2023-09-30

Ezpelta, Mark, Sofia Cienfuegos, Shuhao Lin, Vasiliki Pavlou, Kelsey Gabel, Lisa Tussing-Humphreys, Krista A. Varady. (2024). "Time-Restricted Eating: Watching the Clock to Treat Obesity." *Cell Metabolism.* 36(2): 301-314. https://doi.org/10.1016/j.cmet.2023.12.004.

Fadnes, Lars T., Carlos Celis-Morales, Jan-Magnus Økland, Solange Parra-Soto, Katherine M. Livingstone, Frederick K. Ho., Jill P. Pell, Rajiv Balakrishna, Elaheh Javadi Arimand, Kjell Arne Johansson, Øystein A. Haaland and John C. Mathers. (2023). 'Life Expectancy Can Increase by Up to 10 years Following Sustained Shifts Towards Healthier Diets in the United Kingdom.' *Nature Food.* 4:961-965.

Fairbank, Rachel. (2024). 'What Working Long Hours Does to Your Body.' *National Geographic.* https://www.nationalgeographic.com/science/article/working-long-hours-health-effects

Fried, Linda P., Catherine M. Tangen, Jeremy Walston, Anne B. Newman, Calvin Hirsch, John Gottdiener, Teresa Seeman, Russell Tracy, Willem J. Kop, Gregory Burke, Mary Ann McBurnie. (2001). 'Frailty in Older Adults: Evidence for a Phenotype.' *The Journals of Gerontology: Series A.* 56(3): M146-M157.

Fuller, Richard, Philip J. Landrigan, Kalpana Balakrishnan, Glynda Bathan, Stephen Bose-O'Reilly, Michael Brauer, Jack Caravanos, Tom Chiles, Aaron Cohen, Lillian Corra, Maureen Cropper, Greg Ferraro, Jill Hanna, David Hanrahan, Howard Hu, David Hunter, Gloria Janata, Rachael Kupka, Bruce Lanphear, Maureen Lichtveld, Keith Martin, Adetoun Mustapha, Ernesto Sanchez-Triana, Karti Sandilya, Laura Schaefli, Joseph Shaw, Jessica Seddon, William Suk, Martah Maria Telez-Rojo, Chonghuai Yan. (2022). 'Pollution and Health: A Progress Update.' *Lancet Planet Health.* 6:e535-47.

Garmany, Armin, Satsuki Yamada, and Andre Terzic. (2021). 'Longevity Leap: Mind the Healthspan Gap.' *NPJ Regenerative Medicine.* 6(57): 1-7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8460831/.

Garo-Pascual, Marta, Christian Gaser, Linda Zhang, Jussi Tohka, Miguel Medina and Bryan A. Strange. (2023). 'Brain Structure and Phenotypic Profile of Superagers Compared with Age-Matched Older Adults: A Longitudinal Analysis from the Vallecas Project.' *The Lancet Healthy Longevity.* 4(8): E374-E385. https://doi.org/10.1016/S2666-7568(23)00079-X.

GBD21. (2024a). 'Global Age-sex-specific Mortality, Life Expectancy, and Population Estimates in 204 Countries and Territories and 811 Subnational Locations, 1950-2021, and the Impact of the COVID-19 Pandemic: A Comprehensive Demographic Analysis for the Global Burden of Disease Study 2021.' *The Lancet.* 403:1989-2056. https://www.doi.org/10.1016/S0140-6736(24)00476-8

GBD21. (2024b). 'Global Incidence, Prevalence, Years Lived with Disability (YLDs), Disability adjusted Life-years (DALYs), and Health Life Expectancy (HALE) for 371 Diseases and Injuries in 204 Countries and Territories and 811 Subnational Locations, 1990-2021: a systematic analysis of the Global Burden of Disease Study 2021.' *The Lancet.* 403: 2133-61. https://doi.org/10.1016/S0140-6736(24)00757-8

GBD21 Forecasting Collaborators. (2024). 'Burden of Disease Scenarios for 204 Countries and Territories, 2022-2050: A Forecasting Analysis of the Global Burden of Disease Study 2021.'

The Lancet. 403: 2204-56. *The Lancet.* 404(10469): 2278-2298. https://doi.org/10.1016/S0140-6736(24)00685-8

GBD 2021 US Obesity Forecasting Collaborators. (2024). 'National-level and state-level prevalence of overweight and obesity among children, adolescents, and adults in the USA, 1990-2021, and forecasts up to 2050.' *The Lancet.* 404(10469): 2278-2298. https://www.doi.org/10.1016/S0140-6736(24)01548-4.

Hamadeh, Nafa, Catherine Van Rompaey, Eric Metreau and Shwetha Grace Eapen. (2022). 'New World Bank Country Classifications by Income Level: 2022-2023.' World Bank Data Blog. July 1. https://blogs.worldbank.org/en/opendata/new-world-bank-country-classifications-income-level-2022-2023.

Hamzelou, Jessica. (2024). 'The Quest to Legitimize Longevity Medicine.' *Technology Review.* March 18. https://www.technologyreview.com/2024/03/18/1089888/the-quest-to-legitimize-longevity-medicine/.

Harrison, Theresa M., Sandra Weintraub, M.-Marsel Mesulam, and Emily Rogalski. (2012). 'Superior Memory and Higher Cortical volumes in Unusually Successful Cognitive Aging.' *J Int Neuropsychol Soc.* 18(6): 1081-1085. https://doi.org/10.1017/S1355617712000847.

Herskind, A.M., M. McGue, N.V. Holme, T.I.A. Sørsensen, B. Harvald and J.W. Vaupel. (1996). 'The Heritability of Human Longevity: A Population-based Study of 2872 Danish Twin Pairs Born 1870-1900.' *Human Genetics.* 97: 319-323.

Hosseini, Roozbeh, Karen A Kopecky, and Kai Zhao. (2022). 'The Evolution of Health over the Life Cycle.' *Review of Economic Dynamics*. 45: 237–263.

Inchauspé, Jessie. 2022. *Glucose Revolution: The Life-Changing Power of Balancing Your Blood Sugar.* Simon and Schuster, New York.

Institute for Health Metrics and Evaluation (IHME). (2024). 'Global Burden of Disease 2021: Findings from the GBD 2021 Study.' Seattle, WA: IHME. https://www.healthdata.org/research-analysis/gbd

Janin, Alex. (2024). 'To Get Ahead of Diseases, It May Help to Find Your Organ Age." WSJ.com, March https://www.wsj.com/health/wellness/aging-biological-age-organs-health-9b6a4798

Janin, Alex and Allison Pohle. (2024). 'The Longevity Vacation: Poolside Lounging With an IV Drip.' *Wall Street Journal.* April 15. https://www.wsj.com/health/wellness/living-longer-vacation-longevity-8fa3530f?mod=article_inline.

Janin, Alex, Dominique Mosbergen and Am Dockser Marcus. (2024). 'Star Scientist's Claim of 'Reverse Aging' Draws Hail of Criticism.' *Wall Street Journal.* April 27. https://www.wsj.com/health/wellness/david-sinclair-longevity-aging-criticism-645fddc5

J.P. Morgan. (2023). 'The Increase in Appetite for Obesity Drugs.' J.P. Morgan Global Research. November 29. https://www.jpmorgan.com/insights/global-research/current-events/obesity-drugs#section-header#0

Jones, Damon, David Molitor and Julian Reif. (2019). "What Do Workplace Wellness Programs Do? Evidence from the Illinois Workplace Wellness Study." *Quarterly Journal of Economics.* 134(4):1747-1791. https://doi.org/10.1093/qje/qjz023.

Kim, Eric S., Koichiro Shiba, Julia K. Boehm and Laura D. Kubzansky. (2020). 'Sense of Purpose in Life and Five Health Behaviors in Older Adults.' *Preventative Medicine.* 139: 106172. https://doi.org/10.1016/j.ypmed.2020.106172.

Kinge, J., J. Modalsli, S. Overland, H. Gjessing, M. Tollanes, A. Knudsen, V. Skirbekk, B. Strand, S Haberg, S. Vollset. (2019). 'Association of Household Income With Life Expectancy and Cause-Specific Mortality in Norway, 2005-2015.' *JAMA.* 321(19):1916-1925. https://doi.org/10.1001/jama.2019.4329

Kirkwood, T.B.L. (1977). 'Evolution of Aging.' *Nature.* 270: 301-4.

Kivipelto, M., F. Mangialasche, and T. Ngandu. (2018). 'Lifestyle Interventions to Prevent Cognitive Impairment, Dementia and Alzheimer Disease.' *Nat Rev Neurol* 14: 653–666. https://doi.org/10.1038/s41582-018-0070-3.

Lane, Melissa M., Elizabeth Gamage, Shutong Du, Deborah N. Ashtree, Amelia J. McGuinness, Sarah Gauci, Phillip Baker et al. (2024). 'Ultra-processed Food Exposure and Adverse Health Outcomes: Umbrella Review of Epidemiological Meta-analyses.' *BMJ.* 384: e077310. https://dx.doi.org/10.1136/bmj-2023-077310.

Levine, M.E., A.T. Lu, A. Quach, B.H. Chen, T.L. Assimes, S Bandinelli, et al. (2018). 'An Epigenetic Biomarker of Aging for Lifespan and Healthspan.' *Aging.* 10(4): 573-591.

Li Y., A. Pan, D.D. Wang, X. Liu, K. Dhana, O.H. Franco, S. Kaptoge, E. Di Angelantonio, M. Stampfer, W.C. Willett, and F.B Hu. (2018). 'Impact of Healthy Lifestyle Factors on Life Expectancies in the US Population.' *Circulation*. 138(4): 345-55. https://doi.org/10.1161/CIRCULATIONAHA.117.032047

Li Y, J. Schoufour J, D.D. Wang, K. Dhana, A. Pan, X. Liu, M. Song, G. Liu, H.J. Shin, Q. Sun, and L. Al-Shaar. (2020). 'Healthy Lifestyle and Life Expectancy Free of Cancer, Cardiovascular Disease, and Type 2 Diabetes: Prospective Cohort Study.' *BMJ.* 368:16669. https://doi.org/10.1136/bmj.l6669.

Lieberman, Daniel E. (2020). *Exercised.* New York: Vintage Books.

Liu, Zuyun, Xi Chen, Thomas M Gill, Chao Ma, Eileen M. Crimmins and Morgan E. Levine. (2019.) 'Associations of Genetics, Behaviors, and Life Course Circumstances with a Novel

Aging and Healthspan measure: Evidence from the Health and Retirement Study.' *PLoS Medicine.* 16(6): e1002827.

Livingston, Gill, et al. (2024). 'Dementia Prevention, Intervention and Care: 2024 Report of the *Lancet* Standing Commission.' *The Lancet.* 404: 10452. P572-628. https://doi.org/10.1016/S0140-6736(24)01296-0.

Ljungquist, B., Berg, S., Lanke, J., McClearn, G. E., & Pedersen, N. L. (1998). 'The Effect of Genetic Factors for Longevity: A Comparison of Identical and Fraternal Twins in the Swedish Twin Registry.' *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 53*(6): M441-M446.

Longo, Valter D. and Rozalyn M. Anderson. (2022). 'Nutrition, Longevity and Disease: From Molecular Mechanisms to Interventions.' *Cell.* 185: 1455-1470. https://doi.org/10.1016/j.cell.2022.04.002.

Lopez-Otin, Carlos, Maria A. Blasco, Linda Partridge, Manual Serrano, and Guido Kroemer. (2023). 'Hallmarks of Aging: An Expanding Universe.' *Cell.* 186: 243-278. https://www.sciencedirect.com/science/article/pii/S0092867422013770

Lustig, Robert H. (2021). *Metabolical: The Lure and the Lies of Processed Food, Nutrition and Modern Medicine: Unpacking the Science Behind Food and Health.* New York: Harper.

Marcus, Amy Dockser, Alex Janin and Shane Shifflett. (2024). "A 'Reverse Aging' Guru's Trail of Failed Businesses." *Wall Street Journal.* December 5. https://www.wsj.com/health/wellness/david-sinclair-reverse-aging-failed-business-8bc4a43d.

Medina, Lauren, Shannon Sabo and Jonathan Vespa. (2020). 'Living Longer: Historical and Projected Life Expectancy in the United States, 1960 to 2060.' *Current Population Reports.* U.S. Census Bureau, Washington, D.C. P25-1145.

Merriam-Webster. (2018). *Dictionary*. https://www.merriam-webster.com/wordplay/what-is-health-span.

Mertens, Stephanie, Mario Herberz, Ulf J. J. Hahnel, and Tobias Brosch. (2021). "The Effectiveness of Nudging: A Meta-analysis of Choice Architecture Interventions Across Behavioral Domains." *PNAS.* 119(1):e2107346118. https://doi.org/10.1073/pnas.2107346118

McGrane, Kelli and Rachael Ajmera. (2024). 'A Quick Guide to GLP-1 Medications: Cost, Effectiveness and More.' *Healthline.* May 20, 2024. https://www.healthline.com/health/weight-loss/glp1-for-weight-loss#how-to-get-a-prescription

McKinsey. (2022). 'Still Feeling Good: The US Wellness Market Continues to Boom.' McKinsey insights.

https://www.mckinsey.com/industries/consumer-packaged-goods/our-insights/still-feeling-good-the-us-wellness-market-continues-to-boom.

McKinsey. (2024). 'The Trends Defining the $1.8 Trillion Global Wellness Market in 2024.' McKinsey Insights. https://www.mckinsey.com/industries/consumer-packaged-goods/our-insights/the-trends-defining-the-1-point-8-trillion-dollar-global-wellness-market-in-2024#/

Mitnitski, Arnold, Alexander Mogilner, and Kenneth Rockwood. (2001). 'Accumulation of Deficits as a Proxy Measure of Aging.' *The Scientific World* 1: 323–336.

Monteiro, C. A., G. Cannon, J.C. Moubarac, R.B. Levy, M.L.C. Louzada, and P.C. Jaime. (2018). 'The UN Decade of Nutrition, the NOVA Food Classification and the Trouble with Ultra-processing.' *Public Health Nutrition*, *21*(1), 5-17.

Mortensen, L., J. Rehnberg, E. Dahl, F. Diderichsen, J. Elstad, P. Partikainen, D. Rehkopf, L. Tarkiainen, and J. Fritzell. (2016). 'Shape of the Association between Income and Mortality: A Cohort Study of Denmark, Finland, Norway and Sweden in 1995 and 2003.' *BMJ Open.* 6: e010974. https://doi.org/10.1136/bmjopen-2015-010974

National Academy of Medicine. (2022). 'Global Roadmap for Healthy Longevity.' https://nam.edu/initiatives/grand-challenge-healthy-longevity/global-roadmap-for-healthy-longevity/

National Academies of Sciences, Engineering, and Medicine. (2021). *High and Rising Mortality Rates Among Working-Age Adults*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25976.

National Academies of Sciences, Engineering, and Medicine. (2024). *Launching Lifelong Health by Improving Health Care for Children, Youth, and Families.* Washington, DC: The National Academies Press. https://doi.org/10.17226/27835

Nature Aging. (2025). "Seventy May Really Be The New Sixty for English Baby Boomers." *Nature Aging* Research Briefing. 5:19-20.

Neville, Sarah. (2024). 'Big Rise in Diseases Linked to Ageing and Lifestyle Increases Healthcare Burden.' FT.com, May 16. https://www.ft.com/content/256d69f3-adcf-4740-aae7-9afa9ee59026

Newman, Phil and Christine Belleza. (2024). 'Annual Longevity Investment Report 2023.' Longevity.techology. https://longevity.technology/investment/

Newman, Saul Justin (2024). 'Supercentenarian and Remarkable Age Records Exhibit Patterns Indicative of Clerical Errors and Pension Fraud.' *bioRxiv.* March 14, 2024. https://doi.org/10.1101/704080.

Oeppen J. and Vaupel, J.W. (2002). 'Demography. Broken Limits to Life Expectancy.' *Science.* 296. 1029-1031.

Oh, Hamilton Se-Hwee et al. (2023). 'Organ Aging Signatures in the Plasma Proteome Track Health and Disease.' *Nature.* 624: 164-172.

Olshansky, S. Jay, Bruce A. Carnes and Aline Désesquelles (2001). 'Prospects of Human Longevity.' *Science.* 291(5508): 1491-1492.

Olshansky, S. Jay and Bruce A. Carnes. (2019). 'Inconvenient Truths About Human Longevity.' *The Journals of Gerontology: Series A.* 74 (supplement 1): December 2019. S7-S12.

Olshansky, S. Jay (2022). 'From Life Span to Health Span: Declaring 'Victory' in the Pursuit of Human Longevity.' *Cold Spring Harbor Perspectives in Medicine.* https://perspectivesinmedicine.cshlp.org/content/12/12/a041480.long

Olshansky, S. Jay, Bradley J. Willcox, Lloyd Demetrius and Hiram Beltrán-Sánchez. (2024). "Implausibility of Radical Life Extension in Humans in the Twenty-first Century." *Nature Aging.* https://doi.org/10.1038/s43587-024-00702-3.

Pega, Frank, Bálint Náfrádi, Natalie C. Momen, Yuka Ujita, Kai N. Streicher, Annette M. Prüss-Üstün, Alexis Descatha, Tim Driscoll, Frida M. Fischer, Lode Godderis, Hannah M. Kiiver, Jian Li, Linda L. Magnusson Hanson, Reiner Rugulies, Kathrine Sørensen, and Tracey J. Woodruff. (2021). 'Global, Regional, and National Burdens of Ischemic Heart Disease and Stroke Attributable to Exposure to Long Working Hours for 194 countries, 2000–2016: A Systematic Analysis from the WHO/ILO Joint Estimates of the Work-related Burden of Disease and Injury.' *Environment International*. 154: 106595. https://doi.org/10.1016/j.envint.2021.106595.

Park, Jooho and Dong Wook Shin. (2022). 'Senotherapeutics and Their Molecular Mechanism for Improving Aging.' *Biomolecules & Therapeutics.* 30(60): 490-500. https://doi.org/10.4062/biomolther.2022.114.

Petimar, Joshua, Christina A. Roberto, Jason P. Block, Nadita Mitra, Emily F. Gregory, Emma K. Edmondson, Gary Hettinger and Laura A. Gibson. (2024). 'Association of the Philadelphia Sweetened Beverage Tax with Changes in Adult Body Weight: An Interrupted Time Series Analysis." *The Lancet Regional Health.* 39, 100906. https://www.doi.org/10.1016/j.lana.2024.100906

Pignolo, Robert J. (2019). 'Exceptional Human Longevity.' *Mayo Clinic Proceedings.* 94(1): 110-124.

Ramakrishnan, Venki. (2024). *Why We Die: The New Science of Aging and the Quest for Immortality.* New York: William Morrow.

Rauber, F., M.L. da Costa Louzada, K Chang, I. Huybrechts, M.J. Gunter, C.A. Monteiro, E.P. Vamos, and R.B. Levy. (2024). 'Implications of Food Ultra-processing on Cardiovascular Risk Considering Plant Origin Foods: An Analysis of the UK Biobank Cohort.' *The Lancet Regional Health–Europe*. 43: 100948.

Quinby, Laura D. and Gal Wettstein. (2021). 'Are Older Workers Capable of Working Longer?' *Issue in Brief.* Number 21-12. Center for Retirement Research at Boston College. https://crr.bc.edu/wp-content/uploads/2021/07/IB_21-12.pdf.

Raleigh, Veena S. (2019). 'Trends in Life Expectancy in EU and Other OECD Countries: Why are Improvements Slowing?' *OECD Health Working Papers*. No. 108. OECD Publishing, Paris. https://doi.org/10.1787/223159ab-en.

Reuser, Mieke, Frans J. Willekens and Luc Bonneux. (2011). 'Higher Education Delays and Shortens Cognitive Impairment: A Multistate Life Table Analysis of the US Health and Retirement Study.' *Neuro-Epidemiology.* 26:395-403. https://doi.org/10.1007/s10654-011-9553-x.

Rutledge, Jason, Hamilton Oh and Tony Wyss-Coray. (2022). 'Measuring Biological Aging Using Omics Data.' *Nature Reviews Genetics.* 23. 715-727.

Ruhm, Christopher J. (2022). 'Living and Dying in America: An Essay on *Deaths of Despair and the Future of Capitalism.' Journal of Economic Literature.* 60(4): 1159-1187.

Russo, Nicolò, Rory McGee, Mariacristina De Nardi, Margherita Borella and Ross Abram. (2024). "Health Inequality and Economic Disparities by Race, Ethnicity and Gender." NBER Working Paper 32971. www.nber.org/papers/w32971.

Sadana, Ritu, Erik Blass, Suman Budhwani, Theadora Koller, and Guillermo Paraje. (2016). 'Healthy Ageing: Rising Awareness of Inequalities, Determinants, and What Could Be Done to Improve Health Equity.' *The Gerontologist.* 56: Issue Suppl_2, S178-S193. https://doi.org/10.1093/geront/gnw034.

Schaeffer, Katherine. 2024. 'U.S. Centenarian Population is Projected to Quadruple Over the Next 30 Years.' Pew Research Center Report, January 9. https://www.pewresearch.org/short-reads/2024/01/09/us-centenarian-population-is-projected-to-quadruple-over-the-next-30-years/

Scott, Andrew. (2024). *The Longevity Imperative.* New York: Basic Books, Hachette Book Group.

Shen, Xiaotao, Chuchu Wang, Xin Zhou, Wenyu Zhou, Daniel Hornburg, Si Wu and Michale P. Snyder. (2024). "Nonlinear Dynamics of Multi-omics Profiles during Human Aging." *Nature Aging.* August 14. https://doiorg/10.1038/s43587-024-00692-2.

Shukla, Deep. (2025). 'How to Preserve Muscle on Weight Loss Drugs like Wegovy.' *Medical News Today.* January 7. https://www.medicalnewstoday.com/articles/how-to-preserve-muscle-mass-on-weight-loss-drugs-like-wegovy

Siera, Felipe. (2016). 'The Emergence of Geroscience as an Interdisciplinary Approach to the Enhancement of Health Span and Life Span.' *Cold Spring Harbor Perspectives in Medicine.* 6(4): a025163. https://doi.org/10.1101/cshperspect.a025163.

Sinclair, David A. with Matthew A. LaPlante. (2019). *Lifespan: Why We Age—And Why We Don't Have to.* New York: Atria Books.

Skytthe, Axel, Nancy L. Pedersen, Jaako Kaprio, Maria Antonietta Stazi, Jacob v.B. Hjemlbor, Ivan Iachine, James W. Vaupel, and Kaare Christensen. (2003). 'Longevity Studies in GenomEUtwin.' *Twin Res.* 6: 448-454.

Smith, Dana G. (2024). 'Why Do We Age? Scientists are Figuring It Out.' *New York Times.* March 20. https://www.nytimes.com/2024/03/20/well/live/aging-biology-dna.html.

Steenhuysen, Julie. 2024. 'Alzheimer's Drug Adoption in US Slowed by Doctors' Skepticism.' *Reuters.* April 23, 2024. https://www.reuters.com/business/healthcare-pharmaceuticals/alzheimers-drug-adoption-us-slowed-by-doctors-skepticism-2024-04-23/.

Stibich, Mark. (2022). 'Healthy Life Expectancy and How It's Calculated.' Verywellhealth. https://www.verywellhealth.com/understanding-healthy-life-expectancy-2223919.

Sullivan D.F. (1971). 'A Single Index of Mortality and Morbidity.' *HSMHA Health Rep.* 86: 347–54.

Swiss Re Institute. (2023). 'The Future of Life Expectancy.' Swiss Re Institute, Zurich, Switzerland. https://www.swissre.com/institute/research/topics-and-risk-dialogues/health-and-longevity/future-life-expectancy-long-term-mortality-improvement-insurance.html

US Census Bureau. (Nd). 'International Database: World Population Estimates and Projections.' https://www.census.gov/programs-surveys/international-programs/about/idb.html

US National Institutes of Health. (Nd). 'Geroscience: The Intersection of Basic Aging Biology, Chronic Disease, and Health.' National Institute on Aging Report. https://www.nia.nih.gov/research/dab/geroscience-intersection-basic-aging-biology-chronic-disease-and-health

Van Tulleken, Chris. (2023). *Ultra-Processed People: The Science Behind Food That Isn't Food.* New York: W.W. Norton and Company,

Vaupel, James W., Francisco Villavicencio, and Marie-Pier Bergeron-Boucher (2021). 'Demographic Perspectives on the Rise of Longevity.' *PNAS.* 118(9). 1-10.

Walker, Joseph, Peter Loftus, and Dominique Mosbergen. (2024). 'Alzheimer's Disease Treatments: What to Know About New and Future Drugs.' *Wall Street Journal.* July 2. https://www.wsj.com/health/alzheimers-drugs-new-treatments-11672850623.

Wang, Fan, Yu Gao, Zhen Han, Yue Yu, Zhiping Long, Xianchen Jiang. Yi Wu, Bing Pei, Yukun Cao, Jingyu Ye, Maoqing Wang, and Yashuang Zhao. (2023). 'A Systematic Review and Meta-analysis of 90 Cohort Studies of Social Isolation Loneliness and Mortality.' *Nature Human Behavior.* 7: 1307-1319. https://doi.org/10.1038/s41562-023-01617-6.

Wen, Leana S. (2024). 'How 'Obesity First' Health Care is Transforming Medicine.' *Washington Post.* October 1. https://www.washingtonpost.com/opinions/2024/10/01/obesity-first-health-care-semaglutide-wegovy-ozempic/.

WHO. (Nd.). 'The Global Health Observatory.' Indicator Metadata Registry List. https://www.who.int/data/gho/indicator-metadata-registry/imr-details/66

WHO. (2008). 'Closing the Gap in a Generation: Health Equity Through Action on the Social Determinants of Health – Final Report of the Commission on Social Determinants of Health.' https://www.who.int/publications/i/item/WHO-IER-CSDH-08.1.

WHO. (2015). "World Report of Ageing and Health." https://iris.who.int/bitstream/handle/10665/186463/9789240694811_eng.pdf?sequence=1

WHO. (2020a). 'GHE: Life Expectancy and Healthy Life Expectancy.' World Health Organization Global Health Estimates. Geneva. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-life-expectancy-and-healthy-life-expectancy.

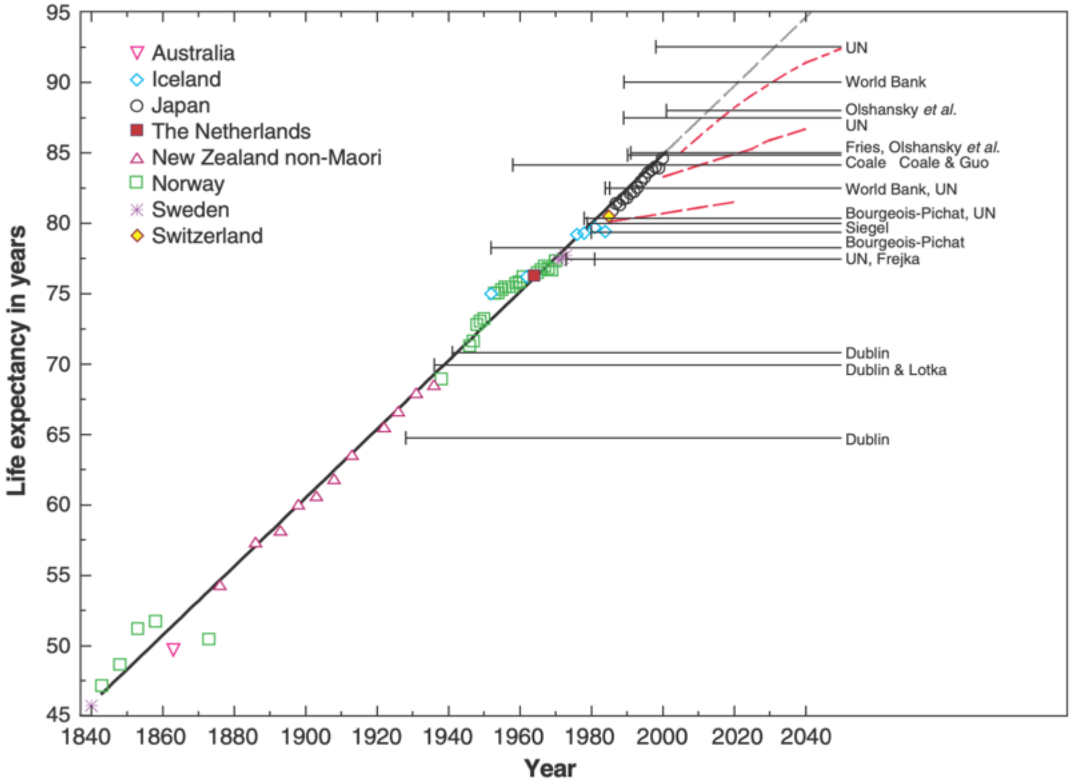
WHO. (2020b). 'WHO Methods and Data Sources for Life Tables 1990-2019.' World Health Organization Department of Data and Analytics. Geneva. Switzerland. https://cdn.who.int/media/docs/default-source/gho-documents/global-health-estimates/ghe2019_life-table-methods.pdf.

Yang, Bo-Yi, Shujan Fan, Elisabeth Thiering, Jochen Siessler, Dennis Nowak, Guang-Hui Dong, and Joachim Heinrich. 2020. 'Ambient Air Pollution and Diabetes: A Systematic Review and Meta-Analysis.' *Environmental Research.* 180: 108817.

Zaninotto, Paola, George David Baatty, Sair Stenhold, Ichiro Kawachi, Martin Hyde, Marcel Goldberg, Hugo Westerlund, Jussi Vahtera and Jenny Head. (2020a). 'Socioeconomic Inequalities in Disability-free Life Expectancy in Older People from England and the United States: A Cross-national Population-Based Study.' *The Journals of Gerontology: Series A.* 75(5): 906-913. https://doi.org/10.1093/gerona/glz266.

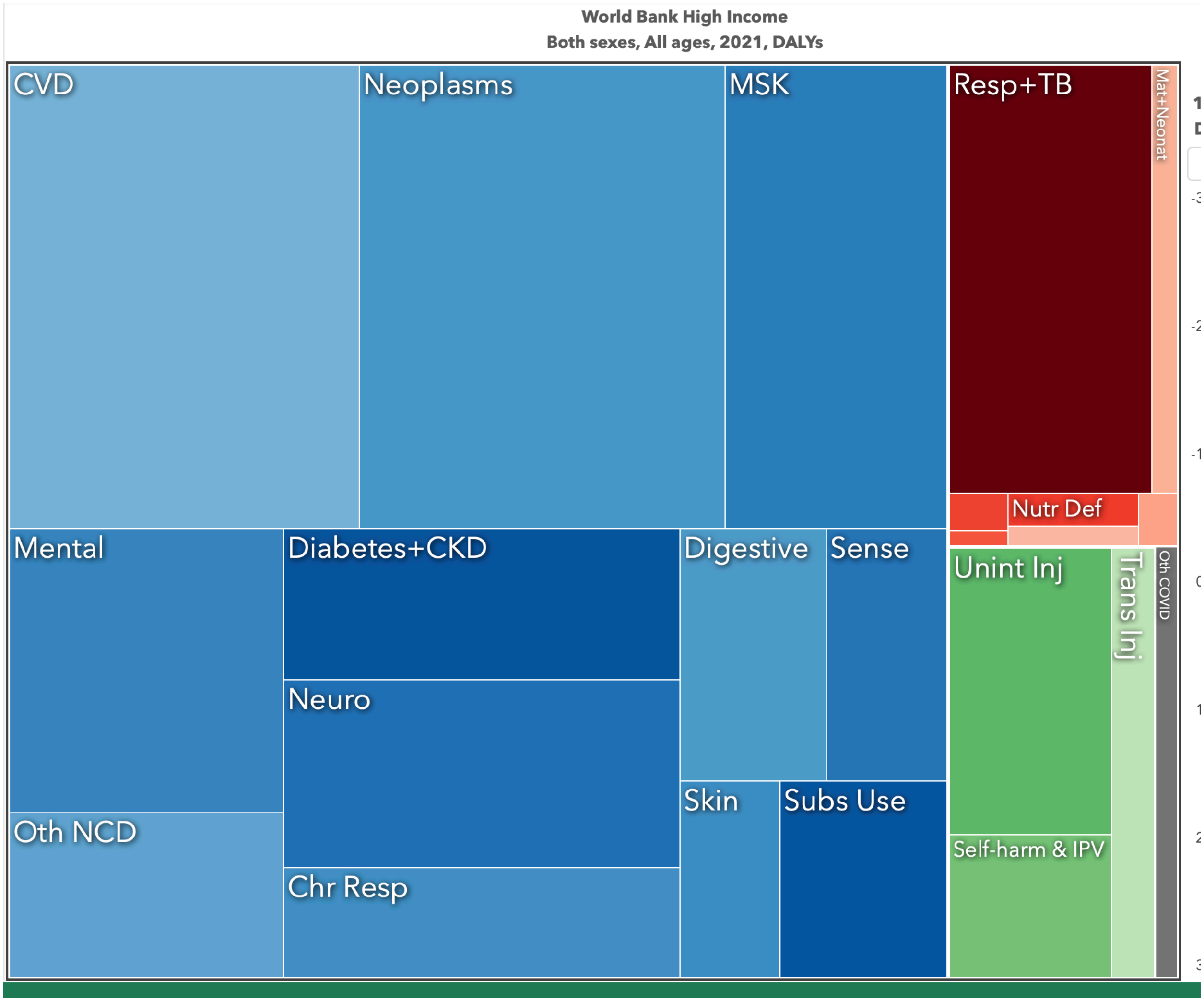
Zaninotto, Paola, Jenny Head and Andrew Steptoe. (2020b). 'Behavioral Risk Factors and Healthy Life Expectancy from Two Longitudinal Studies of Ageing in England and the US.' *Scientific Reports.* 10: Article number 6955. https://doi.org/10.1038/s41598-020-63843-6.

Figure 1. Record Female Life Expectancy from 1840 to the Present



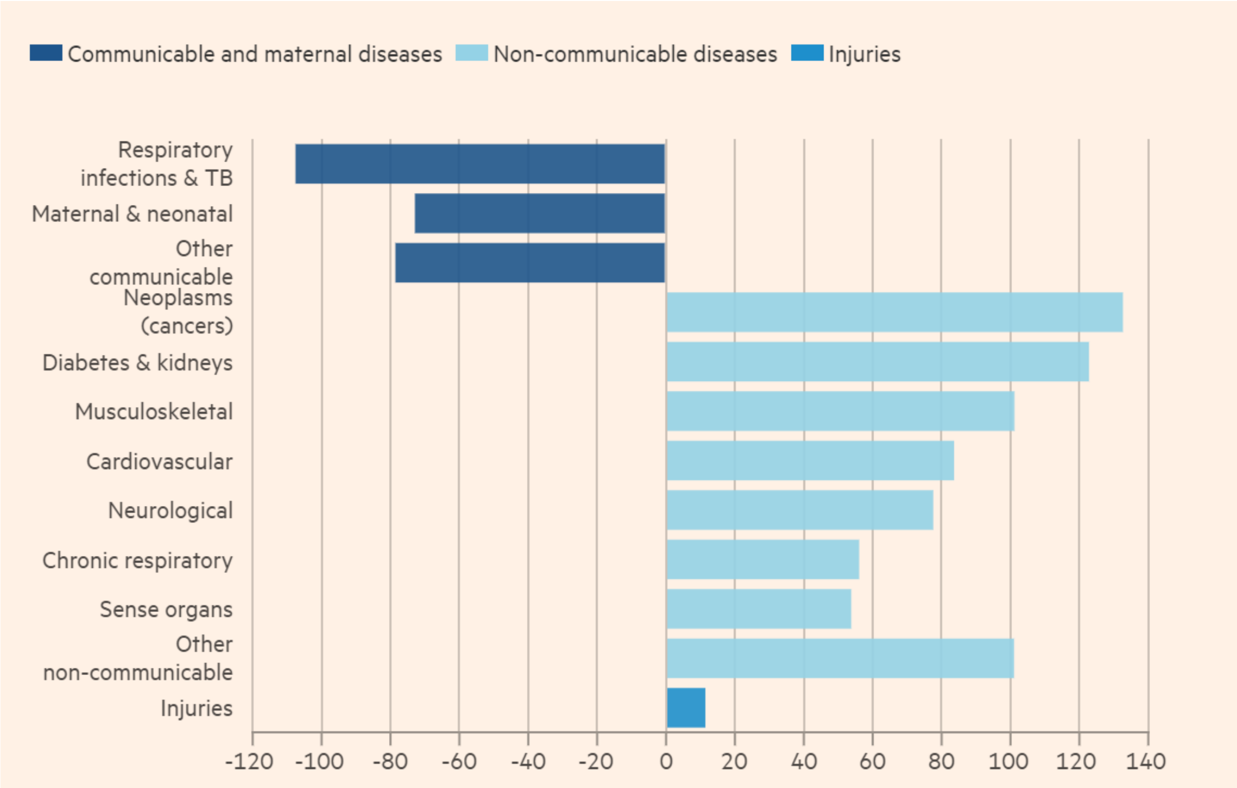
Note: The linear-regression trend is the bold black line (slope = 0.243) and the extrapolated trend is the dashed gray line. The horizontal black lines show asserted ceilings on life expectancy, with a short vertical line indicating the year of publication.
Source: Oeppen and Vaupel (2002).

Figure 2. Disability-Adjusted Life Years for All Causes, High Income Countries, 2021



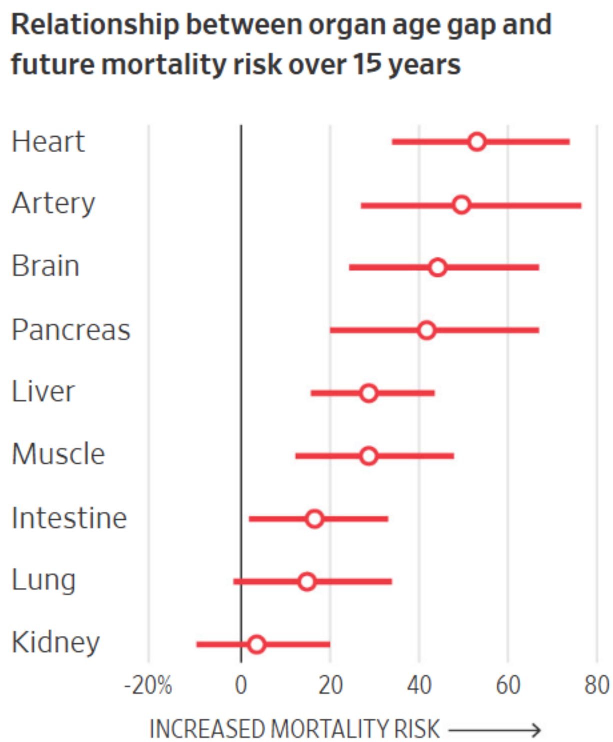
Note: Graphical presentation of DALYs (disability-adjusted life years) for all causes for World Bank upper come countries from GBD 21. See the note for Table 2 for more information on World Bank country income definitions. In the chart above, the area of each block represents the relative proportion of DALYs lost to a given disease or disability; the total graph sums to 100%. CVD = cardiovascular diseasse; MSK = musculoskeletal disability; CKD = chronic kidney siease; other NCD = other non-communicable disease; IPV = interpersonal injury.
Source: Authors' calculations using the GBD21 data analysis tool.

Figure 3. Forecast of Chronic Disease Burden Through 2050



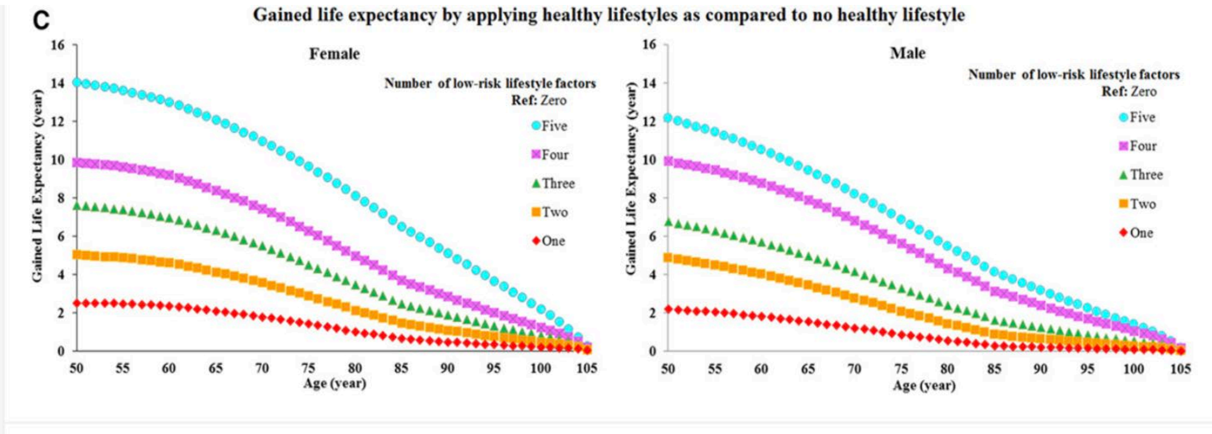
Note: One DALY represents the loss of the equivalent of one year of full health. DALYs are the sum of years of life lost due to premature mortality and years lived with a disability (Total = 481mn).
Source: Neville (2024).

Figure 4. Increased Mortality Risk from Organ Aging



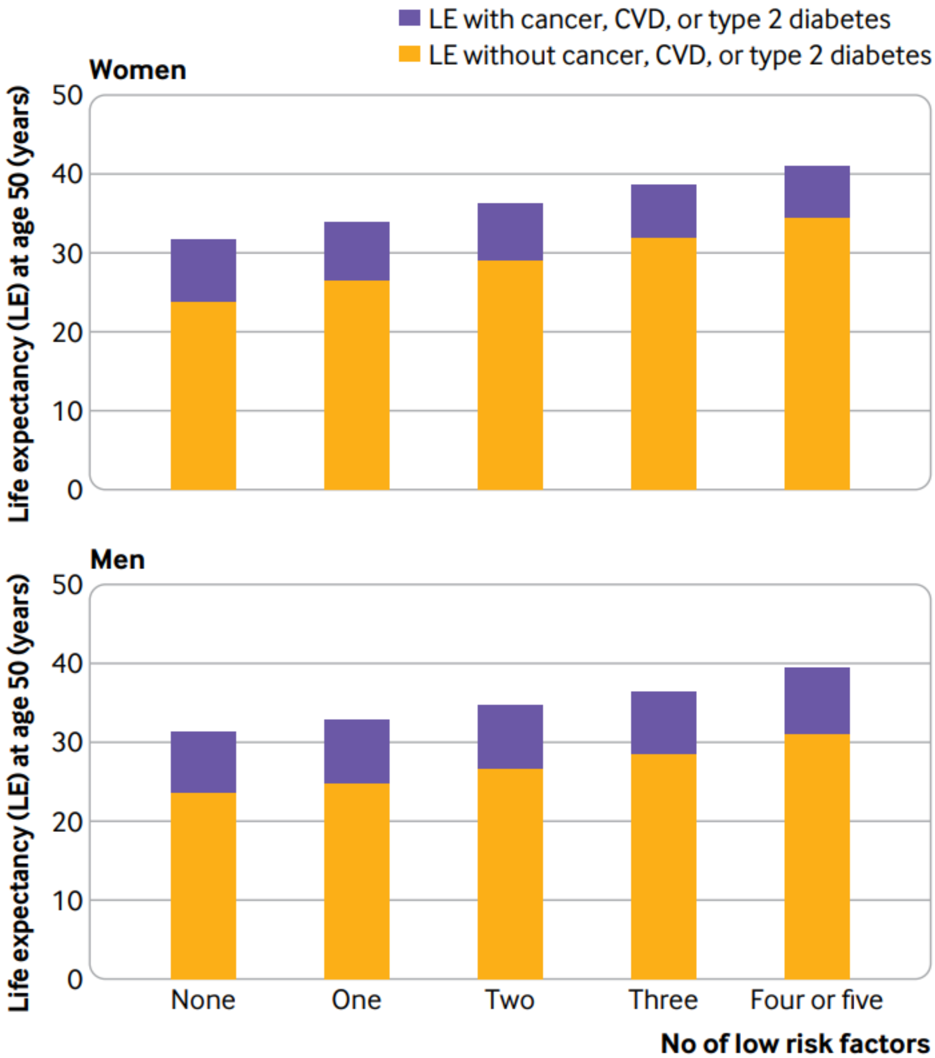
Note: Bars show 95% confidence interval. Organs are one standard increment above baseline organ age.
Source: Janin (2024).

Figure 5. Life Expectancy Gains from Adopting Healthy Lifestyles Compared to Adopting None



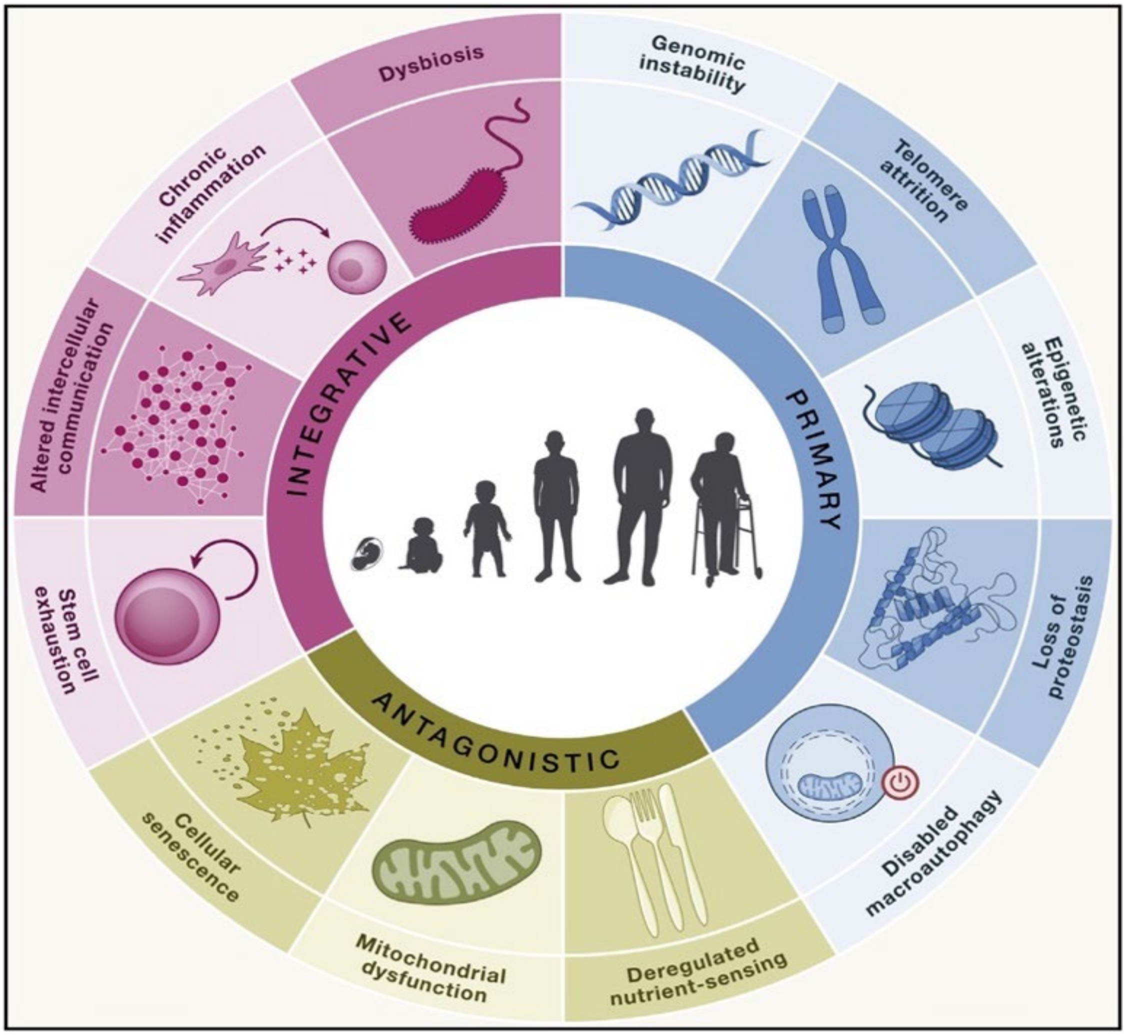
Notes: Low-risk lifestyle factors included cigarette smoking (never smoking), physically active (≥3.5 h/wk of moderate to vigorous intensity activity), high diet quality (upper 40% of Alternate Healthy Eating Index), moderate alcohol intake of 5 to 15 g/d (female) or 5 to 30 g/d (male), and normal weight (body mass index <25 kg/m2). Estimates of cumulative survival from 50 years of age onward among the 5 lifestyle risk factor groups were calculated by applying the following: (1) all-cause and cause-specific mortality rates were obtained from the US CDC WONDER database; (2) distribution of different numbers of low-risk lifestyles was based on the US NHANES 2013 to 2014; and (3) multivariate-adjusted hazard ratios (sex- and age-specific) for all-cause mortality associated with the 5 low-risk lifestyles compared with those without any low-risk lifestyle factors, adjusted for ethnicity, current multivitamin use, current aspirin use, family history of diabetes mellitus, myocardial infarction, or cancer, and menopausal status and hormone use (women only), were based on data from the NHS (Nurses' Health Study) and HPFS (Health Professionals Follow-up Study). CDC WONDER indicates Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research.
Source: Li et al. (2018).

Figure 6. Estimated Life Expectancy Gains at Age 50, With and Without 3 Chronic Diseases



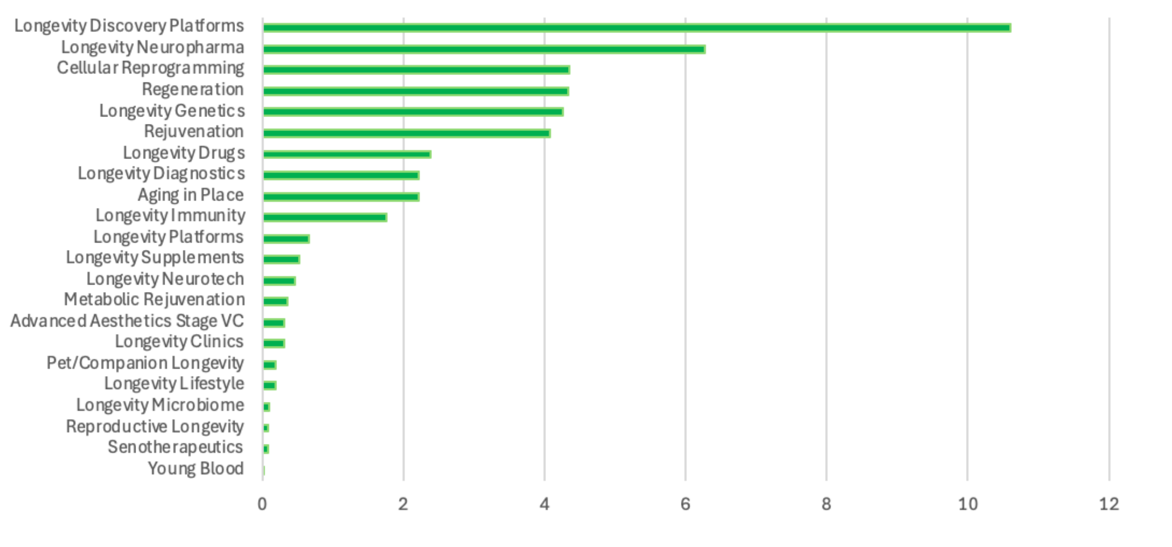
Notes: Estimated life expectancy at age 50 years with and without cancer, cardiovascular disease (CVD), and/or type 2 diabetes among participants of Nurses' Health Study (women) and Health Professionals Follow-up Study (men) according to number of low risk lifestyle factors. Low risk lifestyle factors included cigarette smoking (never smoking), physical activity (≥3.5 hours/week moderate to vigorous intensity activity), high diet quality (upper 40% of Alternate Healthy Eating Index), moderate alcohol intake of 5-15 g/day (women) or 5-30 g/day (men), and normal weight (body mass index <25). Estimates of multivariate adjusted hazard ratios (sex specific) for morbidity and mortality associated with low risk lifestyles compared with people with zero low risk lifestyle factors adjusted for age, ethnicity, current multivitamin use,current aspirin use, family history of diabetes, myocardial infarction, or cancer, and menopausal status and hormone use (women only)
Source: Li et al. (2020).

Figure 7. The 12 Hallmarks of Cellular Aging



Notes: The 12 hallmarks of aging proposed include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis. These hallmarks are grouped into three categories: primary, antagonistic, and integrative.
Source: Lopez-Otin et al. (2023).

Figure 8. Total Financing ($B) in Longevity Marketplace By Investment Domain, 2019-2023



Notes: Total financing ($bn) by domain from 2019-2023. Deal types included in the analysis are: Accelerator/Incubator, Angel, Corporate, Early Stage VC, Later Stage VC, Equity Crowdfunding, IPO, PE Growth/Expansion, PIPE, Public Investment 2nd Offering, and Seed Round. Analysis by Longevity.Technology, according to Pitchbook data as of the 17th of January 2024, based on 967 companies.
Source: Authors' interpretation of data from Newman and Belleza (2024).

Table 1. Global Life Expectancy (LE) and Healthy Life Expectancy (HALE), in years

	1990	2019	2021	Change 1990-2019	1990-2021	2019-2021
A. Global means						
LE	65.5	73.3	71.2	7.8	5.7	(2.1)
HALE	57.1	63.6	62.2	6.5	5.1	(1.4)
LE-HALE	8.4	9.7	9.0			
B. Global means by sex						
LE						
Female	69.1	76.0	74.8	6.9	5.7	(1.2)
Male	63.1	70.8	69.0	7.7	5.9	(1.8)
HALE						
Female	58.4	64.8	63.6	6.4	5.2	(1.2)
Male	55.8	62.5	60.9	6.7	5.1	(1.6)
LE - HALE						
Female	10.7	11.2	11.2			
Male	7.3	8.3	8.1			

Note: Mean life expectancy at birth (LE) and healthy average life expectancy (HALE) globally and by sex from the Global Burden of Disease 21 (GBD21).
Source: Authors' calculations using the GBD21 data analysis tool.

Table 2. Global Life Expectancy (LE) and Healthy Life Expectancy (HALE) by Country Income, in years

By World Bank income categories	1990	2019	2021	*Change* 1990-2019	*Change* 1990-2021	*Change* 2019-2021
LE						
Upper income	75.6	81.2	80.2	*5.6*	*4.6*	*(1.0)*
Upper middle	68.3	76.2	74.9	*7.9*	*6.6*	*(1.3)*
Lower middle	61.4	69.8	67.9	*8.4*	*6.5*	*(1.9)*
Lower	52.7	64.6	62.2	*11.9*	*9.5*	*(2.4)*
HALE						
Upper income	65.5	69.5	68.5	*4.0*	*3.0*	*(1.0)*
Upper middle	60.2	66.8	65.6	*6.6*	*5.4*	*(1.2)*
Lower middle	53.1	60.5	58.8	*7.4*	*5.7*	*(1.7)*
Lower	45.8	56.3	54.4	*10.5*	*8.6*	*(1.9)*
LE - HALE						
Upper income	10.1	11.7	11.7			
Upper middle	8.1	9.4	9.3			
Lower middle	8.3	9.3	9.1			
Lower	6.9	8.3	7.8			

Notes: Mean life expectancy at birth (LE) and healthy average life expectancy (HALE) by World Bank country income from the Global Burden of Disease 21 (GBD21). See Hamadeh et al. (2002) for information on World Bank income categories. In 2021, 37% of 217 rated countries were upper income; 25% upper-middle income; 25% lower-middle income; and 13% lower income.
Source: Authors' calculations using the GBD21 data analysis tool.

Table 3. Years Lost to Premature Death or Disability for Select High-income Countries, 2021

	Years Lost per 100K Inhabitants
Australia	26,047
Norway	26,072
Switzerland	26,745
Canada	29,394
France	30,152
Japan	30,591
United Kingdom	31,852
Italy	32,805
Germany	34,571
United States	38,079

Note: Disability-adjusted life years (DALYs) per 100,000 residents for a select group of high-income countries from the Global Burden of Disease 21 (GBD21).
Source: Authors' calculations using the GBD21 data analysis tool.