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Translational longevity medicine: a Swiss perspective in an ageing country

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Summary

Breakthroughs in medical research in the last century have led to a significant extension of the human lifespan, resulting in a shift towards an elderly population worldwide. Due to the ongoing progress of global development towards elevated standards of living, this study specifically examines Switzerland as a representative nation to explore the socioeconomic and healthcare ramifications associated with an ageing population, thereby highlighting the tangible impact experienced in this context. Beyond the exhaustion of pension funds and medical budgets, by reviewing the literature and analysing publicly available data, we observe a "Swiss Japanification". Old age is associated with late-life comorbidities and an increasing proportion of time spent in poor health. To address these problems, a paradigm shift in medical practice is needed to improve health rather than respond to existing diseases. Basic ageing research is gaining momentum to be translated into therapeutic interventions and provides machine learning tools driving longevity medicine. We propose that research focus on closing the translational gap between the molecular mechanisms of ageing and a more prevention-based medicine, which would help people age better and prevent late-life chronic diseases.

The ageing demographics of Switzerland

Over the past century, Switzerland's cumulative survival over time or lifespan has improved dramatically for both men and women (figures 1A and 1B). Although most reports focus on life expectancy, the field of public health is shifting towards lifespan and healthspan. From 1880 to 2018, mean lifespan increased by 98.34% and 94.61% in men and women respectively: from 41.17 to 81.66 years and from 44.14 to 85.90 years respectively (figures 1A and 1B) [1]. During the late 19th and early 20th centuries, the improvement in overall survival was mainly due to the reductions in infectious disease mortality and in the infant mortality rate from its previously high level [2]. Indeed, in 1876 roughly 20% of infants died within their first year of life [1]. The trend of increasing lifespan has continued into the 21st century [1, 2], albeit at a slower rate, ascribed to – among other factors – a healthier lifestyle and better treatment for cancer and cardiovascular diseases. The median age of the Swiss population has increased steadily even in the last 50 years, except for a brief period, mainly due to immigration [3], in the 1990s (figure 1C) [4]. In contrast, the maximum lifespan increased by a lower amount, by 11 and 14 years to 109 and 112 years in 2018 for men and women, respectively (figures 1A and 1B, data source file 1 [a link is provided at the end of the article]) [5]. The Swiss Federal Statistical Office predicts that the increases in the mean lifespan and – to a lesser extent – the maximum lifespan will continue up to 2150 (figures 1A and 1B) [5]. Although there is debate on whether human lifespan is limited to 115–120 years [6–8], these estimates suggest a maximal human lifespan of 112 and 115 years for Swiss men and women, respectively, in 2150 (data source file 1).

Similar improvements in lifespan have been recorded worldwide, with a steady increase in life expectancies (figure 1D). Life expectancy is the estimated number of years from birth a person is expected to live. In 2017, Japanese women had the highest life expectancy at 87.21 years, followed by Swiss women at 85.67 years, followed by women in higher-income OECD countries at 83.08 years (figure 1D) [9]. OECD longevity has recently been dampened by a stagnating-to-declining (2014 to 2015) life expectancy in the US due to various factors [10], including the opioid crisis, alcoholism, external causes of death (accidents, homicides, suicides, drug-related deaths), obesity and diabetes [11, 12], a trend not observed in Switzerland (supplementary figures 1A–1C). Around 2005, the life expectancy of Swiss men surpassed that of Japanese men and in 2019 they had the highest life expectancy of men of any sovereign nation (figure 1D) [13]. Worldwide, there is a significant gap in life expectancy between men and women, with women living longer (figure 1D). For Switzerland, this sex difference widened during the mid-to-late 20th cen-

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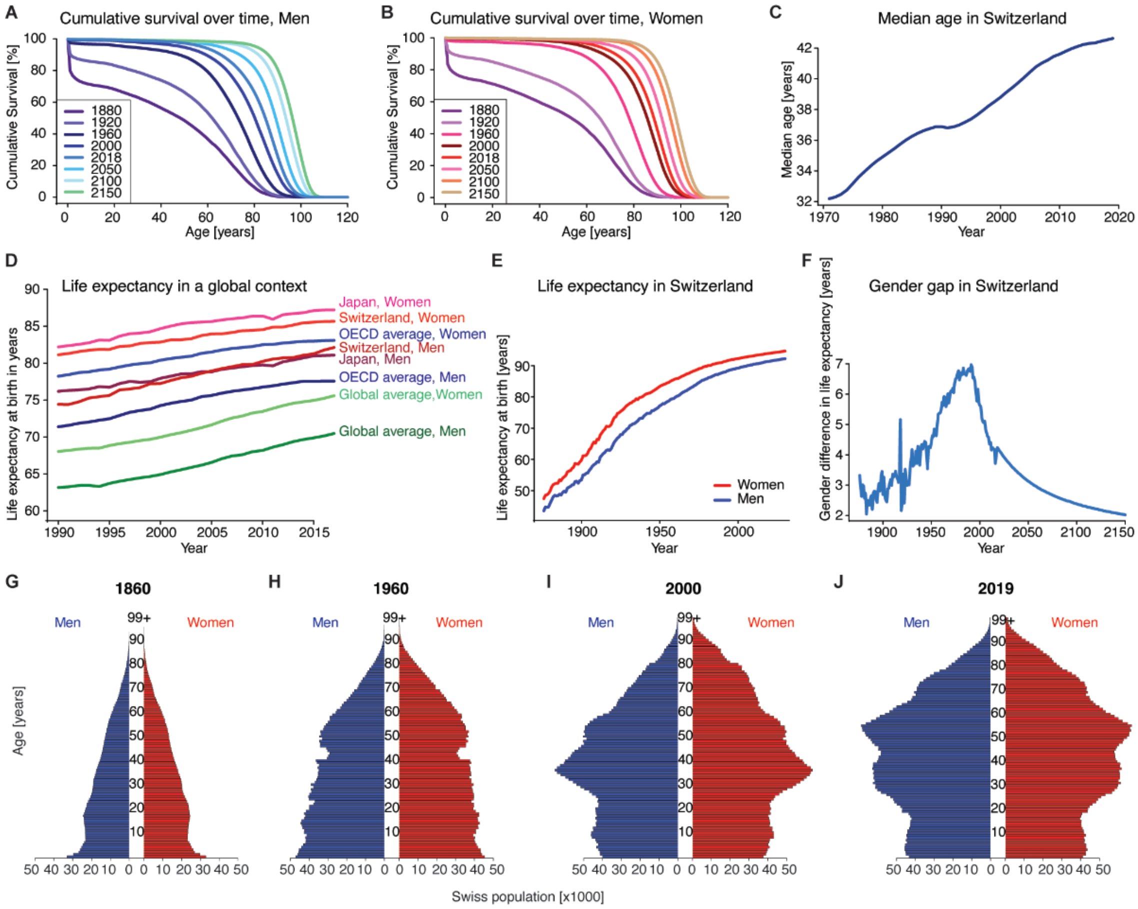
tury (figures 1E and 1F; supplementary figures 1D and 1E). As cardiovascular deaths of men in retirement (>65 years) are being increasingly prevented by better medical care [2], and women more often are exposed to similar risk factors as men (smoking, stress, etc. [14]), the sex gap is decreasing and projected to become smaller in the next hundred years (figure 1F). Compared to other OECD countries, the sex gap in Switzerland is in the lower range [15].

While life expectancy in Switzerland has greatly increased over the last one and a half centuries, birth rates have declined significantly (supplementary figure 1F) [16], now being below the replacement rate of, on average, 2.1 births per woman [17]. These dynamics, fuelled by progress in medical science and increased education, have led to a dramatic change from a younger to an elderly Swiss population, as illustrated in the population pyramids for the years 1860, 1960, 2000 and 2019 (figures 1G to 1J, supplementary video 1).

In the 1960 population pyramid, the indentation at around 40 years of age is caused by reduced birth numbers during the First World War (figure 1H) [18]. At the bottom of the 1960 pyramid, two larger cohorts are observable, both belonging to the Baby Boomer generation (born 1946–1964; figure 1H). By 2000, these two cohorts were approaching 55 and 40, respectively (figure 1I). Their disproportionate size exceeds the emerging Gen Y (the generation born 1981–1996) and Gen Z (the generation born 1997–2012) numbers and results in more of an arrow shape. In the most recent population pyramid, for 2019, this “silver tsunami” has already partially retired; the bulk however is still approaching retirement age (65 and 64 years for men and women, respectively) (figure 1J).

Figure 1: Ageing demographics of Switzerland. (A) and (B) Cumulative survival order at different ages for Swiss men (A) and women (B) in 1880, 1920, 1960, 2000 and 2018 as well as projections for 2050, 2100 and 2150. The survival order for both sexes has increased at all ages for the period examined and is projected to continue to increase. Source: Swiss Federal Statistical Office. (C) The median age of the Swiss population over time. Source: Swiss Federal Statistical Office. (D) Life expectancy at birth for men and women in Switzerland and Japan, and the OECD average, as well as the global average over time. Female life expectancy has noticeably always been above male life expectancy for all geographic areas considered. Of all sovereign nations, Japanese women have the highest life expectancy globally, and Swiss men are the longest-living men since overtaking Japanese men in the early 2010s. The OECD averages for men and women have been rising slower than Swiss, Japanese and global longevity, due among other factors to stagnant-to-decreasing life expectancy for certain populations in the US. Source: IHME Global Burden of Disease study 2017. (E) Life expectancy at birth in Switzerland over time as well as future projections by the Swiss Federal Statistical Office. Female life expectancy has noticeably always been above male life expectancy. Source: Swiss Federal Statistical Office. (F) Sex gap between female and male life expectancy in Switzerland over time as well as future projections by the Swiss Federal Statistical Office. The difference was calculated by subtracting the male life expectancy at birth from the female life expectancy at birth. Source: Swiss Federal Statistical Office. (G-J) Swiss Population Pyramids for the years 1860, 1960, 2000 and 2019. The blue bars on the left represent men, the red bars on the right represent women; each bar represents a 1-year cohort, size indicated on the x-axis. Source: Swiss Federal Statistical Office. Source data and more detailed references are available in source data file 1.



Supplementary video

The supplementary video 1, Ageing demographics of Switzerland from 1861 to 2019 for men and women, is available at: https://doi.org/10.6084/m9.figshare.21922104.v1.

Economic implications of an ever-increasing elderly Swiss population

Along with the increased life expectancy, the number of centenarians, defined here as people aged 99 and over, has risen exponentially in Switzerland and can reasonably be expected to continue to do so (figure 2A, supplementary figure 1G) [19]. When the Swiss social security system (AHV, *Alters-und Hinterlassenenversicherung*) came into effect in 1948 [20], the remaining life expectancy for people aged 65 was 12.09 years for men and 13.66 years for women (data source file 1) [1], and thus the Swiss retirement age was set at 65 years for men and women (later reduced to 64 for women), so men and women would enjoy 12.09 and 13.66 years respectively of retirement covered by the AHV after the original retirement age (data source file 1). The probability of reaching the age of 65 in 1948 was 64.6% and 73.9% for men and women respectively. Since then, life expectancy has increased to 81.66 and 85.90 years for Swiss men and women; years in retirement increased to 19.78 and 23.83 for men and women, respectively, in 2018, taking into account the lowering of the female retirement age; while the probability of reaching retirement age increased to 90.5% and 95.5% for men and women respectively. Furthermore, the decrease in the younger population (figure 1J) and a younger workforce paying into the AHV, along with the increase in the number of retirement years plus the ever-increasing population of people over 65 years (figure 2B), poses a serious problem and increases the expenditure of the AHV (figure 2C). The number of retirement-aged people in Switzerland was 431,200 in 1948. Hence the minimum payout was almost CHF 207 million in nominal terms annually [20]. In 2020, approximately CHF 42,832,824,000 were paid out to 2,438,761 insured retirees, based on December 2020 data [21].

The Swiss First Pillar (AHV), a pay-as-you-go system [22], is projected to enter an operational deficit in the mid-2020s [23] and rapidly drain its remaining fund assets (figure 2D, 2E). Projections by the proponents of a popular initiative assume up to a CHF 200,000,000,000 cost to the fiscal authorities from the hole in Pillar 1 alone [24]. Swiss pension funds (Pillar 2), which are defined contribution systems, on the other hand, are relatively well-capitalised with assets (depending on the definition used) exceeding CHF 1,000,000,000,000 (figure 2F) [25].

With the increasing number of older people and the decreasing size of the working-age population, the ratio of retirement-age people (defined here as over 65 years as used by the OECD) to the working-age population has increased [26, 27]. This is quantified as the Old Age Dependency Ratio (OADR). An increase in OADR is observed not only in Switzerland but also in other countries around the world, particularly OECD countries, and notably Japan, where it is approaching 50% (figure 2G).

Beyond the issue with pension funds and the AHV, as the fraction of workers relative to the total population (labour force participation rate) (supplementary figures 2A and 2B) declines, GDP growth is likely to decline with it along with real (and potentially nominal) interest rates, a phenomenon termed secular stagnation, studied particularly for the US [28] (supplementary figures 2C–2H), but it is a concept just as relevant for other industrialised countries [29], in particular Switzerland, which may face "long-term secular stagnation in the future", though secular stagnation is not (yet) detected in Switzerland according to Klose (2017) [30]. As observed in the US and Japan, the demographic transition and the ageing of society likely reduce output growth, inflation (figure 2H and 2I, supplementary figures 2C–2E, 2H), and the real as well as the nominal interest rate (figure 2H, supplementary figures 2F and 2G). Government policies, including fiscal and monetary stimuli as well as increased social security spending, may have counteracted part of these effects [29]. Swiss nominal GDP growth, inflation as measured by CPI, and both nominal and real bond yields have been declining in a similar fashion to industrialised economy peers. (figures 2H and 2I, supplementary figures 2F and 2G).

A further consequence of the demographic transition, which also puts further strains on pension systems and funds, comes from the reduced real rates of return (figure 2H, supplementary figure 2F), which can be thought of as the interest rate pension systems receive for investing their assets. This lower interest rate can make it harder to fund future pension obligations.

The dynamics of population ageing and potential secular stagnation in Switzerland and the rest of Europe have, to a certain extent, already been observed. As shown in figure 2G, the OADR in Japan is by far the highest of any major economy, and its rise began earlier and was steeper than the OECD average. Colloquially, the secular stagnation dynamics caused by population ageing are also referred to as "Japanification" [31]. In 1991, a large asset bubble burst in Japan, followed by a deep and long recession, where asset price movements played a role, and both Japanese economic growth and asset prices have been subdued since [32]. Goodhart and Pradhan [33] argue that several factors in Japan actually softened its fall in GDP growth and that these may be absent for (part of) the rest of the industrialised world (supplementary figure 2H).

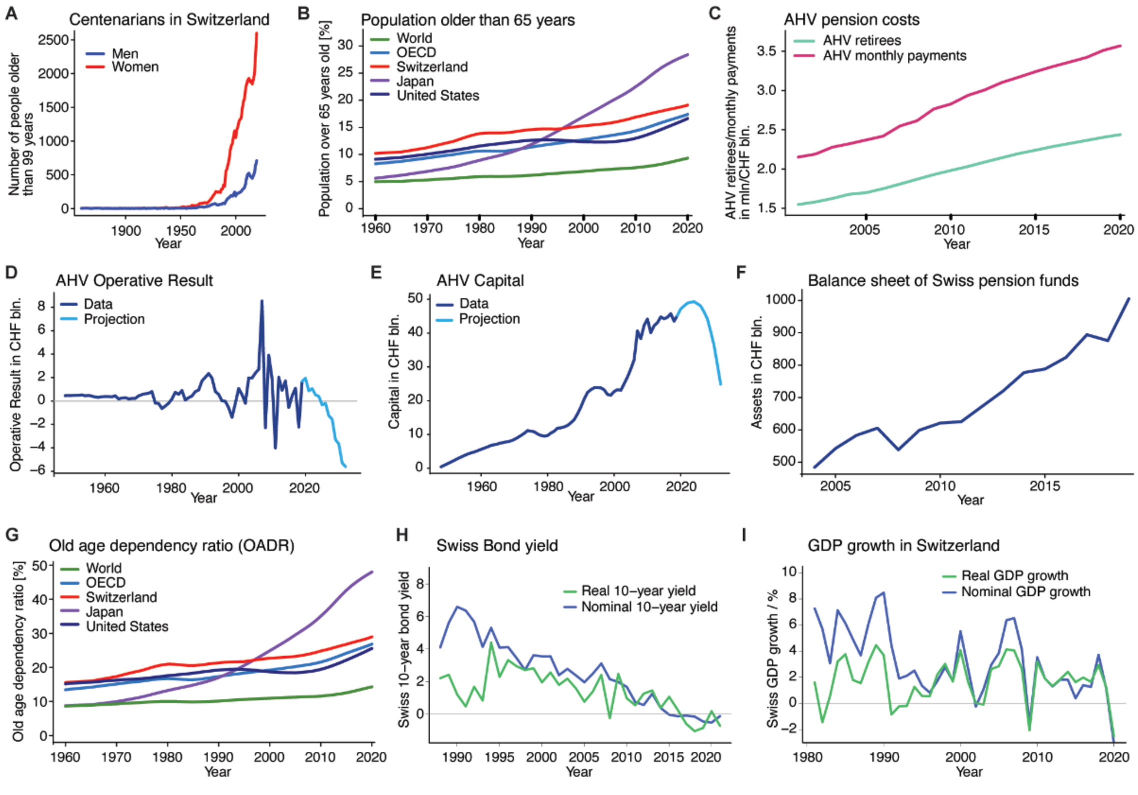
Goodhart and Pradhan [33] argue that recent demographic trends have contributed to rising inequality, and this inequality of income, wealth and opportunity, or at least the perception of it, as well as the stagnation of real wages in uneducated the so-called white non-Hispanic demographic in the US, among others, and the accompanying "sense of hopelessness" has, in turn, contributed to rising mortality in this demographic, particularly due to deaths of despair, such as suicide, drug alcohol poisoning and alcohol-related liver disease [34]. While several other advanced economies experience similar trends at a lower amplitude than the US [34], Switzerland does not show a similar trend (supplementary figures 1A–1C, supplementary figures 2I–2M). Therefore, the US does not represent an ideal comparison for the effects of an ageing population.

Health and medical implications of an elderly Swiss population

Although it is a remarkable achievement that we live longer, the increase in lifespan also comes with an increased prevalence of age-related and chronic diseases (figures 3A–3E). This is particularly remarkable for age-related diseases such as cardiovascular diseases (figure 3A) and neurodegenerative diseases (Alzheimer's disease and dementia; figure 3B), which respectively increase linearly after the age of 40 or exponentially after the age of 70. Other chronic diseases including diabetes (figure 3C) and neoplasms/tumours (figure 3D) show a steep incline at the age of 40 but then decline after the age of 70, maybe due to poor survival of the patients. Comparable to OECD, the US or worldwide, the prevalence of cardiovascular diseases and diabetes increases steadily with ageing (figure 3E; supplementary figures 3A–3C) [35]. Some of the diseases occur either earlier in life, for example, multiple sclerosis, for which less than 10% of patients have the late-onset disease (after the age of 50) [36]. The persistent prevalence of multiple sclerosis in patients older than 60 is due to these late-onset diseases and to a slower progression of multiple sclerosis, which is mainly observed in older patients (figure 3E) [37]. Thus, the increased occurrence of these chronic diseases during old age results in an overall more than linearly increased risk of dying from the age of 75 years (figure 3F), resulting in a steep decline in cumulative survival (figure 3G).

As outlined above, these chronic diseases are the leading causes of death, markedly decreasing the cumulative survival of the Swiss population, as illustrated in figure 4A. In the last 50 years, the ranking of the top ten causes of death has remained more or less unchanged, except for dementia (and accidents in men) (figures 4B–4G, supplementary figures 4A–E). The proportion of deaths due to cardiovascular diseases decreased more markedly in women, while cancer deaths increased mainly in men (figures 4F–G, supplementary figure 4A). The increase in dementia is more pro-

Figure 2: Economic and financial implications of an ageing Swiss population. (A) Number of men and women in Switzerland aged 99 years or older over time. While the number of centenarians remained in the single and low double digits in the 19th and early 20th century, towards the end of the 20th century, the number increased rapidly, with women far overtaking men in the number of centenarians. Source: Swiss Federal Statistical Office. (B) Fraction of the population aged 65 years or older in Switzerland, the US, Japan and the OECD and global averages. The fraction of people over 65 years is generally increasing in the displayed geographies, especially in Japan, where recent data show more than a quarter of the population was older than 65 years. Source: World Bank. (C) The number of retirees, in millions of people, insured under the Swiss AHV social security system is displayed in turquoise green; total monthly payments made to retirees, in CHF billion, are displayed in red. Source: Swiss Federal Statistical Office, Swiss Federal Social Insurance Office. (D) Annual operating result (Umlageergebnis) of the Swiss AHV/IV system as well as future projections based on the current modus operandi. Swiss Federal Statistical Office, Swiss Federal Social Insurance Office. (E) Capital of the Swiss AHV/IV system as well as future projections based on the current modus operandi. Swiss Federal Statistical Office, Swiss Federal Social Insurance Office. (F) Balance sheet of Swiss pension funds (Bilanzsumme ohne Aktiva) over time. Source: Swiss Federal Statistical Office.(G) Old age dependency ratios (OADRs) over time in Switzerland, the US, Japan, and OECD and global averages. This ratio is obtained by dividing the population aged 65 years or older by the working-age population. While the path over time is slightly different from (B), the general trend of increasing OADRs holds, with the Swiss OADR approaching 30% and the Japanese OADR approaching 50%, i.e. two working-age people supporting one retiree, in 2020. Source: World Bank. (G) The annual yield on a 10-year Swiss government bond in nominal and inflation-adjusted (real) terms over time. Source: Swiss Federal Statistical Office, Swiss National Bank.(I) Year-on-year growth in Swiss GDP in nominal and inflation-adjusted (real) terms over time. Source: Swiss Federal Statistical Office, Eurostat. Source data and more detailed references are in source data file 1.



nounced in females because dementia is a progressive and disabling disorder of the elderly, and women have longer survival and therefore a higher risk of dementia (figures 4F–G) [38]. The estimated cost of Alzheimer's disease alone is CHF 11.8 billion with direct costs (e.g. the cost of care, medical treatment, medications, diagnostics) representing 53% (CHF 6.3 billion) of the cost, according to the Swiss cost of dementia study published in 2019 [39]. However society also bears indirect costs of CHF 5.5 billion due to informal care.

Other non-communicable diseases also cause notable costs to the economy, both direct and indirect. In 2011, the sum of direct and indirect costs of musculoskeletal diseases was CHF 8.7 billion; CHF 4 billion for cancer; CHF 1.6 billion for chronic respiratory diseases; and CHF 1 billion for diabetes [40]. The total economic cost of obesity was estimated at CHF 7.99 billion as of 2012 [41]. Cardiovascular diseases are the leading cause of death but have declined over the past 50 years (figures 4A–H). Similarly to the reduced cardiovascular deaths in Switzerland (figure 4H), in Japan, for instance, in the last 20 years, ischaemic strokes appeared later in life and were less severe, findings that have been attributed to improved prophylactic measures and treatments [42].

The elderly, especially those with chronic health conditions such as diabetes mellitus [43], are more susceptible to heat and heat waves [44], which are projected to increase globally with climate change [45], with temperatures in Switzerland increasing at up to twice the rate [46].

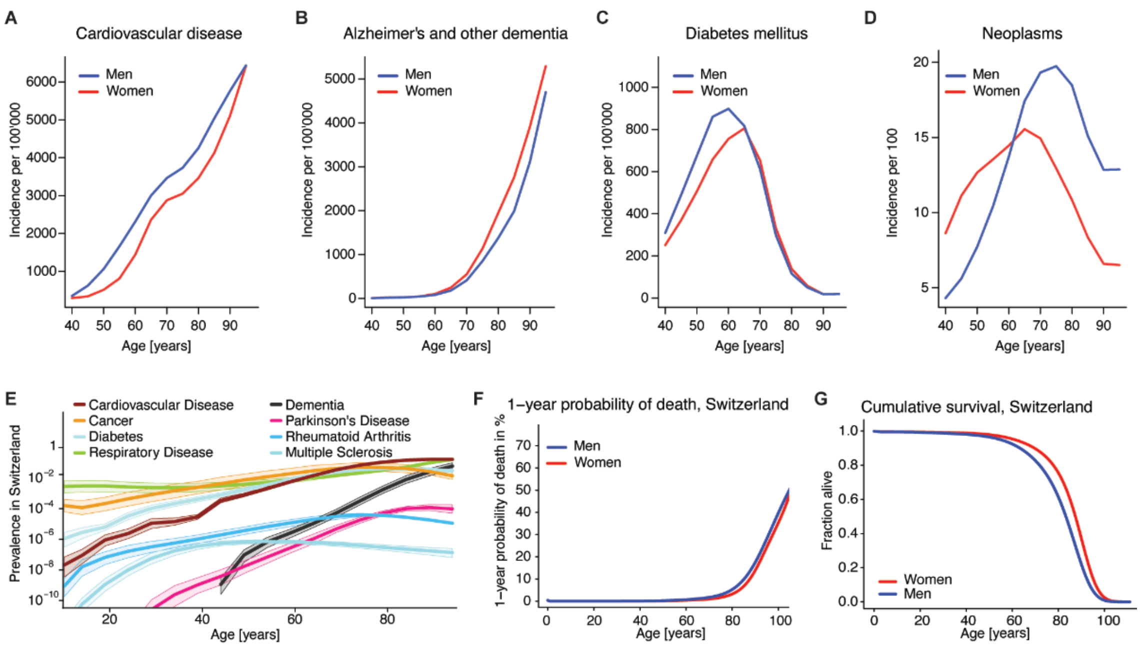
During the COVID-19 pandemic, the elderly population died at a much higher rate than would be expected normally by the Swiss Federal Statistical Office (supplementary figure 4F), especially during the COVID waves in the spring of 2020, autumn/winter of 2020/2021 and winter of 2022 [47]. The risk of dying of COVID-19 drastically increased with older age [48], unlike during the 1918 influenza pandemic [49]. Mortality of the elderly population, especially in autumn and winter, from highly transmissible viruses is not limited to COVID-19 or coronaviruses more broadly: In the late 20th century, the US CDC determined that 80–90% of influenza fatalities were among people 65 years or older [50].

The above raises the question of what can be done to address these socioeconomic and medical problems. This means that in addition to research on cardiovascular diseases and cancer, research on different kinds of dementia and cognitive diseases should be encouraged and supported.

Geroscience is linking molecular ageing research to late-life diseases

Medical improvements resulted in increased survival of the Swiss population (figure 4, supplementary figures 4A–4E).

Figure 3: Disease incidence, prevalence, and cumulative survival. (A) Incidence rate of cardiovascular disease (including ischaemic and rheumatic heart disease and stroke) for men and women in Switzerland during 5-year age ranges. Source: IHME Global Burden of Disease study, 2019 data. (B) Incidence rate of Alzheimer's disease and other dementia for men and women in Switzerland during 5-year age ranges. Source: IHME Global Burden of Disease study, 2019 data. (C) Incidence rate of type I and type 2 diabetes mellitus for men and women in Switzerland during 5-year age ranges. Source: IHME Global Burden of Disease study, 2019 data. (D) Incidence rate of neoplasms for men and women in Switzerland during 5-year age ranges. Source: IHME Global Burden of Disease study, 2019 data. (E) Prevalence of cardiovascular diseases (including ischaemic and rheumatic heart disease and stroke), cancers, diabetes, chronic respiratory diseases (including COPD), dementia, Parkinson's disease, rheumatoid arthritis and multiple sclerosis in Switzerland at various ages. Prevalence is on a logarithmic scale as YLDs (Years Lived with Disability). Source: IHME Global Burden of Disease study, 2019 data. (F) The 1-year probability of death for men and women at various ages. The value indicates the probability of dying at a certain age conditional on being alive at the beginning of the observed life year. Source: Swiss Federal Statistical Office, Swiss mortality tables 2008–2013. (G) Cumulative survival for men and women at various ages according to Swiss mortality tables 2008–2013. This number indicates the fraction of hypothetical men and women alive at a given age from their hypothetical birth cohort, at current mortality rates. Source: Swiss Federal Statistical Office. The data are from Swiss mortality tables 2008–2013. Source data and more detailed references are in source data file 1.

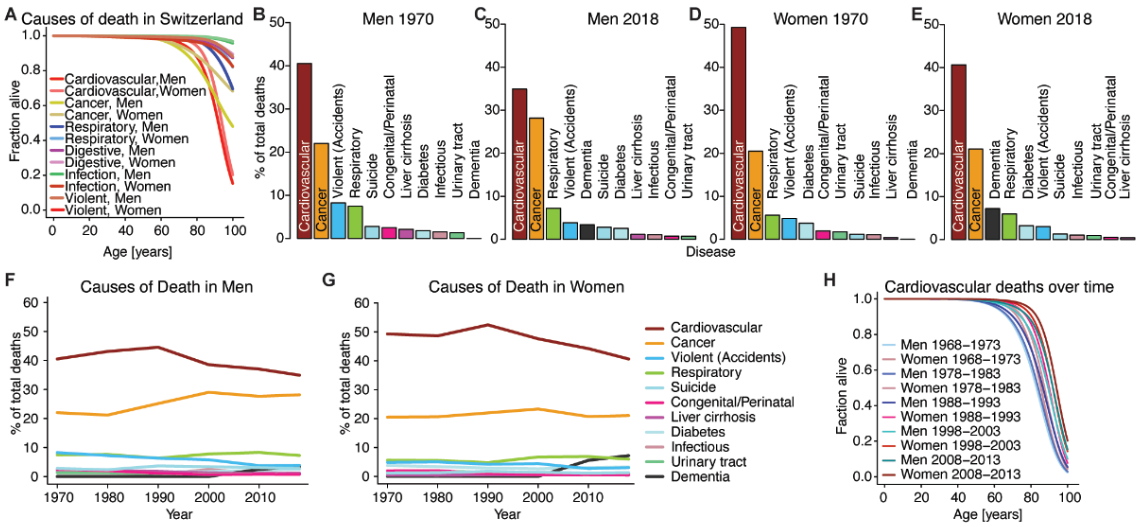


The way the research and medical system is currently set up addresses each chronic disease in isolation. While this is a good strategy, the common denominator and highest risk factor of each of these diseases is age. Research into ageing itself, or geroscience, is still a relatively small interdisciplinary field combining research on basic ageing biology, chronic diseases and healthy ageing [51]. Although the ageing process is complex, recent molecular insights revealed a finite number of only nine fundamental hallmarks of ageing [52]. Furthermore, ageing is malleable, and intervening with any of these hallmarks extends the lifespan of model organisms [52]. Thus, the goal of geroscience is to understand the ageing process leading up to and enabling disease and to exploit these insights to prevent, ameliorate or delay these age-dependent diseases, thereby improving the health of humans during ageing and compressing years of sickness (figure 5A).

Although our lifespans have increased, the time we spend in good health, i.e. healthspan, has not followed this trend (figure 5B) [53]. Swiss men and women spend on average around 14.1% and 17.2%, respectively, of their lifespan in poor health [1, 54], i.e. sickspan, with late-life comorbidities [53, 55]. In a self-rated health report of the Swiss National Cohort of 17,000 people, an average of about 6–10% of the life expectancy beyond 30 years was spent in poor health, depending on the level of school education [53]. Currently, by the Swiss retirement age of mid-60s years of age, more than half of the Swiss population has a score of at least 3 on the Thurgau Morbidity Index [56], which corresponds to three or more mild-to-moderate conditions, while over 80% take at least one medication chronically [56]. It has been estimated that if we could defer the health-related consequences of one of these late-life diseases, such as cancer, cardiovascular disease (CVD), diabetes or Alzheimer's disease, then the lifespan and healthspan would increase by about three years [57]. However, we have to be aware that if we cure one morbidity in a person, another one will set in (figure 5B). Alternatively, if we could delay the onset of age-related diseases by one year, it would save USD 38 trillion, as estimated only for the US [58]. Assuming a proportional benefit for the Swiss population and purchasing power parity in the exchange rate calculation, the benefits of deferring the morbidities in Switzerland would amount to approximately CHF 900 billion (calculation shown in source data file 1). Delaying the onset of the sickspan, even at a very old age, and even reversing ageing is biologically possible, as demonstrated in model organisms [59–62]. Furthermore, centenarians (figure 2A, supplementary figures 1D–1G) are living examples of healthy ageing and display a delayed onset and a lower incidence rate of late-life morbidities [63–68]. The recent breakthroughs in geroscience are starting to be translated and tested in clinical trials with tantalizing results indicating pharmacological strategies for reversing ageing at the cellular and tissue levels in humans (figure 5C) [69–79].

These pilot clinical trials pave the way for identifying interventions that promote healthy ageing. However, ageing is not classified as a disease, making it challenging to design and run clinical trials targeting the ageing process [80–84]. Currently, the clinical trial strategy is to use indications associated with the ageing process as surrogate

Figure 4: Causes of death in Switzerland. (A) Specific survival order of men and women in Switzerland with regard to the following causes of death: cardiovascular cause, cancer, respiratory disease, diseases affecting the digestive tract, violent death (including suicides, accidents and homicides). Source: Swiss Federal Statistical Office. The data are from Swiss mortality tables 2008–2013. (B) and (C) The leading causes of death in Switzerland for men in 1970 and 2018: Most men die of either cardiovascular causes (including heart attack and ischaemic stroke) or cancers, with the fraction of cardiovascular deaths in men declining from 1970 to 2018 due to better therapy of chronic cardiovascular disease, among other factors. Progress has been slower in the therapy of cancer. Source: Swiss Federal Statistical Office. (D) and (E) The leading causes of death in Switzerland for women in 1970 and 2018: Most women die of either cardiovascular causes (including heart attacks and ischaemic strokes) or cancers, with the fraction of cardiovascular deaths in women declining from 1970 to 2018, like for men. Dementia is a more frequent cause of death in women than men and only appears in the statistics in the 21st century. Source: Swiss Federal Statistical Office. (F) and (G) The leading causes of death as a percentage of total deaths in Switzerland for men (I) and women (J) over time from 1970 to 2018. Age-standardised mortality has declined for almost all causes of death; however, with an ageing society and better therapeutics for certain chronic diseases, some causes of death become relatively more frequent. Source: Swiss Federal Statistical Office. (H) Specific survival order of men and women at different ages in Switzerland with regard to cardiovascular causes of death during several 6-year observation periods for mortality tables. Source: Swiss Federal Statistical Office. The data are from Swiss mortality tables 2008–2013. Source data and more detailed references are in source data file 1.



markers for ageing. These include frailty (NCT03451006) [79], vascular stiffness (NCT01842399) and reprogramming of transcriptional gene expression to a more youthful state (NCT02953093, NCT02432287). Other secondary markers used in clinical trials to indicate efficacy in slowing ageing are epigenetic ageing clocks [69, 71, 72], immunological changes (NCT03451006) [72, 75] and regeneration of the thymus [72]. Furthermore, recent efforts are trying to establish clinical trials with companion dogs since they live in our households and enjoy sophisticated healthcare but age faster than us, making them ideal for long-term longitudinal and intervention studies on ageing [85].

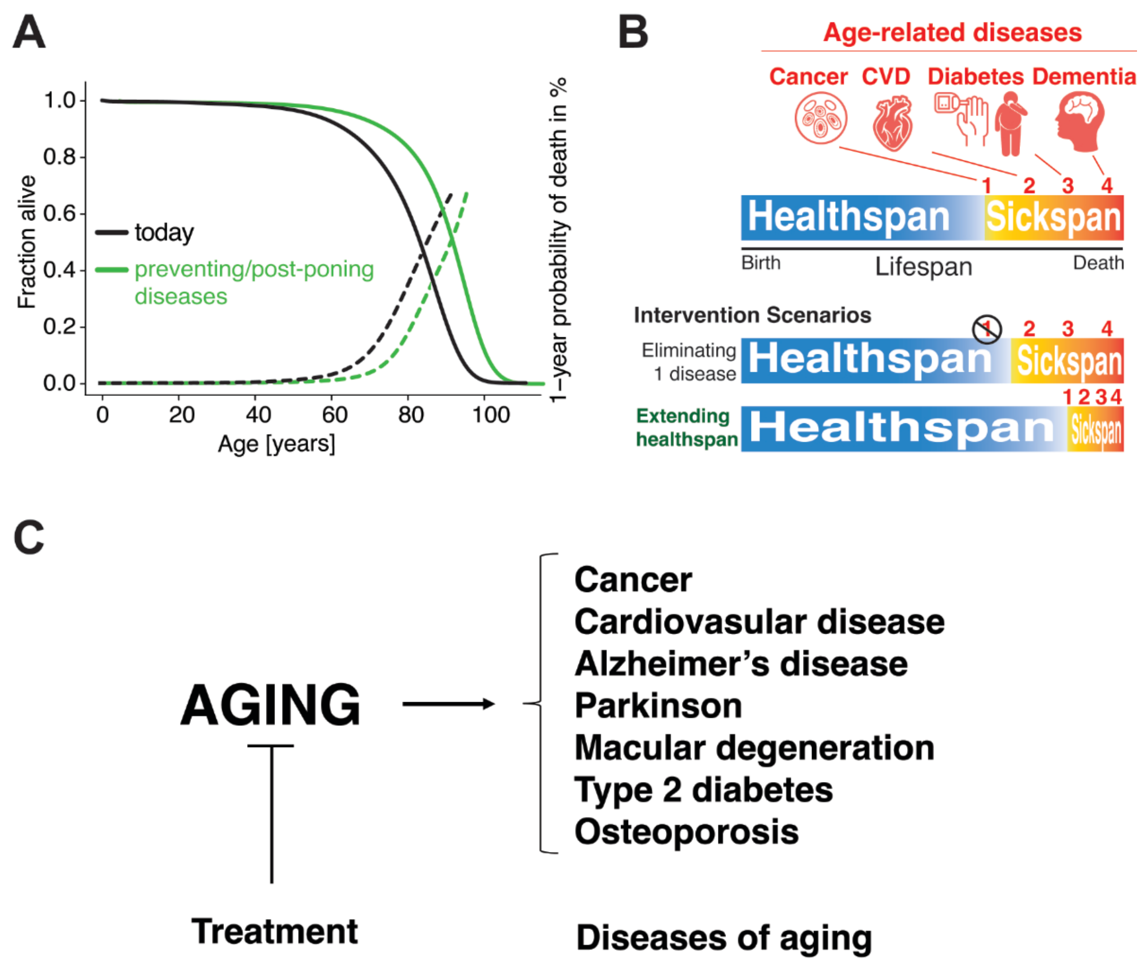
Thus, novel biomarkers and indicators of healthy ageing are needed. Today's geroscience brings systems biological understanding of underlying mechanisms of ageing to enable and form a more preventive model of medicine, helping people to age better by postponing or preventing late-life chronic pathologies (figure 5C).

The problem of dealing with multimorbidities in current healthcare systems

Rates of multimorbidity keep rising due to increased life expectancy and improved medical treatment. Chronic diseases and conditions become more common with ageing [86], with an estimated prevalence of over 65% among adults aged 65 years or older [87] and exceeding 75% between the ages of 85 and 89 years [88]. Multimorbidity, defined as having two or more co-occurring chronic diseases, challenges healthcare systems around the world [89] and emphasises the need to improve the care of patients with co-occurring chronic conditions rather than focusing on individual chronic diseases. Although most people with a chronic condition suffer from multiple conditions, patients with multiple chronic conditions are commonly underrepresented in clinical trials [90], and evidence-based treatment for patients with multimorbidity is limited [91] and too often not addressed in professional guidelines and clinical resources [92, 93]. This situation raises treatment safety issues, such as polypharmacy, which is a common challenge when caring for patients with multimorbidities. The increased risk of drug-disease and drug-drug interactions leads to therapeutic conflicts and contra-indicated treatments in about 50% of cases [94]. This leads to a dilemma for patients and healthcare workers who want to make appropriate treatment decisions.

Multimorbidity imposes a substantial economic burden on health systems and society [95] and increases the demand

Figure 5: The goals of geoscience and longevity medicine. (A) Medicine increases lifespan by increasing survival rates and hence decreasing mortality. (B) With an effective longevity intervention, the onset of many ageing-related diseases could be postponed, and, besides achieving a longer lifespan, the sickspan, the time spent in poor health, could be shortened, hence healthspan, the time spent in good health, could be prolonged. CVD = cardiovascular disease. (C) Schematic representation of the working model of geroscience. Instead of targeting each chronic disease individually, the aim is to slow the ageing process in order to extend the healthspan.



for healthcare resources [96]. This complexity also negatively impacts patients' functional impairment, everyday life and quality of life [86].

Consultation length and continuity of care may also need to be substantially enhanced in order to adequately address older patients' health needs, as it has been reported that older adults perceive a general unwillingness from their providers to treat their multiple health conditions and address their individual preferences for care. Older adults may require more in-depth communication with their providers in addition to individualised treatment plans that address their preferences for comorbidity management [97]. Consequently, as the prevalence of multimorbidity continues to rise, countries face not only the challenges of providing quality care but also the economic burden it incurs.

Health practitioners, and especially primary care teams, have a key role in managing patients with multimorbidity using a patient-centred generalist approach. This will require a radical change in how healthcare systems are organised and funded in order to effectively meet the challenges of multimorbidity [98].

Healthy longevity medicine

The recent advancements in artificial intelligence (AI), big data collection and analysis, technologies, and the emergence of geroscience as an interdisciplinary approach to the enhancement of healthspan and lifespan have given rise to a new field of medicine that aims to restore and optimise the biological age of a specific individual, along their lifespan [99]. Longevity medicine's core target is to extend a person's healthspan by integrating innovations in human and AI and creating applicable trajectories to identify, mitigate and optimally also eliminate the risk of (age-related) diseases (most of which are the main contributors to the global burden of diseases). Current medicine still has a reactive pillar and a preventive pillar.

Longevity medicine: translating and applying the hallmarks of ageing into practice

This new burgeoning medical discipline is of a distinct character, shaped by multidisciplinarity (virtually all disciplines of clinical medicine, including genetics, radiology and pathology) [100] and interdisciplinarity (AI, computational science, gerontology, geroscience, engineering, etc), with strong roots in internal medicine dealing with the complexity of comorbidity and multimorbidity.

In Switzerland, longevity medicine is particularly important due to the country's ageing population. As discussed above, as people are living longer, the prevalence of age-related diseases such as dementia, arthritis and cardiovascular disease is increasing. Longevity medicine can help to prevent or delay the onset of these conditions, allowing individuals to maintain their independence and live healthier, more active lives for longer.

A prime example of a longevity medicine approach is the interconnection of ageing and cancer. Ageing is the primary risk factor for cancer [101] and the incidence of most types of cancer increases with advancing age (figure 3E). The crossroads and valuable knowledge of ageing and cancer, as well as the insights from treatment and diagnosis of the oldest cancer patients (which arrived only late due to the exclusion of this population from most clinical trials), brought a new area in medicine called geroncology [102]. This field aims to identify further and specific targets of mechanisms that contribute to both ageing and cancer and to develop strategies to prevent or treat age-related cancers. Geroncologists not only investigate and translate into daily practice the complex relationships between genomic instability, epigenetic changes, cellular senescence and immune dysfunction in the context of ageing and cancer but also apply the longevity diagnostics, such as biological age measurement or speech recognition for natural language processing (NLP), into the standard clinical protocols and use those tools to navigate therapies and follow-up, striking a balance between toxicity and quality of life for patients [103]. By integrating knowledge from diverse fields such as genetics, immunology and oncology, geroncologists seek to uncover new insights into the underlying biology of age-related cancers and to develop innovative approaches to prevention and treatment.

In addition to its importance in the clinic, longevity medicine can also be applied in daily life through the adoption of healthy habits such as exercising regularly, eating a balanced diet and getting enough sleep. These habits can help to promote healthy ageing and reduce the risk of age-related diseases and conditions. Overall, the importance of longevity medicine in the clinic and in daily life cannot be overstated, as it has the potential to greatly improve the lives of older individuals and promote healthy ageing.

Longevity medicine has not yet been officially defined by a central medical body, but expert recommendations suggest that longevity medicine is AI-driven precision medicine guided by biological age determination with ageing clocks [99]. The formal definition might be further enriched by the core goal of longevity medicine, which is to establish and restore the biological age of an individual at each specific point of time to the biological age of optimal individual performance [84]. Longitudinally and cumulatively, this leads to mitigation and, ideally also, elimination of risks of age-related and overall morbidity. Therefore, the main focus of longevity medicine is to prolong life lived in good health, both physically and mentally, ergo: extension of the healthy lifespan and not solely the healthspan (simple prevention) or solely the lifespan (reactive medicine, i.e. sickcare) [84]. Recent attempts to implement ageing as a disease in the ICD code would allow longevity medicine to set up more randomised controlled trials and thus allow the validation of biomarkers of ageing and the creation of clinical guidelines. Currently, ICD-11 has not implemented this core step in the categorisation; however, the debate stimulated more clinicians to be alert, and experts shifted the focus of their argumentation to longevity medicine as a discipline to quantifiable measurements and biomarkers and to the necessity for clinicians to have the (coding) tools [84].

Longevity physicians

Longevity medicine is an evolving field fuelled by the exponentially growing arena of geroscience and AI, as well as implementable point-of-care (POC) and inpatient technologies, which allow a longitudinal measurement of objective and subjective assessments with high granularity.

With the advent of deep learning models, the establishment of deep ageing clocks (DACs) in 2018 opened the possibility for clinicians to vigilantly track the progress of a patient's/individual's biological age based on various modalities, e.g. haematological tests, methylation, metabolomic or microbiome. Both static values and rate of ageing are of value, while an integrative comprehensive biological age clock at each of the organism levels (tissue, cell, omics, etc.) would provide the greatest value.

Concluding remarks

Life expectancy in Switzerland has steadily increased with a decreasing rate over the past few decades. Along with life expectancy, the OADR has also increased. As ageing is associated with many morbidities, their prevalence is destined to further increase unless further measures are taken. The increased OADR will lead to secular stagnation in the economy and threaten the sustainability of pension systems.

The demographic transition and ageing population, therefore, pose important challenges to Swiss society from several perspectives. Given our findings here, we suggest the following potential strategies to address these challenges. By researching the molecular mechanisms involved in the biology of ageing and expanding epidemiological and clinical research on ageing, we should aim to bridge the gaps between basic research of geroscience and medical applications. We need to establish protocols for clinical trials on ageing that include functional capacity, frailty and time to events of onset of age-related diseases. For this, we need to establish clinically relevant biomarkers of healthy ageing and incorporate a more complete interconnected picture of comorbidities. Applying AI-powered solutions to disease diagnosis and monitoring could help to shift towards a more preventive medical approach. With this, we can hopefully improve the quality of health in the ageing population.

Without changes in the biological and medical fields, the socioeconomic impacts of ageing might become devastating. Hence it is indispensable to invest in the future of ageing research.

Materials and methods

Data analysis

All plots were made using the R Project for statistical computing, the "readxl" package and the "RColorBrewer" package [104].

The demographic data for the population pyramids and centenarians were taken from three sources: The data up to and including 1980 originate from the census ("VZ") data (https://www.bfs.admin.ch/bfs/en/home/basics/census.html).

In order to avoid discrepancies, especially at older ages, between the data sets from 1981 onwards, a dataset [19] harmonising the ESPOP (1981–2010; https://www.bfs.admin.ch/bfs/de/home/statistiken/bevoelkerung/erhebungen/espop.html) and STATPOP (from 2010 onwards; https://www.bfs.admin.ch/bfs/de/home/statistiken/bevoelkerung/erhebungen/statpop.html) statistics was used for the period 1981–2009. From 2010 onwards, the STATPOP dataset was used.

Source data

All sources are cited in the text. All source data that we used for our analysis are provided as data source file 1. Figshare: https://doi.org/10.6084/m9.figshare.21922095.v2

All data used for graphs are publicly available from the sources stated, mainly the Swiss Federal Statistical Office.

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All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest was disclosed.

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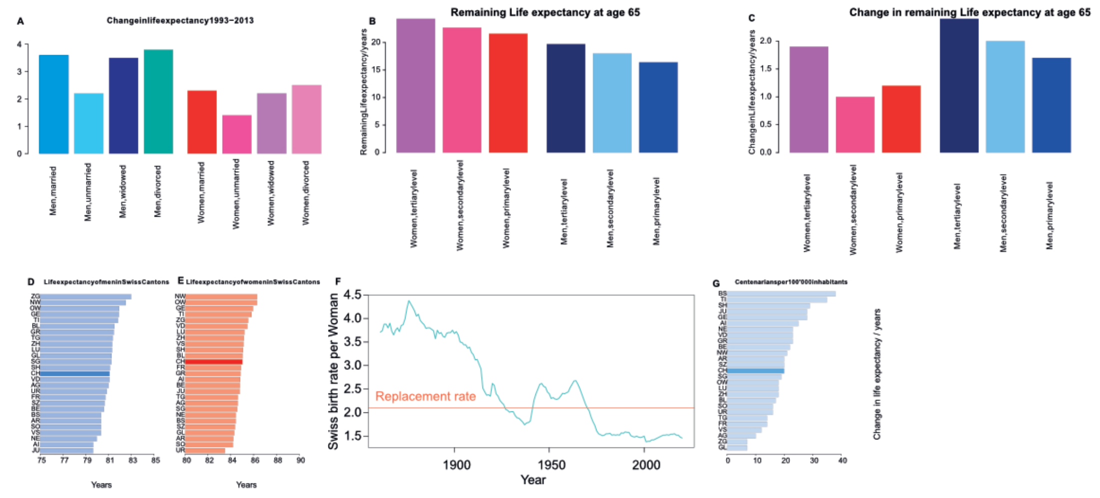
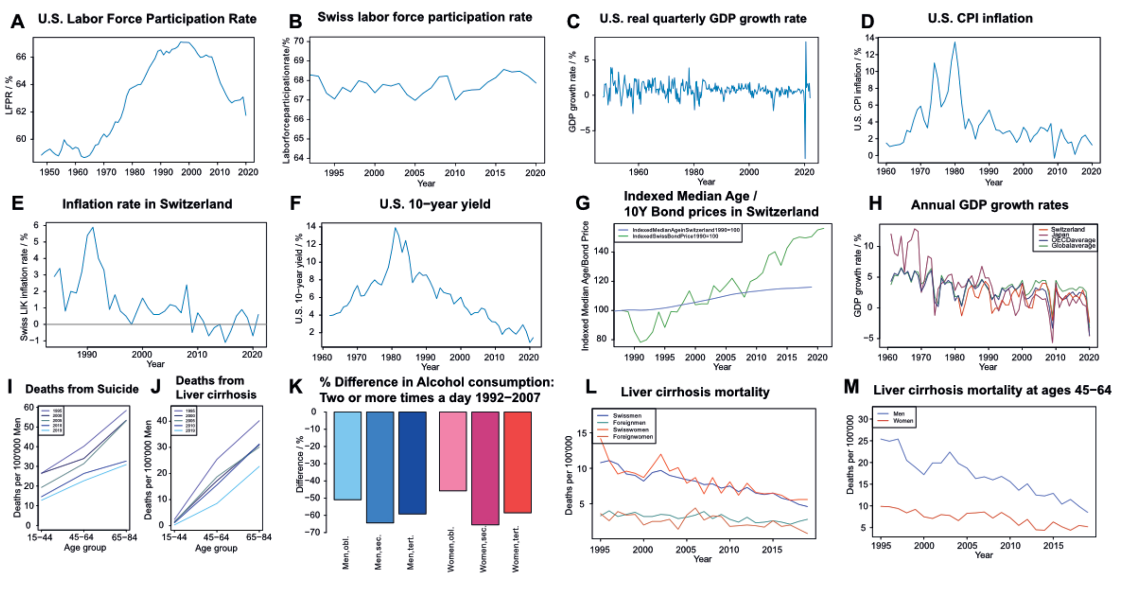
Appendix

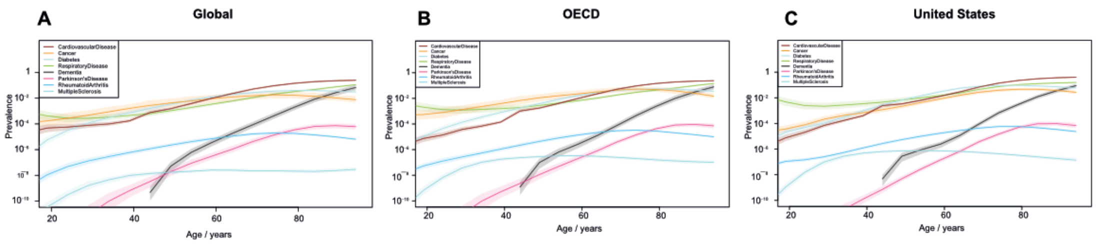
Supplementary figure 1: Life expectancy and centenarians in Swiss cantons; birth rates. (A) Change in life expectancy in Switzerland at age 65 conditional on being alive from the 1988-1993 period to the 2008–2013 period, in years, by marriage status: married, unmarried, widowed, divorced. While divorced men and women have gained the most ground in the observed period, married men and women still live the longest. (B) Remaining life expectancy at age 65 conditional on being alive in the period 2000–2005. Grouped by sex and education level. (C) Change in remaining life expectancy at age 65 conditional on being alive from 1990–1995 to the 2000–2005 period. Grouped by sex and education level. Both in men and women, the more educated, the longer lived. Men and women with tertiary education have also seen the most increase in life expectancy from 1990–1995 to the 2000– 2005 period. (D) and (E) Life expectancy at birth of men (D) and women (E) in the Swiss Cantons and the Swiss average. (F) The birth rate in Switzerland as per live births per woman. The UN-defined replacement rate of 2.1 births per woman is indicated as a horizontal line. (G) The number of centenarians per 100’000 inhabitants in the Swiss Cantons as well as the Swiss average.



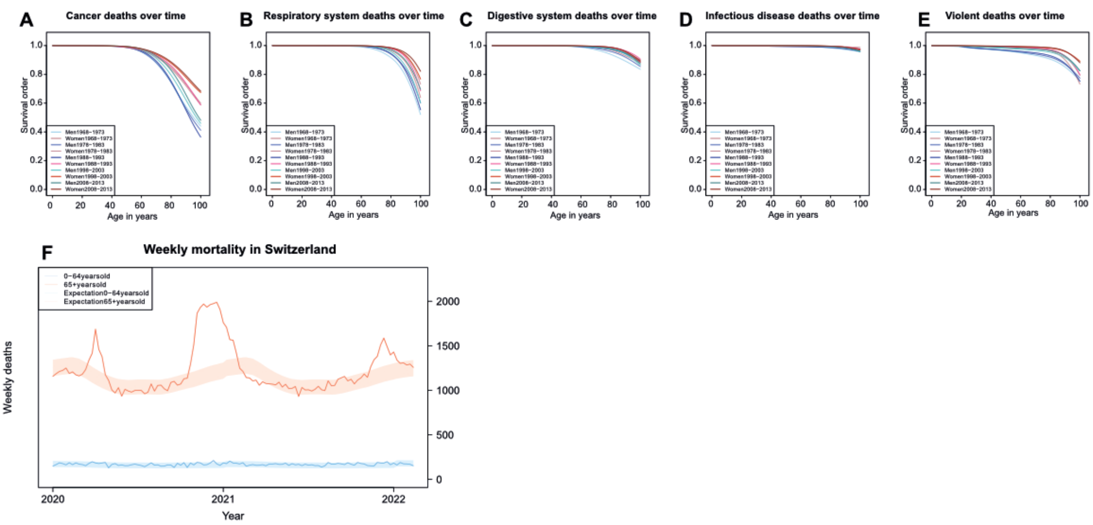
Supplementary figure 2: Economic data for Switzerland, the United States, and global comparisons, as well as Swiss inequality data. (A) and (B) Labor force participation rate in the United States (A) and Switzerland (B) as the fraction of people in the labor force divided by the population over time. (C) United States quarter-on-quarter growth in real (inflation-adjusted) gross domestic product. (D) United States consumer price inflation as the annual rate in percent over time. (E) Annual inflation rate measured as LIK (“Landesindex der Konsumentenpreise”) in Switzerland over time. (F) Nominal annualized yield on 10-year United States government bonds over time. (G) The median age of the Swiss population over time indexed to 100 in 1988, and the price of a hypothetical 10-year Swiss government bond indexed to 100 with the yield of 1988. The yield and price of a bond are negatively correlated. No causative correlation can be extrapolated, though a general uptrend with a similar shape is visible for both. Asset prices, for example, bond prices, are, in general, inversely correlated to the future rate of return on that asset. Since the financial crisis, asset prices have increased broadly (asset price inflation) [28], as shown here with the example of a hypothetical Swiss bond (=asset) that increases in value as its interest rate decreases. Of course, a causal relationship cannot be implied, but it is notable that both the median age of the Swiss population and the bond price moved upward in a similar fashion. (H) The year-on-year annual percentage growth rate of GDP at market prices is based on constant local currency in Switzerland, Japan, the OECD average, and the global average over time. Global GDP growth has exceeded OECD growth every year this millennium, as have emerging economies. While the Japanese economy grew very fast in the 1960s and 1970s and continued to largely grow faster than the global and OECD averages until 1990, the bursting of the asset bubble and economic crisis of the 1990s has led to Japan growing slowly ever since, with Switzerland, also a comparatively slow-growing economy, mostly advancing faster than Japan. The two large drops in 2008/2009 and 2020 are due to the great financial crisis and the COVID-19 pandemic, respectively, both of which severely affected the Japanese economy, especially the great financial crisis, from which Japan struggled to emerge with positive real growth rates despite large fiscal and monetary stimulus. The Swiss economy, on the other hand, while also being adversely affected by both crises, was overall more resilient in terms of GDP growth than Japan as well as the OECD as a whole. One possible explanation is that Switzerland has been described by Nassim taleb as “antifragile” (ISBN 978-0-14-103822-3), getting stronger in turmoil and shock, due to a variety of factors, including its political, monetary, and economic systems (https://fortune.com/2012/12/14/antifragility-how-disorder-makes-us-stronger/). (I) and (J) Mortality as the number of deaths from suicide (I) and liver cirrhosis (J) per 100’000 people at risk in three age groups (15–44, 45–64, and 65–84) in 1995, 2000, 2005, 2010 and 2019 for men. (K) % Change (not % point) in consumption of alcohol at least twice a day from 1992–2007 for men and women that have completed obligatory, secondary, or tertiary education in Switzerland. (L) Mortality rates (Deaths per 100’000 people at risk) in Switzerland (all ages) with liver cirrhosis as a cause of death, over time, by sex and citizenship status. (M) Mortality rates (Deaths per 100’000 people at risk) in the 45–64 age group in Switzerland with liver cirrhosis as a cause of death, over time, by sex. **Remarks concerning Supplementary figures 2 (I)-(M):** Overall, Supplementary Figures 2 (I)-(M) show that some of the negative trends in mortality observable in many industrialized economies, especially English-speaking ones, do not appear to be present in Switzerland to a noteworthy degree. While in the US, and other countries, to a lesser degree, White non-Hispanics (WNHs), especially middle-aged, non-college-educated WNHs, have experienced a rise in mortality, dominated by deaths of despair (liver disease from excessive alcohol consumption, alcohol, and drug poisoning, suicide), Swiss men (and women) have seen a significant decline of suicide and liver cirrhosis mortality in middle age (45-64) from 1995 to 2019 (I), (J), (L) and (M), while the vast majority of people residing in Switzerland are part of the WNH demographic. When comparing middle-aged people with foreign citizenship with people with Swiss citizenship within Switzerland, mortality from suicide and liver cirrhosis appears lower for foreigners. Men are more likely to die of suicide than women, both in the Swiss and foreigners, which is a concerning trend also observed in other OECD countries. Liver cirrhosis mortality does not differ significantly between sexes, but the lower mortality of foreigners might be explained by some foreign cultures and religions being less tolerant of the consumption of alcohol.Very frequent alcohol consumption of 2 or more times a day has decreased dramatically in men and women of all three educational strata assessed from 1992–2007 (K). This contrasts with the US, where the better educated (at least a Bachelor’s degree) have seen a decrease in mortality and are less afflicted by alcohol-related deaths, while less educated WNHs see an increase in alcohol and drug-related deaths. Overall, Switzerland does not exhibit the concerning trends of the WNH middle-aged demographic (rising suicide and substance abuse) in other advanced economies, with the US being at the front line.Footnote: Some of the figures were partially used in an unpublished previous assignment by MMR. They were created by him using the data cited.



Supplementary figure 3: Disease prevalence generally increases with age globally. (A)-(C) Prevalence of cardiovascular diseases (including ischemic and rheumatic heart disease and stroke), cancers, diabetes, chronic respiratory diseases (including COPD), dementia, Parkinson’s disease, rheumatoid arthritis, and multiple sclerosis globally (A), in the OECD average (B) and in the United States (C) at various ages according to the IHME Global Burden of Disease data. Prevalence is on a logarithmic scale as YLDs (Years Lived with Disability).



Supplementary figure 4: Specific Survival orders for various causes of death over time. Specific survival order of men and women at different ages in Switzerland with regards to (A) cancer, (B) respiratory system, (C) digestive system, (D) infectious disease, and (E) violent (accidents, suicides, homicides) related causes of death during several six-year observational periods for mortality tables. (F) Weekly mortality in Switzerland during the early 2020s, with the blue line representing mortality at ages 64 and below and the red line for ages 65 and above. The shaded areas indicate the range of expected weekly deaths based on previous years as estimated by the Swiss Federal statistical office. During the waves of COVID infection in spring and winter 2020, and winter 2021, the mortality exceeded the range of expected values.



Supplementary figure 5: Incidence rates of diseases in Switzerland. Incidence rate of Parkinson's disease (A), multiple sclerosis (B), kidney disease (C), injuries from falls (D), rheumatoid arthritis (E), and osteoarthritis (F) in Switzerland for men and women in Switzerland during 5-year age ranges according to the IHME Global Burden of Disease data.