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Biomarkers of aging: from molecules and surrogates to physiology and function

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Abstract

Many countries face an unprecedented challenge in aging demographics. This has led to an exponential growth in research of aging, which, coupled to a massive financial influx of funding in the private and public sectors, has resulted in seminal insights into the underpinnings of this biological process. However, critical validation in humans have been hampered by the limited translatability of results obtained in model organisms, additionally confined by the need for extremely time-consuming clinical studies in the ostensible absence of robust biomarkers that would allow monitoring in shorter time frames. In the future, molecular parameters might hold great promise in this regard. In contrast, biomarkers centered on function, resilience and frailty are available at the present time, with proven predictive value for morbidity and mortality. In this review, the current knowledge of molecular and physiological aspects of human aging, potential anti-aging strategies, and the basis, evidence, and potential application of physiological biomarkers in human aging are discussed.

Abstract

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Graphical abstract.

Keywords

Aging; biomarkers; exercise; healthspan; longevity; $\dot{V}O_{2max}$; grip strength; gait speed; muscle mass

1 Introduction and background

The process of biological aging has preoccupied humans throughout history, exemplified by religious lore, myths and stories about achieving long, healthy lives, even immortality, in almost every culture world-wide, with the Mesopotamian Epic of Gilgamesh as one of the earliest recorded examples, possibly dating back to 2100 BCE, in which the secret for everlasting live is desperately, and unsuccessfully, sought after (1). In comparison to prehistoric humans living as hunter-gatherers (2), human life expectancy has tremendously increased, in particular in the last 200 years, driven by various factors, including industrialization and the related abundance of food, processes that improved food preparation and preservation (e.g. those developed by Louis Pasteur), sanitation and hygiene in the public sector (e.g. drinking water treatment, sewage collection and purification) and clinical settings (e.g. hygiene promoted by Ignaz Semmelweis), as well as progress in the prevention (e.g. development of vaccines by Edward Jenner) and treatment (e.g. discovery of penicillin by Alexander Flemming) of infectious diseases or other pathologies (e.g. insulin by Frederick Banting, Charles Best and John Macleod, general anesthesia by

William Morton, or statins by Akira Endo). In addition, other factors, such as social changes including universal public health care, better education and awareness, or advances in the prevention and treatment of other diseases have also contributed to the almost unabated rise in average life expectancy, at least until recent years (3). Intriguingly, this increase has initially been driven by reduced mortality at a young age, which later extended to improvements in middle and old age, thereby elevating median life expectancy, while maximal life span remained largely unaffected (4–6). Indeed, arguments for and against a limit of human lifespan have been put forward (4, 7–13), and various morphological and functional data indicate that humans might already be a long-lived species (e.g. based on resting heart rate (14), body mass (15, 16), metabolic rate (17), time of development of sexual maturity (17, 18), brain mass (17), DNA methylation rate (19) or epigenetic signature (20)), arguing for a possible lifespan maximum and restricted window to push these limits in the absence of decisive new scientific, clinical, technological, social/societal or ecological/environmental advances and breakthroughs (21, 22). In line, the current “world record” of an age of 122 years and 164 days set by Jeanne Calment has not been broken (or even approximated) since her death in 1997 (23). In fact, at the moment, the difference between her age and that of the second oldest person, Kane Tanaka (119 years and 107 days, death in 2022) is with 3 years and 57 days larger than the difference between places 2 to 10 (Chiyo Miyako, 117 years and 81 days, death in 2018) of 2 years and 26 days.

Intriguingly, in the longest living countries, the rise in life expectancy has been slowing down since the 1990s (24). Moreover, even though higher intrinsic capacity related to cognitive, locomotor, psychosocial and sensory function have been measured in individuals of a certain age compared to their counterparts of earlier generations (25, 26), there is also evidence of an increasing gap between life- and healthspan (the number of years spent in good health), indicating that gains in life expectancy might not be matched with corresponding improvements in healthy aging (27). Indeed, it is indisputable that for many diseases, most of which are chronic in nature, age is by far the largest and most common risk factor (28). On a societal level, a strong demographic trend towards an aging population is observed in a number of countries (6), e.g. forecasted to triple the number of those 85 years of age or older in the United States from 2022 to 2050 (29). This trend now extends beyond high-income countries: world-wide, the proportion of individuals aged 65 or higher progressed from 5% in 1950 to 9% in 2020, and is expected to continue to rise to 16% by 2050 (30). This aging segment is now the fastest growing, by 2019, for the first time in human history, having outnumbered that of children younger than 5 years of age (31), reaching 2.1 billion individuals aged 60 and over by 2050 (32). Similarly, the population of 80+ years old will expand to 426 million in the next 25 years, approximately triple that of 2020 (32). Overall, the challenges emerging from this aging trend might surpass those of overall population growth, which has declined in recent decades and is projected to continue to slow (33). Therefore, the urge to understand the aging process, and, in the optimal case, prolong human life, or at least healthspan, is understandable in light of the functional decline, disease risk, and inevitable death faced at old age, and the societal challenges that arise from the changing demographics. To do so, first, aging *per se*, disentangled from age-associated diseases, has to be investigated (34) since at the moment, our understanding of the fundamental mechanisms driving aging is poor. For example, the

concept of chronological and “biological” age as potentially diverging entities describing separate aging trajectories is still nebulous and ill-defined (35–39). In fact, no consensus on the principles and processes of aging has been reached at the moment (40). Second, the definition of “healthspan”, or even “health” in general should be sharpened to provide the framework for measuring and improving this important parameter (41). Good arguments exist to extend “health” and “healthspan” beyond the mere absence of disease and infirmity, and, as suggested by the World Health Organization (WHO), include physical, mental and social well-being (42). Such insights and advanced could help to bring the “Decade of Healthy Aging”, declared for 2021-2030 by the United Nations (UN) General Assembly (43) based on an initiative of the WHO in 2020 (44), to a successful conclusion.

1.1 Aging: a biological/physiological program, stochastic deterioration, or a disease?

In contrast to post-natal development and puberty culminating in adulthood, generally recognized as genetically encoded and evolutionary selected biological programs, the underpinnings of aging, in particular after reproductive age, are highly debated (45). Evolution results in the retention of favorable genetic traits in a given environment, which are only stable if passed on to the progeny. Human aging beyond reproductive age (after the menopause in women) thus could be a.) evolutionary neutral, resulting in random deterioration and accumulation of damage, b.) under evolutionary pressure for an accelerated process, for example to remove non-reproducing individuals from the competition for scarce resources, or c.) inversely, favor a decelerated program, allowing post-reproductive individuals to care for the particularly dependent human infants, permitting adult humans to commit more time for resource provisioning by hunting and gathering (“Grandmother hypothesis”) (46, 47). Survival after menopause is rare in the animal kingdom, so far described in the wild in elephants (48), toothed whales (49) and chimpanzees (50), but might be more common mammals in captivity (51). Of note, a significant post-reproductive lifespan is also observed in pre-industrial humans, in absolute and/or relative length surpassing that of most animals, including non-human primates (48, 51, 52). Hence, unlike most species, humans substantially exceed reproductive age and exhibit remarkable longevity.

1.1.1 Insights into the aging process from long- or short-lived humans:

Unraveling the underpinnings of human aging is not easy: for example, the study of (super)centenarians is marred by the tiny sample size (53). The prevalence of centenarians is estimated at about 1 per 2’200 (of which 85% are women and 15% men), and that of supercentenarians at about 1 per 1 million individuals (of which 90% are women and 10% are men) (54). Genetic studies of long-lived individuals has led to the discovery of more than 50 genetic loci, albeit with small effect size (55). Most of these are linked to (cardio-metabolic) disease risk, e.g. apolipoprotein E (ApoE) (55), with the potential exception of the transcription factor forkhead box O3 (FoxO3), for which the underpinnings of the impact on human aging and longevity remains to be elucidated (56). Intriguingly, centenarians, despite exhibiting a longer lifespan, have lower disease rates throughout life and thus uncouple the association of old age from the normal occurrence of major age-related diseases seen in the normal population (57). Overall, “escapers” with no clinically demonstrable disease at the age of 100 (about 15%), “delayers” having no

age-related disease until the age of 80 years or later (about 43%), and “survivors” who experienced pathologies before the age of 80 years (about 42%) have been described (54). Next, so-called “Blue Zones” have been proposed as confined geographical regions with an apparent significant accumulation of healthy individuals at old age (58, 59). At the moment, no identifiable genetic signature has emerged from the study of these regions beyond potentially disease-relevant genes (analogous to those found in (super)centenarians), primarily investigated in the population of Sardinia (60, 61). Instead, the healthy longevity has mostly been attributed to lifestyle factors, including low smoking prevalence, ample physical activity, favorable nutrition, or strong social contracts (62, 63). While these factors are generally applicable and accepted (see section 3 below), others are more puzzling and contrary to broader associations, for example the fact that at least some of these “Blue Zones” are economically disadvantaged. Moreover, in some of these regions, e.g. Okinawa in Japan or Nicoya in Costa Rica, the proposed advantages seem only valid for certain populations, and are vanishing in the present time (64, 65). Whether these developments are caused by a changing environment, for example in dietary habits in Okinawa (66), or if these are based on incorrect classification is currently debated (63, 67, 68). Importantly, the overall concept of such “Blue Zones” has been questioned due to poor record keeping (68, 69) and/or other causes of over-inflated records of (healthy) longevity, including claims related to pension fraud (70, 71). It thus is unclear whether “Blue Zones” will decisively help in our understanding of aging (72). Finally, so-called “premature aging” diseases, e.g. progeria, are caused by monogenic mutations in genes of DNA repair, genomic maintenance, fidelity of DNA replication and/or nuclear architecture, thus poorly representing the complexity and multifactorial aspects of *bona fide* physiological aging (73). In fact, the overall contribution of gene variants to aging is unclear: estimates for life span heritability range from 15-30% (74), while results from twin studies imply an even more moderate contribution (75), possibly below 10% (76). Similar to the findings in centenarians, exceptional parental longevity has been associated with reduced cardiovascular disease risk in the offspring (77). Interestingly, in such rare cases of favorable genetic endowment, benefits on health and survival are observed even with suboptimal lifestyle, socioeconomic status or nutrition (77, 78). Heterogeneity in familial longevity however implies additional factors to modulate the contribution of genetic factors in heritability (79). Overall, a genetic contribution to aging, in particular to exceptional lifespans, seems highly probable, but this most likely is based on multigenetic effects with individually very small effect sizes. Nevertheless, a healthy lifestyle and other factors, discussed below), can override an unfavorable genetic endowment to a significant extent.

1.1.2 The use of model organisms to understand the aging process:

Investigating the aging process in humans is challenging due to reasons outlined in the previous paragraph and the fact that longitudinal aging studies would require decades. Consequently, human data are often based on cross-sectional associations, and molecular mechanisms of aging have primarily been studied in model organisms, with much fewer data in humans. While lower organisms are extremely valuable for mechanistic and causality investigations, translatability of aging insights to humans might be hampered for several reasons. First, as outlined above, human aging is characterized by a long post-reproductive period and humans are potentially already reaching upper limits of longevity. Second, the

most commonly used model organisms in the aging field show pivotal biological differences compared to humans (80–84). For example, in *Saccharomyces cerevisiae* (baker's yeast), replicative aging and chronological lifespan describe different processes for which direct human equivalents are missing. The same is true for spore formation under starvation conditions in yeast. Similarly, *Caenorhabditis elegans* (roundworm) can either be males or hermaphrodites, will enter a Dauer stage in starvation, are prototypical post-mitotic organism in regards to the somatic cells in the adult stage (85), and initiate a self-destructive reproductive program in which somatic biomass is used at the expense of yolk production, leading to reproductive death (86). *Drosophila melanogaster* (fruitfly) exhibit a marked fecundity – longevity trade-off, and can enter a reproductive diapause, for example when exposed to low temperatures. Starvation leads to a torpor state in *Mus musculus* (mouse), characterized by significantly reduced metabolic rates. In contrast, under non-starvation conditions, the metabolic rate, which is closely related to body size, is substantially higher in mice than in humans (approximately 7 times higher when comparing a 30-g mouse to a 70-kg human) (87). Similarly, heart rate is considerable higher in mice with ~600 beats/min, which is nearly ten times that of humans (87).. Furthermore, mice exhibit a ~30-50 times faster genomic response in different inflammatory conditions (88). Moreover, mice and *Rattus norvegicus* (rat) have up to 10 times longer telomeres compared to humans (89). In addition, kinetics of other processes such as RNA and protein turnover are higher than the human counterparts, with protein turnover being ~10 times faster (88). Finally, all of these model organisms have a profoundly shorter lifespan than humans, from about 14 days (chronological) in yeast, ~3 weeks in *C. elegans*, ~2-3 months in *D. melanogaster*, ~2-3 years in *M. musculus* to ~3-4 years in *R. norvegicus*. As such, one human year is approximately the equivalent of 13.7 rat days (88). The most commonly used non-human primate model, *Macaca mulatta* (rhesus monkey) reaches about 27 to maximally 40 years, thus only up to half of *Homo sapiens* (human) average lifespan. Mechanisms, interventions and pharmacological treatments that emerge from the study of these canonical model organisms might therefore not be directly extrapolatable to humans, or not feasible due to concerns of tolerability, safety and adverse effects, the development of tolerance, evasion, feedback mechanisms, compensation or decompensation in the much longer timescale of application in humans. Better results might emerge from the study of other long-lived species, many of which however are not amenable for large-scale, controlled and standardized investigations (90–93).

Besides these physiological differences, laboratory conditions might also introduce artefacts and differences when compared to the environment and lifestyle of humans "in the wild". Most canonical model organisms are bred, kept and experimented on under strictly standardized conditions (94). For example, rodents are often housed in pathogen-reduced (or –"free") conditions, humidity and temperature are rigorously controlled, often not at thermoneutrality (95) below which a substantial fraction of energy intake is used to maintain body temperature (96). The circadian light-dark cycle is fixed, without seasonal variation. The animals are severely sedentary, receive *ad* libitum diets, and undergo health monitoring, which leads to sick animals being removed from experiments cohorts for ethical reasons, e.g. due to infections or cancer (80–82, 84, 90, 97). Such environmental differences might be of uttermost importance, e.g. when trying to translate findings such as the lifespan

extension in mice with interleukin 11 (IL-11) inhibition (98), which might become an issue in humans that need a fully functional immune system, in addition to the other roles of this cytokine in various tissues (99, 100). Such functions might extend to other contexts, for example the effects elicited by exercise on immune cells and function that contribute significantly to training adaptation, reduction in musculoskeletal diseases and healthy aging (101). Environmental differences might also mask constraints of genetic effects. For example, mutations of the Methuselah gene (or antagonism of the corresponding protein) in *D. melanogaster* increases lifespan, but only in very specific conditions such as sex, food source, mating status and temperature (102). Thus, the apparent longevity is not paralleled by an increase in healthy aging, and achieved at the expense of general fitness, e.g. increased susceptibility to cold, a reduction in reproductive output, and dysfunction of the neuromuscular junction (102).

Despite these caveats, model organisms have yielded insights into mechanistic aspects of aging, and, as opposed to human studies, allow the acquisition of data beyond correlative or associative value. Moreover, in many regards, parallels between the physiology of model organisms and humans exist. Thus, investigations in model organisms are important, and should complement human studies. Moreover, evolutionarily conserved mechanisms allude to fundamental, important molecular principles. Nevertheless, a careful validation in humans is indispensable to avoid unwarranted extrapolation. For example, generally speaking, the reduction of processes involved in growth, anabolism, and sexual reproduction and fecundity, and the increase in maintenance and repair pathways emerged as main targets to increase longevity in various model organisms (103). For example, mice with mutations in the pituitary – growth hormone axis such as Ames or Snell Dwarf mice exhibit an up to 40% increased mean and maximal lifespan, together with a delayed age-related decline in T cell function, improved collagen cross-linking and reduced joint cartilage degeneration as well as osteoarthrosis, better cognitive function, and lower incidence and severity of neoplasms (104). However, these benefits only manifest when housed together with wildtype females since mutated males are killed by wildtype males. Moreover, co-housing is important since these animals have problems maintaining body temperature, spending a long-time in energy-saving torpor. Overall, clear trade-offs between lifespan extension and physical vigor are observed (105, 106). Thus, in the wild, such mutants would be unlikely to survive and show a longevity phenotype. In this case, these findings fail to directly translate to human biology. Analogous mutations to those in Ames or Snell Dwarf mice can also occur in humans, for example in Laron syndrome. These individuals have a reduced risk for cancer and type 2 diabetes. On the other hand, they often suffer from decreased stature, prominent forehead, depressed nasal bridge, underdevelopment of mandible, truncal obesity and micropenis in males (107). Moreover, the risk of cardiac disease mortality is increased, and more frequent deaths are reported from convulsive disorders and other non-aging-related causes (107). Most strikingly, despite a major reduction in “pro-aging signaling” (107), at least as defined in model organisms, mutations of the pituitary-growth hormone signaling axis in humans are not correlated with longevity (18, 108, 109). Collectively, while studies on aging processes in model organisms provide valuable insights into the molecular mechanisms, it is crucial to recognize that these organisms are not simply smaller versions of humans and validation of the findings in human cohorts remains essential.

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2 Proposed anti-aging drugs and interventions

Studies in model organisms, in some cases complemented with human data, have revealed signaling pathways, cellular processes and key regulators to be involved in controlling longevity, so-called “hallmarks of aging”. Hallmarks of aging are defined as processes that 1) exhibit a time-dependent manifestation during aging, 2) accelerate the aging process when intensified, and 3) slow down, stop or even reverse aging when modulated in the opposite direction (110). Twelve hallmarks of aging have been proposed: genomics instability, telomere attrition, epigenetic alterations, loss of proteostasis, compromised autophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation and dysbiosis (110). Even though “hallmarks” and “pillars of aging” have been proposed, these are largely based on associative observations, and fail to differentiate between causal events, epiphenomena, compensation or decompensation (111). Nevertheless, interventions and pharmacological agents have been designed and postulated to exert “anti-aging” effects (112) often aiming at re-establishing dysregulated cellular properties, as defined in the aging hallmarks (Figure 1) (38, 110, 113–128).

Examples include compounds mitigating the accumulation of reactive oxygen species (ROS)-caused damage (e.g. resveratrol, curcumin, astaxanthin, epigallocatechin-gallate, protandim, melatonin, spermidine or methylene blue), increased inflammation (e.g. berberine, 17-α-estradiol, acetylsalicylic acid or nordihydroguaiaretic acid), compromised autophagy (e.g. berberine, spermidine, rapamycin or caloric restriction), impaired stem cell function (e.g. spermidine, young blood/plasma or stem cell therapy), a decline in NAD^+ levels (e.g. NAD^+ precursors and boosters such as nicotinamide riboside or nicotinamide mononucleotide), excess hepatic methionine (e.g. glycine or methionine restriction), disturbed glucose homeostasis (e.g. metformin, acarbose, 17-α-estradiol or canagliflozin), cell senescence (senolytics such as fisetin, dasatinib and quercetin, berberine or curcumin), overactivation of mammalian target of rapamycin (mTOR) signaling, anabolism and dysregulated proteostasis (e.g. rapamycin, spermidine, growth hormone or caloric restriction), an overactive renin-angiotensin-aldosterone (RAA) signaling (e.g. enalapril) or epigenetic drift (e.g. cellular reprogramming or rejuvenation) (38, 110, 113–128). However, at the moment, none of these have been successfully been tested in human aging, and the effects of most of these interventions and drugs fail to be broadly replicated even in model organisms, showing considerable species, strain and sex differences (129). Rapamycin is one of the very few exceptions, with an effect on aging observed in different species and mouse strains (130–132), with positive outcomes in the Interventions Testing Program (ITP) of the National Institute on Aging (NIA) (133, 134). Besides the conceptual conundrum of a single compound to be able to alleviate multifactorial aging, other caveats exist that caution the use of many of these drugs in humans. (135)In the following sections, several examples will be presented that illustrate the potential and pitfalls of “anti-aging” medication. A comprehensive discussion of all proposed interventions is beyond the scope of this review, indeed might be futile considering the missing clinical data on human health and longevity at the present time. For future development, challenges for translatability of pharmacological interventions have been described (135). In addition to these, a couple of

additional steps should be considered. First, reproducibility in pre-clinical models, as for example assessed in the ITP, might help to prioritize compounds. Second, validation in short-term randomized clinical trials should be benchmarked against biomarkers of aging with reliable data such as the physiological parameters discussed below. If positive, both in terms of efficacy of biomarker modulation as well as safety and tolerability, long-term randomized clinical trials should be done, which, even if costly, would provide data on hard clinical endpoints including mortality and disease risks. Moreover, such long trials would also reveal the safety, tolerability and adverse effects profile in chronic treatment. At the moment, none of the proposed pharmacological or interventional agents fulfill these criteria.

2.1 Pharmacological agents: repurposed and new drugs

2.1.1 Resveratrol: Resveratrol is a polyphenol hailed as activator of sirtuin 1 (SIRT1) and as a strong promoter of health and longevity (136, 137). However, initial findings could not be reproduced in mice (138), fruit flies (139), roundworms (139) or yeast (140). In fact, binding of resveratrol to SIRT1 (or the yeast orthologue Sir2) might have been an experimental artefact (140–142). Moreover, the nature of sirtuins, including SIRT1, as “longevity genes” has been questioned (143). It thus was of little surprise that a multi-million endeavor of developing drugs based on the resveratrol/SIRT1 hypothesis failed (38, 143, 144). Nevertheless, resveratrol has been tested in various clinical trials for different indications, however to date with little success, controversial results and poor evidence for efficacy (145–147).

2.1.2 Metformin: Metformin is one of the most widely prescribed medication for type 2 diabetes. This drug is in general safe and well-tolerated, can however be associated with severe side effects including lactic acidosis, vitamin B12 deficiency, nephrotoxicity and lower testosterone levels (148, 149). Promising initial results of lifespan extension in model organisms could not be universally reproduced (150). Similarly, early results of improved survival of type 2 diabetes patients on metformin were not substantiated (151, 152). Thus, while the usefulness of metformin in type 2 diabetes is uncontested, a potential application in healthy individuals is strongly debated (153). Intriguingly, in a 40-months study in 12 male cynomolgus monkeys, signs of improved brain function and morphology, and attenuated transcriptional fluctuations in several tissues were reported, along with mitigation of some of the proposed aging hallmarks (154). Whether these effects contribute to broad and *bona fide* aging benefits on health and longevity remains to be determined, as will translatability to humans (155).

2.1.3 Rapamycin: Rapamycin, a pharmacological inhibitor of mTOR activity, has originally been used as an immunosuppressant drug, e.g. in organ transplantation, but is in the meantime applied more broadly, for example in coronary stents to prevent restenosis, lymphangioleiomyomatosis, vascular malformations, facial angiofibroma or in different types of cancer (156). Based on the robust and highly reproducible effect of rapamycin on health- and lifespan in different model organisms, the use of rapamycin or rapalogs, compounds derived from the parent drug, in anti-aging treatment of humans has been proposed (157). Surprisingly, in terms of gene expression, rapamycin treatment however results in pro- and anti-aging profiles, at least in skeletal muscle (158). Moreover, different

muscles seem to exhibit divergent responses to rapamycin treatment (158, 159). It is now also clear that, contrary to initial hypotheses (160), rapamycin is not a “caloric restriction mimetic”, since rapamycin treatment and caloric restriction engage overlapping and distinct signaling pathways, and thus lead to at least partially divergent outcomes on the aging process (159, 161). To date, no clinical trials evaluating the effect of rapamycin on longevity or healthspan have been performed. However, a number of clinical trials using rapamycin or rapalogs in healthy individuals and patients suffering from age-associated diseases have led to mixed outcomes, and thus necessitate additional studies (162). Of note, most of these clinical trials were relatively short, some with a single dose of rapamycin or a rapalog. Extrapolation of tolerability, safety and potential adverse effects to a potential longer-lasting “anti-aging” treatment thus is difficult. Importantly, adverse effects occurred in these trials, even though to a lesser extent than those reported in long-term treated kidney transplant patients (162).

Geroprotective use of rapamycin and rapalogs will thus have to be done under consideration of expected on-target and potential adverse effects. First, the inhibition of mTOR by rapamycin in B and T cell activation is leveraged for the immunosuppressive effect in organ transplant recipients, linked to an increased susceptibility for life-threatening infections and sepsis in these and cancer patients (163). Immunosuppression obviously would not be desired in geroprotection, and might have not been seen in pathogen-shielded animal studies. However, signs of modulated adaptive immunity leading to immunostimulation in some trials indicate that the problem of immunosuppression might be preventable under certain conditions. For example, the rapaglog RAD001 improved adaptive immune function, while the selective mTOR complex 1 (mTORC1) inhibitor RTB101 increased the risk for respiratory illness in an unsuccessful clinical trial (164). A second on-target effect is related to the anti-proliferative effect on endothelial and smooth muscle cells, thereby exerting anti-angiogenic outcomes, one of the main principles of rapamycin treatment of renal carcinoma (165). In fact, the deterioration of vascular function observed during aging can be ameliorated by elevating vascular endothelial growth factor (VEGF) signaling, resulting in enhanced health- and lifespan in mice (166). Hence, this effect could be negatively affected by the suppressive influence of mTORC1 inhibitors on VEGF. Other consequences of the anti-angiogenic action of rapamycin include abnormal growth of the chondro-osseus junction, at least seen in rats (167), as well as diminished wound healing (168), as well as dysregulated menses and uterine growth in women (169, 170). A more general impact on fertility is implied by gonadal dysfunction, as well as impaired spermatogenesis in men (171). Then, a broad metabolic dysregulation has been reported as unwanted response, including the development of hyperglycemia, hypercholesterolemia, hypertriglyceridemia, dyslipidemia and diabetes (162, 172–174). Finally, in preclinical mouse models, microglial mTOR has been found to enhance β-amyloid plaques clearance in an Alzheimer’s model, with inverse effects of rapamycin, indicating that pharmacological inhibition of mTOR could promote the risk for this neurodegenerative disease (175). All of these concerns will have to be addressed before long-term geroprotective treatment with rapamycin or rapalogs will be attempted.

2.1.4 Senolytics: Senolytics target senescent cells ("Zombie cells") that are permanently proliferation arrested and characterized by the senescence-associated secretory phenotype (SASP), with potential detrimental effects on neighboring non-senescent cells (176). Through poorly understood mechanisms, senolytics selectively remove senescent cells that accumulate in different tissues during aging, leading to functional retrieval reminiscent of younger tissue. This strategy is highly promising, with outstanding results in pre-clinical model organisms. However, again, human translation is still missing. Moreover, cell senescence is not merely a byproduct of aging, but a physiological process that is crucial in different contexts, for example embryogenesis, wound healing or tissue/organ regeneration (176–179). Based on this knowledge and pre-clinical studies, a pro-senescence therapy might actually be appropriate in several diseases, including pulmonary hypertension, atherosclerosis, liver and renal fibrosis, glucose intolerance, rheumatoid arthritis as well as cancer prevention and treatment (177). Thus, the choice of pro- or anti-senescence therapy could strongly depend on co-morbidities and differential diagnosis, in particular when senolytics are envisioned as geroprotective treatment in the elderly (177).

2.2 Anti-aging interventions: back to the roots?

2.2.1 Cellular reprogramming and (epigenetic) rejuvenation: During embryonic development, terminally differentiated tissue cells emerge from pluripotent stem cells, and originally from the omnipotent fertilized egg cell (180, 181). Since all of these cells share the same genome, the expression of the genes that define tissue identity has to be tightly regulated, most dominantly by epigenetic modifications that affect chromosomes, histones and the DNA. Conrad Waddington's landscape provides a theoretical framework in which stochastic alterations of epigenetic modifications and gene expression are increasingly restricted and channeled during the developmental decision making process. This unidirectional waterfall model has been challenged and expanded. For example, dynamic changes in epigenetic modifications are observed in cell fate transitions, de-differentiation and trans-differentiation, e.g. in tissue regeneration (181, 182). Moreover, somatic cell nuclear transfer or the production of induced pluripotent stem cells with transcription factors provide further proof that "epigenetic barriers" can be overcome and cells reprogrammed (183). Since, arguably, reprogramming of tissue to pluripotent stem cells could be interpreted as a "rejuvenation" back to a developmentally younger version, this technique has also gained traction as a possible anti-aging intervention (184, 185). In this case, potential age-associated epigenetic events, which could either be stochastic or deterministic, would be reversed. Evidence for such a drift emerges from various observations in aging tissues and organs, including loss of heterochromatin, alterations in histone post-translational modifications and DNA methylation, accumulation of histone and chromatin modifier variants, modifications of the levels and/or activity of non-coding RNAs and transposable elements, or faster and less controlled transcription (186–188). Thus, if such events were reversed, a more youthful and healthy cell function could potentially be achieved. Full reprogramming of an old organisms, for example using the four "Yamanaka factors" Oct3/4, Sox2, Klf4 and c-Myc (OSKM) obviously would be deleterious if all cells were de-differentiated into embryonic-like stem cells, leading to loss of organ function, severe health problems, cancer and death within days (184). For therapeutic purposes, partial reprogramming would be the goal to increase "stemness" without pluripotency acquisition.

Despite various successful reports in rodent animal models, human translation of reprogramming is still elusive. First, the mechanistic underpinnings of reprogramming are only poorly understood, and therefore, the targeting of an exact endpoint in “partial” reprogramming currently is impossible. Accordingly, a large heterogeneity in outcomes is found *in vitro* and *in vivo*. In partially reprogrammed cells in culture, heterogeneity emerges from transient phenotypes/rejuvenation, epigenetic remnants and memory, loss of morphology, cell fate anomalies, or non-natural progenitor phenotypes, of which the extent varies by method, tissue source, progenitor cell age, cell environment and other experimental factors. A similar heterogeneity is observed in mice *in vivo*: abnormal tissue growth, teratoma, tumors and metastases, activation of transposable elements, hepatic and intestinal failure and other pathological events have been reported, frequently leading to premature death (184, 189–191). Again, as outlined in the discussion of drug treatment, partial reprogramming in humans has to consider the much longer lifespan, which could exacerbate many of the reported adverse effects in rodents. Of note, the Yamanaka factors c-Myc and Klf4 can act as oncogenes, while the other two, Oct3/4 and Sox2, often are highly expressed in tumors (190). Inversely, several tumor suppressor genes, including p53 and Ink4a/Arf act as barriers to reprogramming. Moreover, reprogramming is not only stimulated by the presence of cell senescence, but also triggers this process, leading to higher number of senescent cells and the presence of SASP in the microenvironment (184, 190). At the moment, based on our lack of deeper understanding, despite reported success in mice, partial reprograming might be best described metaphorically with a blindfolded shotgun blast leading to a massive effect, but very far from clinical translation.

2.2.2 Hormones, stem cells and young blood: Other attempts at rejuvenation are aimed at restoring youthful function with the use of circulating hormones and other signaling factors, or with stem cells. Sex hormones such as testosterone, estrogen or progesterone, growth hormone, dehydroepiandrosterone (DHEA) or thyroid hormone have been postulated to bring back youthful features when prescribed in elderly individuals (192, 193). However, outside of clinically relevant and accepted applications, there currently is no proof for a general anti-aging effect, and serious reservations about long-term effects, adverse outcomes and risks exist.

Similarly, the injection of stem cells currently lacks evidence for anti-aging properties as opposed to the well-documented use in regenerative medicine in degenerative disorders (194). Several factors might be responsible for that: for example, exogenous stem cells might not be able to fulfill their purpose if the corresponding stem cell niche is aged. Moreover, several hurdles will have to be overcome (194). Since stem cells also undergo aging-related changes that compromise function (195), autologous donor cells might first have to be “rejuventated”, or heterologous donor cells from young compatible donors be used. The optimal type of (mesenchymal?) stem cell will have to be identified. Heterogeneity amongst cells and between donors, acceptors and isolation protocols will have to be accommodated. Adequate *in vitro* expansion and mass production methods will have to be established to meet the very high demand for systemic treatment. Standardization of approaches, as well as methods to track the fate and function of transplanted stem cells

will have to be performed. Finally, potential long-term effects, e.g. tumorigenesis, will have to be considered.

Parabiosis experiments in rodents have shown the potential of young blood to rejuvenate organ function in connected old animals, implying the existence of circulating factors that mediate the corresponding effects (196). At the moment, the identity of such factors is not known. Moreover, based on single heterochronic blood exchange experiments, it might be possible that the extent of detrimental effects of old blood surpasses that of the benefits of young blood, suggesting that at least in part, the rejuvenation in old animals in parabiosis might emerge from dilution of such pathological factors (197). Geroprotective benefits of therapeutic transfusion of young plasma in humans have not been documented so far. Moreover, known risks of infusion of human plasma include presence of infectious agents, serious allergic reactions, transfusion-related acute lung injury or overload of the circulatory system. In light of these risks, and the complete absence of proven clinical benefits on aging or most aging-related pathologies, the FDA currently advices caution for the commercialization of infusion of plasma obtained from young donors (198). Moreover, ethical issues about donor recruitment and compensation, and about disparities in access exist (199). Some of these might be solved once effective factors have been identified and can be recombinantly produced.

2.2.3 Caloric restriction: A seminal study of McCay, Crowell and Maynard, published in 1935, investigated whether undernutrition in rats retards growth (200). Intriguingly, they found that the calorically restricted and growth retarded animals exhibit an increased lifespan. Even though this effect was only seen in males, and not the already longer-lived females, this paper stimulated an exponential interest in caloric restriction as longevity intervention (201). Indeed, the initial observation was replicated and expanded in various canonical and non-canonical model organisms, including yeast, *C. elegans, D. melanogaster*, mice, dogs, and even water fleas, silkworms, spiders or fish (202). Due to the robustness of the effect, caloric restriction has been postulated as the “gold standard” for life-extending interventions. In a general sense, the payoff of caloric restriction on longevity decreases with animal complexity (203), from ~200% in yeast to ~100-200% in *C. elegans*, ~100% in *D. melanogaster*, ~30-50% in mice, and ~15% in dogs (mean, not maximal lifespan (204)), with significant variations between strains and experimental protocols. To get better insights into translatability to humans, two independent trials in rhesus monkeys were undertaken, with surprisingly different outcomes (205, 206). In one study (205), an extension in lifespan was projected based on the available data, which became significant when non-aging-related mortality was excluded (estimated at ~7% (207), thus smaller than the effects in dogs and lower organisms). In the second study (206), no such effect was observed, and the validity of caloric restriction as longevity intervention in non-human primates questioned (208, 209). Importantly, the study design differed in several key aspects (207): first, monkey breeds were not equivalent. Second, the first study had an *ad libitum* fed control group, while the control group in the second trial was food restricted to avoid overfeeding and excessive weight gain. Third, the composition of the food was not the same, with 28.5% sucrose in the first, and 3.9% sucrose in the second trial. Maybe as a direct consequence, co-morbidities were unequally distributed, for example leading to more than 40% of the control animals

to develop diabetes in the first compared to 12.5% in the second trial. Thus, the positive outcome for caloric restriction on health and longevity in the first trial could primarily be based on the reduction of the pathological consequences of overfeeding of a glucose-rich diet. Indeed, in the second study, lower body mass, lower adiposity and improved survival was already observed in the control animals (compared to the counterparts of the first study), thus even in the absence of caloric restriction, at least in the males. As a consequence, the survival of the male control cohort in the second study was the same as the calorically-restricted males in the first and second trials, with no statistical differences. In females, no differences in body mass, adiposity and survival was seen when comparing control and calorically restricted groups in the second study, pointing towards a sex dimorphism in the response to this intervention.

The potential benefits of caloric restriction in extending lifespan by primarily reducing pathological effects of overfeeding or unhealthy diets can also be inferred from studies in rodents. In mice and rats, the lifespan extension directly correlates with the propensity for adult weight gain, thus very little effect in lean, and larger effects in strains that gain more weight, either based on the genetic background, or on differences in food composition in the same strains (210). Similar to the outcome of the first rhesus monkey trial, many reports of lifespan extension in rodents could be due to the experimental conditions with *ad libitum* overfed control mice, unhealthy dietary composition, and a marked sedentary state in normal home cages (83, 84, 97). Indeed, mice caught from the wild have lower body fat (~3-5%) than most laboratory strains (~9-22%, ~22% in C57BL/6) under standard conditions (83), and caloric restriction has no effect on mean longevity in wild mice (211). Even in laboratory mouse strains, the response of lifespan to caloric restriction is far from uniform. In fact, a considerable number of mouse strains react only very little, and some even experience a negative, life-shortening effect (212–214). Indeed, in genetically diverse mice, hereditability had a larger effect on lifespan compared to dietary restriction (215). Of note, in some of these mice, even in those experiencing increased longevity, dietary restriction was associated with compromised health, e.g. loss of lean mass, compromised immune system function, or disruption of erythroid cell populations (215). These findings are of obvious importance when considering the genetic diversity of humans (216). Moreover, as reported by McCay and colleagues in the rat strain used in their study published in 1935 (200), a sexually dimorphic response is seen in many mouse strains, which can lead to diametrically opposite effects of caloric restriction on lifespan in males and females (212–214). Strain-specific responses are not only observed in rodents, but also in *D. melanogaster* and *C. elegans*, in which the naturally top 10% longest-living strain obtain significantly less life-expanding benefits from caloric restriction compared to the bottom 10% (217, 218).

All of these results have high relevance when considering caloric restriction for human health- and lifespan extension, from the decreasing payoff when going from lower to higher organisms to the clear genetic and sex-specific contribution that shapes the response to this intervention. Furthermore, other issues would have to be considered, tested and validated (210, 219, 220). For example, it is not clear what the baseline caloric intake is from which restriction is calculated. How would inter-individual variations in energy metabolism be taken into account, both in terms of basal energy metabolism including non-exercise activated thermogenesis (NEAT) as well as that contributed by physical activity? Then,

the optimal extent of restriction, age of initiation and dietary composition are unknown in humans. Furthermore, adherence might be compromised by the constant, unpleasant feeling of hunger (221). Finally, psychological factors of prolonged caloric restriction, e.g. on mood, depression or aggression, and reported adverse effects, e.g. frailty, reduced cognitive performance, impaired wound healing and immune function will have to be dealt with (94, 222). Based on the data obtained in rodents and primates indicating that the effect of caloric restriction on health- and lifespan might be rather due to an amelioration of pathologies triggered by overfeeding and sedentariness, a balanced and calorically-controlled diet, linked to adequate physical activity, likely is the healthier, safer and more efficient choice, lacking many of the potentially adverse effects, drawbacks and limitations of caloric restriction (or other specialized diets) in humans (94). Indeed, no clear evidence of longevity benefits of *bona fide* caloric restriction in humans currently exist (66, 202). Moreover, similar to the non-human primate data, human studies such as the multicenter, phase 2, randomized controlled Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) trial indicate that health benefits, in this case in a young (21-50 years) population after 24 months of a caloric restriction of 25% from baseline calorie intake, primarily segregated to men and individuals with a higher body mass index (BMI) (223).

2.2.4 Telomere lengthening: Other interventions have been proposed, some if which have even been commercialized even though little to no human data on benefits exist, and significant adverse effects could ensue. For example, based on the shortening of telomeres in the aging process, telomerase gene therapy has been proposed as an anti-aging strategy, introducing this enzyme, which can elongate telomeres, with adeno-associated viral vectors (AAVs) or cytomegalovirus vector (CMV) (224). At the moment, there is no proof of efficacy of therapeutic benefits in humans. Moreover, several caveats should put a brake on such endeavors: first, telomerase re-activation is seen in ~85% of cancers (225). In fact, overlong telomeres are also associated with diseases in humans, e.g. familial clonal hematopoiesis (226), as well as increased cancer risk (227). The levels of telomerase after overexpression with viral vectors will be difficult to be adequately titrated in different cell types and tissues in order to evoke “healthy” telomere lengthening. Finally, viral vector-based gene therapy has inherent risks that might overshadow the so-far non-existent evidence of beneficial effects in human aging (228, 229). It thus is not surprising that such “treatments”, based on telomerase, follistatin or klotho, are not approved for clinical application in the USA or Europe for aging or related fields, and extreme caution is warranted towards commercial offers in countries with lax or non-existing regulation. Notably, most of these suppliers do not guarantee safety or efficacy (230).

3 Lifestyle-based interventions in health and longevity

3.1 Nature: coincidence, genetics and epigenetics

In contrast to these experimental approaches, a number of interventions, lifestyle and behavioral choices have been shown to provide not only a good correlation with, but even predictive power for human morbidity, mortality, health- and lifespan (Figure 2) (231–233).

Apart from the fixed **genetic endowment** and the **stochastic outcome of random events** (e.g. accidents), most of the other parameters can be voluntarily changed, although some require a societal and political effort beyond the capability of an individual. Of note, genetic and lifestyle factors associate with lifespan in an independent manner, indicating that a healthy lifestyle can overcome genetic risks and convey health benefits even in a genetically "unfavorable" context (234). Moreover, environmental aspects by far exceed polygenic factors in the explanation of premature mortality (235).

The dynamic makeup of the **epigenetic landscape** can be inherited, predetermined and yet be pliable. For example, the epigenetic changes elicited by the experience of famine, e.g. the Dutch hunger winter during World War II, were imprinted in the individuals that experienced this traumatic event, and were transmitted to their children and grandchildren, in this case with detrimental health effects on disease risks and life expectancy (236). Obviously, you cannot chose your parents based a benevolent genetic endowment, and you cannot influence their environmental exposures and lifestyle choices, which can result in favorable or unfavorable genetic traits and epigenetic marks for health, aging and longevity. However, all of the lifestyle choices and behaviors discussed here will most likely result in epigenetic changes that can be beneficial or detrimental. While for most of these factors, this still has to be reliably shown, ample evidence for exercise-mediate epigenetic modifications with favorable health outcomes has been provided (237, 238). These effects can be potentiated with diet and potentially other interventions (239).

3.2 Nurture: lifestyle and other factors modifiable on the individual level

Importantly, none of the modifiable factors (including physical activity, nutrition, restorative sleep, no excessive alcohol, no smoking or opioid use, stress management and social connections) are mutually exclusive, and additive or synergistic effects can be achieved when combined (240–253), even at old age (254), or in regard to various diseases such as dementia (255, 256), frailty (257), diabetes (258), brain health (259, 260), stroke (261), or cancer (262). For example, while adopting one lifestyle factors reduces the mortality risk by 26%, the implementation of eight factors results in a lowering of the mortality risk of 87% (241). Of these, **physical activity** is by far the best intervention ("Exercise is Medicine" (263)), and is modifiable on a personal level with clear benefits for health and longevity (264–285), far beyond cardiovascular mortality (286–290), and regardless of age (291) or sex (292, 293). Health benefits of physical activity have already been proposed in ancient cultures, since two and more millennia ago (294, 295). Exercise, like aging, is multifactorial, affecting almost every organ and tissue in the human body (296). It thus is not surprising that all of the proposed hallmarks of aging are ameliorated by this intervention (297–300). The underpinnings of this potent effect are however unclear: one hypothesis proposes that the stress elicited by an acute exercise bout mimics some of the changes observed in aging, and, if done repeatedly in training, provoke a better protection and resilience against these processes (301). However, it is noteworthy that despite an apparent risk-protection paradox, for example due to the marked stress exerted on the cardiovascular system during an endurance exercise bout, regular physical activity reduces mortality risks and optimally prepares the body for ensuing perturbations in an effective and long-term sustainable manner (302). Exercise accordingly rivals existing drugs in terms of efficacy

to prevent and treat a number of pathologies (303–305). Inversely, a sedentary lifestyle is a strong and independent risk factor for many chronic diseases and mortality (264, 306–310). Of note, most data on the effect of physical activity on mortality are derived from observational studies as opposed to the very rare randomized clinical trials with mortality as specified primary endpoint (311). Nevertheless, the wealth of data indicates a higher probability for a direct, causal relationship compared to mere association (311). Physical activity and exercise will be discussed in more detail in the sections below.

Dietary patterns and **nutrition** scores are likewise associated with frailty and mortality (312, 313). However, the effect of different diet modalities and macronutrient enrichment in human aging remains debated (94). Moreover, rodent studies, e.g. showing a beneficial effect of low protein and amino acid diets on longevity, might not be extrapolatable to humans (94), in which anabolic resistance necessitates higher protein supplementation to mitigate age-associated muscle mass loss and frailty (314–319), and in whom high protein diets might improve sarcopenia (320) or mortality, even in patients with chronic kidney disease (321). Such effects of higher protein intake are significantly boosted by concomitant resistance exercise training (322). In any case, it is clear that a **balanced** (for all necessary macro- and micronutrients (323, 324)) **and calorically-controlled diet**, possibly devoid of ultra-processed food (325), is crucial to lower the risk for obesity, cardiovascular and metabolic disorders, thereby helping to maintain health from young to old age (326–328), in combination with adequate hydration (329). The higher relevance of the overall healthy eating patterns over specific macronutrient depletion/enrichment was accordingly highlighted in the Dietary Guidelines for Americans (DGA) 2020-2025 (327). Moreover, the impact of healthy food choices on mortality has been demonstrated (330, 331), in particular in, but not limited to elderly individuals who are often plagued by malnutrition and inadequate protein intake (332). In the future, individual differences in food absorption, metabolism and excretion might be leveraged to design precision/personalized nutrition, conferring additional health benefits (333, 334). However, better ways of monitoring and recording dietary habits will have to be devised to circumvent often unreliable self-reporting (335, 336).

The optimal amount of **sleep** is age-dependent, with a recommended duration of 7-9 hours per night for young adults and adults, and of 7-8 hours per night in older adults, following a healthy pattern with little interruptions, insomnia, snoring or other events that lower sleep quality (337, 338). Both shorter (<6 hours) as well as longer (>9 hours) sleep is associated with an increased mortality risk, most prominently for cardiovascular, but also other types of mortality (339–344) or dementia (345). Similar to most other lifestyle interventions, sleep is interdependent on other lifestyle and societal factors, for example socioeconomic status, depression and further psychiatric issues, alcohol dependence or a sedentary behavior (346). Interestingly, mortality associated with overlong sleeping seems to be predominantly affected by such environmental factors, while that of shortened sleeping exhibits a stronger heritability component (347). Overall, sleeping patterns not only contribute to the prediction of body characteristic (e.g. visceral adipose tissue) and disease risks (e.g. insulin resistance), but can inversely also be inferred by lifestyle factors to over 50% (348). Importantly, changes in sleeping behavior towards optimal patterns can reduce mortality risks (339), even

when performed in the form of weekend catch-up sleep (349). Sleep quality can for example be promoted with endurance or resistance training (350, 351), in normal sleep as well as in the context of sleep disorders (352). At least somewhat related to sleep patterns, disruption of circadian rhythms with bright night- and dimmed day-time light is sufficient to increase mortality risks (353).

In the elderly, poor **cognitive performance** is an independent risk factor for mortality (354, 355). Unfavorable results in cognitive tests could be the consequence of an unhealthy lifestyle or co-morbidities, with limited effects of cognitive training in old age (356). Accordingly, a causal relationship between sarcopenia and cognitive impairment (357) or a correlation between physical activity levels, muscle strength, working memory, and cognitive function have been postulated (358). Nevertheless, despite studies showing positive effects in healthy individuals (359), the efficacy of exercise to improve cognitive abilities in the elderly, in particular with already compromised function, is controversial (360–365), but might be boosted by multi-domain interventions that include physical activity (366, 367). When undertaken at earlier age, interventions, e.g. focused on healthy diet, physical activity and abstinence from smoking, might help to build a cognitive reserve, with clear benefits of lifetime intellectual and cognitive engagement (356, 368, 369). Of note, skeletal muscle mitochondrial oxidative capacity, a parameter that is highly pliable by endurance training, is associated with preserved brain structure, in particular of areas involved in cognition, motor function and sensorimotor integration, hinting at a correlation of exercise adaptations and muscle mass with brain health and structure (370–377). Finally, early detection and monitoring of trajectories could be improved by combining functional (378), imaging- and blood biomarker-based approaches (379) and might help to distinguish inter-individual differences present from birth/young age from those arising during aging (380).

Preventative health checks and monitoring can contribute to the risk assessment for various diseases and disease-specific and overall mortality (381), e.g. by periodical recording of blood pressure, body mass as well as waist-hip ratio, cholesterol, lipid and glucose levels. However, for many screenings, clear benefits have not been established, and problems with false positive and false negative findings can arise. Thus, in a healthy population, random general health checks might not help to decrease mortality risks (382). In contrast, well-designed, evidence-based health monitoring, combined with an up-to-date vaccination status (383, 384), will help in the prevention, early detection and treatment of pathologies, thereby reducing mortality risks (385, 386). Moreover, such programs can trigger healthy lifestyle behavioral changes in the monitored population (387).

Risk behavior can be a strong driver of mortality, for example in adolescents (388). However, also in later stages throughout life, engagement in risky behavior such as violence, substance abuse, unsafe sexual habits, or reckless driving highly increase the chance of death (389). In a number of countries including the USA, gun ownership is likewise associated with a higher mortality risk, with an influence on both homicide as well as suicide rates (390–393), and constituting one of the leading causes of death in children and adolescents (394). This is one of the reasons why life expectancy in the USA lags behind that of other rich countries (395).

S**moking** still is one of the strongest modifiable drivers of premature mortality, even though smoking rates are declining in many countries (396, 397). Interestingly, smoking habits could contribute to the sex differences in life expectancy (398, 399). The abuse of other recreational drug likewise increases mortality risks. Alcohol, for example, can not only directly lead to fatal pathological events (400), but also increases risk behavior such as reckless driving, other violent and non-violent injuries, accidents, and can exacerbate psychiatric disorders and suicidal behavior (401, 402). Similarly, the opioid crisis in the USA leads to an estimated 3.1 million years of life lost (38 years per death), and contributed to the decrease in life expectancy between 2019 and 2022 (390, 403).

With regard to social and mental factors, **psychosocial stress** and stress-related disorders are associated with the risk for several chronic diseases and increased mortality (404–407). Intriguingly, a bidirectional association between sedentary behavior and psychosocial stress has been reported (408). In contrast, **optimism** shows a positive association with cardiovascular events, mortality and longevity (409–411). The amount and quality of **social interactions** are also predictors of mortality (412, 413). Loneliness and isolation promote stress, while interpersonal helping behavior decreases stress-related mortality risks (414–416). As with other lifestyle factors such as overlong sleep, loneliness could constitute a causal or a surrogate marker, being potentially indicative of comorbidities such as frailty (417), anorexia or sarcopenia (418), socio-economic constraints or other confounders (419).

All of these lifestyle factors can be influenced by behavioral decisions. To a certain extent, this is also the case for **sun exposure**, although geographical and climate-based limitations exist. Insufficient sun exposure increases the risk for many pathologies, and ultimately leads to a significant number of preventable deaths (420–422). Notably, many of the health benefits of adequate sun exposure are independent of vitamin D production, and supplementation falls short in preventing the pathological outcomes of insufficient sun exposure (420, 421). Obviously, harms of excessive sun exposure, in particular the development of skin cancer, should be avoided, such as sunburns or inadequate protection of eyes and skin at times or seasons with high ultraviolet radiation levels (420, 421, 423, 424).

3.3 Nurture: societal and political aspects

The opportunities for a change in **socioeconomic status** depend on a variety of factors, many of which, for example access to high-quality and affordable education, fair income and taxation systems, or absence of discrimination and “glass ceilings”, can only be achieved on the societal and political level. Educational disparities (425) and low socioeconomic status increase mortality risks even when adjusted for other risk factors (426–429), with up to 20 years of life expectancy disparities between poor and wealthy areas in the USA (430, 431). In fact, at least in the USA, of all social determinants, socioeconomic factors have been proposed to contribute most to health outcomes, length and quality of life, (about 40-47%), surpassing health behaviors (30-34%), clinical care (16-20%) and the physical environment (3-10%) in importance (432, 433). It is noteworthy that these effects apply to years lost and years of functioning lost (434). Moreover, an accumulation of the consequences of low socioeconomic status on health and life expectance over the course of lifetime has been proposed, with consequences of experience in childhood affecting adult health (435).

Thus, the childhood postcode can, at least in certain countries like the USA, predict lifetime risks for many pathologies reasonably well (436), together with other environmental factors much better than contemporary polygenic scores (235, 437). Strategies to overcome socio-economic hurdles and provide the means to achieve a healthy lifestyle have been proposed but, in many cases, remain to be implemented (438, 439).

The socioeconomic status might also limit the availability of or access to affordable high-quality **healthcare** in countries in which this is restricted, e.g. those without universal health care (233), or where inequalities in access such as to primary care physicians exist (440), or differences in health care spending are observed (441). Such disparities lead to a high number of preventable deaths (442, 443). Most prominently, vast differences in global probability of premature death are observed, in part driven by infectious and maternal health conditions more prevalent in certain regions, e.g. sub-Saharan Africa, than others (233, 444). Amongst the Organization for Economic Co-operation and Development (OECD) high-income countries, the USA is an outlier in terms of healthcare costs and outcomes (445–450). Both when expressed as per person or as percentage of gross domestic product (GDP), healthcare spending is substantially higher in the USA compared to the other countries. Even though the situation has improved with the historic passing of the Affordable Care Act, a significant proportion of the population in the USA remains uninsured, whereas in the other OECD countries, health care is mandatory through public and/or private programs. Despite the higher spending, life expectancy at birth is three years lower in the USA compared to the OECD average, and the share of avoidable deaths (normalized to 100’000 people) higher, including having the highest OECD rates for infant and maternal mortality (451, 452). These data illustrate that even in countries where the highest quality and cutting-edge medical care is available for those who can afford this, socioeconomic barriers and ethnic/racial disparities exist, with significant consequences on overall health and mortality outcomes (453, 454). Finally, as recent events have shown, healthcare policy should include an agenda for pandemic prevention, preparedness, response and recovery/reconstruction on the national as well as the global level (233). In fact, a chance of greater than 20% for a pandemic to occur in the next 10 years that will kill as many individuals as COVID-19 has been estimated (233). Related, but not limited to the COVID-19 pandemic, high quality **education** should not only aim at improving knowledge on the basis and application of all aspects of a healthy lifestyle, but also convey methods for critical thinking, assessment, and classification of scientific evidence and hypotheses, facts, mis- and disinformation, or fake news (455, 456).

Changing the consequences of anthropogenic **climate change** and **air pollution** are beyond the capabilities of individuals, and will require a coordinated effort on the nation and global scale. Nevertheless, clear effects on mortality have been reported. For example, the increasing fluctuations and extremes temperatures caused by human-made climate change will lead to deaths beyond affecting only the most susceptible populations, those with low socioeconomic status, infants and the elderly (457–460). Even in moderate climate zones, particulate air pollution is strongly associated with all-cause, respiratory, cancer, cardiovascular and other types of disease-specific mortalities (461, 462), as well as with brain health (463). This can be synergistically exacerbated by high temperatures (464).

Other types of pollution, for example environmental microplastics (465–469), endocrine-disrupting chemicals (470, 471), or (transportation) noise (472–474) might exert similar effects on disease and mortality risks.

4 Age-reversal-age-extension (ARAE) paradox: more might not be better

4.1 Interference between “anti-aging” drugs and epigenetic programming

For the lifestyle- and behavior-based factors that influence mortality, additive or synergistic effects have been shown, in the absence of adverse interactions or side effects. This seems to be somewhat different for the proposed preclinical treatments and interventions, in which some combinations result in additive or synergistic outcomes (475), while others could be irreconcilable. For example, the age-reversal-age-extension (ARAE) paradox has been proposed for epigenetic programming, in which drugs that promote genomic stability are incompatible with the reprogramming that flattens the epigenetic landscape to enable upward movement in the Waddington landscape (184). Such effects have been shown for some of the proposed “anti-aging” drugs that interfere with epigenetic reprogramming, including metformin starting at a concentration of 10 μM (age intervention are often tested at 100 μM), rapamycin starting at 1-2 nM (human plasma concentrations in rapamycin-treated patients range from 5-30 nM, and 50 nM are often used in longevity studies), or resveratrol starting at 20 μM (most health benefits in model organisms are seen with concentrations of 10-25 μM) (184). Thus, even if clinical benefits were achieved, potential interactions might preclude combination-based approaches of these proposed therapies.

4.2 Many of the proposed “anti-aging” drugs dampen exercise training adaptation

Additionally, the ARAE paradox or analogous paradigms can be expanded to other unfavorable interactions. As described above, epigenetic programming is inversely associated with cell senescence, thus facilitated by the presence of senescent cells, and itself triggering cell senescence (184). The outcome of a combination therapy based on reprogramming and senolytics therefore is uncertain. These issues are theoretical since all of these approaches are still experimental. More concerning are interactions with proven lifestyle interventions that have been reported in human trials. These have been mostly shown for exercise (37, 38, 476, 477), but might also apply to others. For example, resveratrol blunts the positive effect of endurance exercise on cardiovascular health and reduces the training effect by ~45% (478–480). Metformin dampens adaptations to endurance (481, 482) and resistance (483, 484) training by ~50%, and increases the rate of perceived exertion (485). Anti-oxidants (486), e.g. high doses of vitamin C and E, reduce the positive effect of exercise on insulin sensitivity (487), delay recovery from endurance (488), and diminish peak torque and total work in resistance training (489, 490). At least in mice, nicotinamide mononucleotide (NMN) reduces exercise benefits on hepatic triglyceride accumulation, insulin secretion from islets, and glucose tolerance in diet-induced obesity (491). Moreover, NMN might be associated with other adverse effects, in particular in certain patient populations (492, 493) or the elderly (494). Finally, inhibition of mTORC1, a key regulator of anabolism in resistance training (495–497), with rapamycin reduces stimulation of skeletal muscle fractional protein synthesis rates and growth in experimental settings of muscle hypertrophy in rodents (498, 499) and in resistance exercise in humans

(500). Interference with endurance training has not been tested so far. However, mTOR is also activated in this type of training modality (501). Moreover, one of the key therapeutic targets in rapamycin therapy in cancer, a reduction of angiogenesis and neovascularization (165, 167), could be relevant for endurance exercise-induced vascularization of muscle tissue, an important process in endurance training adaptation (296). Indeed, adverse outcomes on other types of physiological angiogenesis have been reported, e.g. uterine growth and menses or wound healing in which this process can be impaired in rapamycin-treated patients (168–170). Mechanistically, at least in part, the anti-angiogenic effect of rapamycin has been attributed to a positive effect of mTORC1 on the hypoxia-induced factor 1α (HIF-1α) (165). Since different exercise modalities result in reduced physoxia in skeletal muscle tissue, HIF-1α plays an important role in exercise adaptation (296), which could be impaired by rapamycin administration. Such potential harmful interference of drugs with exercise obviously should be avoided (37, 38, 97, 476, 477, 502, 503). For some, adjusted dosage and timing have been proposed to minimize potential antagonistic effects on exercise adaptation. For example, it has been speculated that restricted use of rapamycin on non-training days could mitigate adverse effects on muscle protein synthesis stimulated by resistance exercise. This however is questionable, and needs to be critically tested, in light of the long anabolic window with increased muscle protein synthesis (up to 48 hours and more) after a resistance exercise training bout (504, 505). Other factors should furthermore be considered. First, it is unlikely that the benefits of single compounds exceed those elicited by the multifactorial adaptations in exercise. Thus, failure to achieve optimal health outcomes might ensue due to the mitigation of the broad and proven effects of exercise that is not outweighed by the narrow effects of single pharmacological compounds. Second, even besides potential direct interactions, the use of an “anti-aging” drug could lead to reduced adherence to and compliance with lifestyle interventions, including physical activity or a balanced diet. Psychological effects of a false sense of “pharmacological health”, seemingly induced by geroprotective agents and putative “exercise” or “caloric restriction mimetics”, might diminish the motivation to engage in time-consuming, long-term and arduous activities if an attractive alternative seems as easy as taking a daily pill.

5 Molecular biomarkers of aging

Many of the problems that affect the study and potential treatment of human aging boil down to the long timeframe that is needed based on human life expectancy, as well as on our ignorance on the evolutionary and molecular underpinnings of this process (506, 507). Following large cohorts over years to decades in prospective clinical trials necessitates a high financial and logistical commitment. However, aging, a physiological (?) process experienced by every human, is not recognized as a disease by regulatory agencies, at least not at the moment. Accordingly, treatment and trials would by definition be performed in “healthy” individuals, with very high regulatory and ethical standards. To get around these issues, model organisms with shorter lifespans and lower ethical hurdles for experimentation are studied (80, 81). Furthermore, human aging biomarkers as surrogates to measure more short-term effects of treatments on aging progression are being investigated (507–511).

5.1 Molecular clocks: from epigenetics to metabolites

A number of such molecular biomarkers of aging have been proposed, from epigenetic marks to telomere length, transcriptomic and proteomic signatures, or glycoprotein profiles (507, 509, 512–516) (Figure 3).

Epigenetic clocks are based on the observation of changes in epigenetic modifications from embryonic development to aging. As described above, epigenetic programming attempts to roll these back to a more youthful state. Initially, DNA methylation events measured in saliva or blood samples were used to establish models to predict “biological age”. Later, epigenetic clocks were also measured in other tissues and cell types. At the moment, a lack of understanding of the molecular causes and consequences of these DNA methylation changes hamper obtaining mechanistic insights beyond the current correlative value. Recently, **histone marks** of aging have been proposed to perform with similar predictive power as epigenetic modifications (517). **Transcriptomic clocks** rely on the assessment of age-dependent gene expression profiles, e.g. in peripheral blood mononuclear cells or dermal fibroblasts. Most of these clocks however have only been tested in small cohorts, and are marred by inherently large transcriptional noise, in particular in aging.

Advances in mass spectrometry, antibody- or aptamer-based techniques have facilitated the development of **proteomic clocks**. Plasma protein signature however can be affected by organ function, e.g. that of the kidney. Nevertheless, recent attempts at establishing blood plasma protein biomarkers based on large human cohorts have shown promising results in terms of predictive power for organ health, morbidity and mortality (518–530). Indeed, of all the molecular/-omics clocks, plasma proteome biomarkers seem most advanced, both technologically as well as in terms of high-throughput human application and validation (531, 532). The continuous improvements in detection sensitivity and proteome coverage of mass spectrometry and DNA aptamer-/antibody-based platforms, combined with machine learning algorithms, will help to eventually push this approach to broad clinical application, even though costs currently are still prohibitive (531). **Metabolomic clocks** (533) have likewise benefited from better mass spectrometry methods, as well as state of the art nuclear magnetic resonance (NMR). However, many of the metabolites identified by NMR are of unknown structure, limiting the usability of untargeted metabolomics, further exacerbated by the noise in measurement. Nevertheless, metabolomics studies that include physiological biomarkers show promising associations in longitudinal human trials (534). Compared to these approaches, attempts at creating clocks based on **protein glycosylation, advanced glycation end products (AGE), chromatin marks** or state have so far been more limited. Finally, as an example for a non-omics based clock, **telomere analysis** determines telomere length as a function of age (535). Methodological issues however can lead to considerable variation, both between individuals, tissue types, or even between sampling sites in the same tissue (or heterogeneity between peripheral blood mononuclear cells) (536).

5.2 Molecular clocks: current state and challenges

At the moment, no consensus on methodology and clock as standard biomarker for human aging has emerged. For most of these biomarkers, the physiological and functional relevance are unclear, the predictive value for morbidity and mortality in humans is poor, there is

little overlap between different types of clocks, and even between clocks of the same type (508, 509, 537, 538). For example, in a recent study investigating the effect of long-term caloric restriction in healthy adults on DNA methylation, the DunedinPACE clock showed a slight reduction in “biological age” in the restricted group, while two other clocks (PhenAge and GrimAge) did not produce this effect (539). Significant deviations between technical replicates of the same samples can exist, in one study with a median and maximal deviation of 3 years and 8 years, respectively (540). Another study of 6 epigenetic clocks using the same samples resulted in deviations of up to 9 years (541). Moreover, epigenetic clocks differ between organs and cell types (542, 543), even between the same cell type depending on spatial location within a tissue (544). In fact, some tissues, for example skeletal muscle, are only poorly represented by epigenetic clocks (545). Then, time of sampling can affect the results, as many epigenetic clocks exhibit circadian oscillations (546). Furthermore, results obtained in model organisms might be misleading. For example, the naked mole rat is considered as a demographically non-aging animal, with exceptional longevity and almost complete absence of cancer and cardiovascular diseases. Nevertheless, this animal exhibits epigenetic aging (547). Such findings might indicate that many of the epigenetic events that are measured might not correlated with *bona fide* aging, but rather represent physiological and pathological consequences to different types of events. In fact, epigenetic clocks often result in overlapping outcomes when comparing old and cancer cells (509). Moreover, the transient modulation and subsequent regression of DNA methylation marks in pregnancy or infection might not be a sign of increasing and decreasing “biological age” (548), but a normal response to these types of stressors (549). Hence, it is essential that a biomarker is robust and not affected by acute physiological perturbations or by technical or pre-analytical variability. Thus, at the moment, all of these molecular clocks will have to be used with caution, awaiting validation in longitudinal human studies in large cohorts (550, 551).

Efforts to standardize the development and validation of such clocks are currently underway, and will be indispensable for breakthroughs in this area (507, 552). More specifically, different types of biomarker validation have been proposed that might help to improve the discovery and implementation of biomarkers (Box 1) (507, 552).

First, biomarkers are especially valuable when they originate from pathways that actively drive aging (biological validation), rather than simply being correlated with this process. Second, if a biomarker targets conserved pathways and is validated in multiple species (cross-species validation), it is more likely to be linked to the fundamental process of aging. Third, the predictive value of a biomarker for future age-related outcomes (predictive validation) in a prospective rather than retrospective study should be assessed. Fourth, the assessment/analysis of the biomarker should be standardized (analytical validation), including the collection, storage and analysis procedure of the sample to facilitate the determination of the sensitivity, specificity and reproducibility of the biomarker. Finally, it is important to establish the clinical value (clinical validation) of a biomarker in terms of improving our understanding of the disease or the potential effects of an intervention on health outcomes. Collectively, broad validation across these dimensions is instrumental to ensure that molecular biomarkers are robust, reproducible, and clinically meaningful, and can therefore be used to predict “biological age”, health outcomes in response to an intervention, the risk to develop diseases and mortality.

Furthermore, multi-omics approaches might help to improve such clocks (553), analogous to attempts in the field of muscle exercise biology (554). However, even with the current lack of a comprehensive understanding of the aging process, a multicomponent mechanism, with pleiotropic outcomes, affecting all cells, tissues and organs of the human body is more likely than a single pathway/molecule common to all somatic cells. Accordingly, until our knowledge improves, compound measures and indices that describe systemic, or at least multi-organ health, relevant for resilience and functional retention, might have the highest chance to monitor aging progression and provide feedback on potential interventions (discussed below). Nevertheless, it is conceivable that the study of theses molecular clocks will help to better understand the mechanisms underpinning human aging. Moreover, the use of integrated or combination approaches, e.g. combining plasma proteome with human phenome data (555) or metabolome with genomic information (556), and the increasing use of machine learning of large datasets might help to improve the quality of these clocks (509, 531, 553, 557–559). Attempts at integrating physical fitness or other lifestyle-/behavior-related parameters in epigenetic clocks (560–562) however might be better served by measuring the real thing instead of a proxy of uncertain value. In fact, clinical “aging clocks”, based on anthropometric, (patho)physiological and molecular parameters have been proposed to predict healthy and unhealthy aging trajectories (563, 564). In any case, proven, physiological biomarkers of aging should be used to benchmark any new molecular biomarkers (565–568).

6 Physiological biomarkers of aging: ready for prime time!

As outlined above, physical activity remains one of the best interventions for human health and longevity. It thus is not surprising that the assessment of morphological, anthropometrical and functional parameters that describe the outcome of exercise training provides strong predictive power for health, morbidity and mortality. In fact, these physiological biomarkers of aging provide an assessment of functional aspects (569), relevant in everyday life, e.g. on fatigability, strength or gait speed, that affect daily tasks such as walking across a pedestrian crossing, moving up stairs, carrying groceries, having social interactions or being able to clean the apartment, thereby markedly impacting on quality of life and independence (570). Despite proven associations (507) and current indispensability as benchmarks in pre-clinical as well as endpoints in clinical trials (571), these parameters surprisingly often are underappreciated in contemporary discussions of biomarkers of aging. Thus, to increase the recognition of these measures, and to draw a direct comparison, the physiological biomarkers will be positioned in the proposed framework of aging biomarkers (Box 1, adapted from ref. 507) in this review. As outlined below, this will show that the physiological biomarkers of aging fulfill the requirements and challenges that have been put forward (552). Broadly, the physiological biomarkers of aging can be categorized in terms of cardiorespiratory fitness, muscle mass, muscle strength and power, leisure time activity, neuromuscular function and frailty. The most common parameters and tests will be described in more detail in the following sections. Of note, the deterioration of these tissues and organs, combined with neurodegeneration and a reduction in bone mass and mineral density, is universally observed, and thus could be considered true

"physiological hallmarks of aging", with a clear and causal relationship to the decline in functional capacity, morbidity and mortality (Figure 4).

6.1 $\dot{V}O_{2\,max}$/cardiorespiratory fitness

6.1.1 $\dot{V}O_{2max}$: principle and testing: At the moment, cardiorespiratory fitness is the most studied and best predictor of morbidity and all-cause as well as disease-related mortality (Figure 5A and B) (572–583). Cardiorespiratory fitness is assessed by measuring the maximal rate of oxygen consumption $\dot{V}O_{2max}$. This concept has been introduced by Archibald Hill and Hartley Lupton in 1923 (584), and developed ever since (585, 586). $\dot{V}O_{2max}$, sometimes also reported as $\dot{V}O_{2peak}$ (the highest recorded $\dot{V}O_2$ in tests failing to reach a $\dot{V}O_{2max}$ plateau, therefore potentially underestimating the true maximum (587, 588)), is a readout obtained in cardiopulmonary exercise tests that correlates with cardiorespiratory fitness and endurance capacity (589–593). Most often, $\dot{V}O_{2max}$, either reported as an absolute rate (mL/min) or normalized to body mass (mL/min/kg) (sometimes also normalized to lean body or skeletal muscle mass), is typically determined in graded maximal exercise tests by measuring ventilation and respiratory O_2 concentrations (reaching a plateau), often combined with determination of blood lactate concentrations (e.g. approaching or exceeding 10.0 mmol/L), heart rate (reaching a plateau), respiratory exchange ratio (≥1.1) and perceived exertion (e.g. 19-20 on the Borg scale from 6 to 20 or 9-10 on a Borg Category-Ratio 10 (CR10) scale from 1 to 10, even though variations between protocols for some of these thresholds exist (594–596). The results depend on the exercise modality: treadmills or cycle ergometers are commonly used, but $\dot{V}O_{2max}$ values can be acquired in any exercise setting that is amenable to breath-based oxygen analysis, e.g. rowing ergometers, all of which involve different sets of muscles. The $\dot{V}O_{2max}$ often differs between testing modalities, and prior task habituation: for example, runners might reach higher values on the treadmill, while cyclists or triathletes can excel on cycle ergometers (597). The choice of testing paradigm therefore depends on availability, practicality, intention for assessing task specificity, co-administration of other tests (for example electrocardiography might be easier on cycle ergometers due to minimal upper body movement) and other factors.

$\dot{V}O_{2max}$ integrates functional aspects of a number of organs and tissues that contribute to oxygen intake, distribution, extraction and usage (Figure 5C) (598). Intake is affected by pulmonary capacity and function, in part depending on respiratory muscle functional capacity, which can be improved by specific training even in older adults (599). Distribution combines cardiac output parameters, oxygen carrying capacity by red blood cells, blood volume and vascular properties. Extraction and usage, at least in the case of cardiopulmonary exercise tests, is mainly determined by the degree of tissue vascularization (hence the proximity of blood vessels and muscle cells), intramyofibrillar trapping of oxygen by myoglobin, and the rates of mitochondrial oxidative phosphorylation. The rate limiting step that determines $\dot{V}O_{2max}$ can be variable, and for example shift depending on the training state, from oxygen usage in muscle fibers in the untrained to oxygen provisioning by cardiac output and tissue vascularization in trained athletes.

6.1.2 $\dot{V}O_{2max}$: age dependence and health/mortality prediction: $\dot{V}O_{2max}$ decreases progressively with age, at a rate of about 7-10% per decade (corresponding to 4-4.6 mL/min/kg) (600–602), down to an "aerobic frailty threshold" of 17.5-18.0 mL/min/kg that is required for an independent lifestyle (574, 603, 604). At this point, individuals have to utilize almost their maximum aerobic capacity for tasks related to daily life and independence, associated with severe physical fatigability (605). In the worst case, this deterioration continues to fall below 10.5 mL/min/kg, when about 30% of oxygen is used to maintain basal metabolic rate, potentially leading to fatal outcomes (574, 603). Accordingly, the assessment of $\dot{V}O_{2max}$ constitutes a strong and independent predictor of morbidity and mortality in different populations, young and old, healthy and clinical (574, 576, 606). In fact, this strong link with mortality and various chronic conditions including heart failure, hypertension, stroke, chronic kidney disease, dementia and depression was consistently demonstrated in an overview of meta-analyses that included more than 20.9 million observations (576). More specifically, having a low cardiorespiratory fitness is associated with a 41-53% higher relative risk for all-cause mortality compared to those with a high cardiorespiratory fitness (607). Strikingly, even in unfavorable conditions, such as abnormal glycemic status (608) or obesity, being fit is a strong predictor for reduced all-cause and cardiovascular disease mortality (609–612). In fact, relatively fit obese men (top 80% of the age-specific cardiorespiratory fitness) have a 50% lower cardiovascular disease mortality risk compared to normal-weight unfit men (lowest 20% of the age-specific cardiorespiratory fitness) (610). Indeed, cardiorespiratory fitness can mitigate risks of obesity in a significant manner, beyond those of unfit, normal-weight individuals (613). Similarly, high cardiovascular fitness can overcome an unfavorable genetic predisposition for dementia (614). Furthermore, cardiovascular fitness is a strong inverse predictor of heart failure risk irrespective of BMI (615). Importantly, even though up to 50% of the variability in $\dot{V}O_{2max}$ in sedentary individuals is estimated to be of genetic origin (616) as well as other biological and methodological factors (617), trajectories can be strongly affected by exercise at young and old age (618–623), and even a moderate increase by 3.5 mL/min/kg (1 metabolic equivalent of task/MET), achievable after 2-3 months of training (603), reduces the risk of heart failure by 18% (572) and all-cause mortality by 11-17% (576, 607). Interestingly, despite exhibiting lower $\dot{V}O_{2max}$ values, older athletes can reach high performance levels due to the ability to perform work closer to the $\dot{V}O_{2max}$ compared to younger counterparts (624). Lifelong exercise habits provide most benefits to mitigate age-related declines in $\dot{V}O_{2max}$ (625), and can confer benefits in old age (626). However, even in the very old, cardiorespiratory fitness can be improved, as exemplified in the case study of a 101-years-old cyclist (627).

6.1.3 $\dot{V}O_{2max}$: Additional tests, benefits and alternative assessment methods: A cardiopulmonary exercise test can provide additional health-relevant parameters, and can easily be expanded (589–592, 628). For example, this test often includes a measurement of the rate of carbon dioxide production ($\dot{V}CO_2$). The respiratory exchange ratio (RER, $\dot{V}CO_2$ divided by $\dot{V}O_2$) indicates fuel utilization, from oxidation of fatty acids (RER approx. 0.7) to glucose (RER=1.0). Thereby, the metabolic preference and transition during a cardiopulmonary exercise test can be assessed, and the switch to anaerobic metabolism

observed when the RER exceeds 1, sometimes used as exhaustion endpoint criterion. The RER, heart rate, minute ventilation $\dot{V}E$ (composed of the tidal volume multiplied by the breathing frequency), or work rate can be set into relationship to $\dot{V}O_2$ and $\dot{V}CO2$, thereby providing insights into the relative efficiencies and potential deficiencies of the cardiopulmonary system, e.g. by calculating the ventilatory equivalents VEqO2 and $VEqVCO_2$ (corresponding to the ventilation required to take up or exhale a given amount of O_2 and CO_2, respectively, by dividing $\dot{V}E$ by $\dot{V}O_2$ or $\dot{V}CO_2$). Additional health-relevant parameters are obtained from simultaneous (and/or post-exercise) acquisitions of stress electrocardiograms (629, 630), blood pressure (631, 632), pulse oximetry or arterial blood gas measurements (633), cardiac magnetic resonance imaging (634), heart rate response and recovery (635–637), heart rate variability (638, 639), invasive cardiopulmonary hemodynamics with a pulmonary artery catheter in the internal jugular vein (640), or other parameters. Furthermore, timed blood sampling and determination of lactate levels help to pinpoint the lactate threshold, or, when combined with $\dot{V}CO_2$ measurement, the anaerobic threshold, even though this concept remains somewhat contentious (641, 642). Outside of clinical testing, $\dot{V}O_{2max}$ correlates with endurance exercise capacity, but itself is only one of the key parameters besides fractional utilization of $\dot{V}O_{2max}$ (related to the individual lactate threshold and critical power), exercise economy, and physiological resilience to determine performance (643–645). Optimally, all four are measured and optimized in athletic training. It is important to point out that many of the clinically used techniques, parameters and readouts have emerged from the study of elite athletes (646), who, even though few in numbers (647), represent the upper limit of human performance capabilities (296, 648). Of note, various protocols exist to estimate $\dot{V}O_{2max}$ in other settings, including submaximal efforts, from maximal and resting heart rates, or based on the Fick equation with cardiac output and the arteriovenous oxygen difference as parameters, e.g. in health-compromised individuals. Therefore, readouts for cardiorespiratory fitness can also be acquired without measuring actual $\dot{V}O_{2max}$ (649). For example, time on treadmill, peak speed, incline, work performed and other parameters have been used to assess cardiorespiratory fitness, showing good correlation with measured maximal oxygen uptake and with mortality risks (650–658). Other parameters such as sex, age, BMI, waist circumference, resting heart rate, physical activity levels, and smoking status can be used to approximate the state of cardiorespiratory fitness (659, 660). In fact, over 28 equations have been proposed, using overlapping and distinct metrics, all of which significantly correlate to measured cardiorespiratory fitness, albeit with differences in accuracy (661). Even though measured cardiorespiratory fitness provides better discriminative ability, estimated cardiorespiratory fitness is a valid indicator of health status and mortality risks (660, 662–664). For example, activity-induced oxygen uptake, expressed as MET (3.5 mL O_2/min/kg), can be calculated with the heart rate index (the ratio of maximal to resting heart rate during and before an activity, respectively) (METs = (6*heart rate index)-5) (582, 665).

6.2 Relative lean/muscle mass

6.2.1 Body mass index and the obesity paradox: Historically, even though controversial (666), an “obesity paradox” has been reported, indicating reduced mortality of patients with an elevated BMI (expressed in kg body mass /m^2 height) beyond the normal/

healthy range (667). Different explanations have been put forward for this observation, for example based on data indicating that when using measures of fat depot distribution, the "obesity paradox" disappears (668). Since such measures are independent of differences in muscle mass, they support the muscle mass hypothesis, suggesting that only those patients for whom the elevation in BMI is to a significant extent caused by higher muscle mass, experience the health benefits, at least in certain pathologies and populations (667, 669–672). The BMI thus is an imperfect marker for obesity (673). Indeed, the relative amount of lean or, better, actual skeletal muscle mass (often normalized to body mass) is a much better predictor of all-cause and disease-specific mortality (674–685). Muscle mass is of particular significance in aging (sarcopenia) and cancer (cachexia), with strong correlations to functional capacity, quality of life, morbidity and survival (686–694).

6.2.2 Relative lean/muscle mass: methods: In contrast to the BMI, which can easily be measured using a scale and a measuring tape, determination of the vastly more meaningful body composition requires specialized equipment, with variances in preciseness and accuracy (695–705). Moreover, these methods have different capabilities in determining compartments such as adipose-tissue free mass (ATFM, body mass – adipose tissue mass), fat-free mass (FFM, residual mass (organs such as liver, pancreas etc) + fat-free skeletal muscle mass + bone mass), lean soft tissue (LST, residual mass (organs such as liver, pancreas etc) + fat-free skeletal muscle mass) or actual skeletal muscle mass, which contributes about 45%-50% to fat-free mass (706). Sometimes, compartments are normalized to other anthropometric measures, e.g. in the fat-free mass index (FFMI) that is indexed to height (expressed in kg FFM / m^2). Commonly used methods to measure muscle mass or surrogates thereof include (707–711): Skin fold measurements with a measuring caliper, in which body composition is inferred from the thickness of subcutaneous fat in different body areas; circumference of various muscles such as mid-upper arm or calf; bioelectrical impedance analysis (BIA), recording the electrical resistance with multiple electrodes and in multi-frequency measurements in a body segment-separated manner; dual energy X-ray absorptiometry (DEXA), in which spectral imaging using two X-ray beams with different energy levels allows the acquisition of body composition data in total body and regional segments (including assessment of bone mass and mineral density); ultrasound, applied to multiple body regions similar to the skin fold calipers; quantitative magnetic resonance (QMR) or magnetic resonance imaging (MRI), in which magnetic fields are used to quantify, and in the case of MRI also visualize, fat and lean mass independent on hydration status; hydrostatic weighing or air displacement plethysmography, using object displacement of water and air, respectively, to calculate body density and subsequently composition; computed tomography (CT), in which multiple X-ray measurements are processed for a tomographic reconstruction of a body, sometimes combined with positron emission tomography (PET) to assess metabolic activity such as glucose metabolism. Finally, in deuterated creatine dilution, skeletal muscle mass is determined non-invasively since almost 98% of the creatine pool is found in muscle, co-localizing with sarcomeric structures, which are the functional components of muscle (712–714). Therefore, skeletal muscle mass measured by this method strongly correlates with strength, functional capacity and mortality risks (715, 716). As in all areas of medical diagnosis (717), the use of machine learning techniques and artificial intelligence might help to improve the predictive

strength of imaging-based techniques for body composition in the future (718). Moreover, improvements and/or the acquisition of additional parameters will further boost the use. For example, the phase angle (PA, angular transformation of the ratio of capacitance (Xc) to resistance (R) - arc tangent (Xc/R)*180°/**π**) measured at 50 Hz in BIA is an indicator of cell health and function, and correlates with disease risk and mortality (719–721). However, as with most of these methods, better standardization and more normative data for different instruments and populations will help to improve this measure (722–724).

6.2.2 Relative lean/muscle mass: adipose tissue content and distribution: Of note, costly bespoke determinations can sometimes be circumvented by leveraging other, already existing radiological images, e.g. to estimate temporalis muscle thickness in cranial imaging as a marker for muscle mass predictive of disability and mortality (725). As an added benefit of some of these methods, information on adipose tissue distribution (e.g. abdominal vs. subcutaneous), or even fat content of different organs (726) (including myosteatosis (727) or intermuscular adipose tissue (728)) is acquired, both of which are linked to pathological processes in cardio-metabolic diseases (729), all-cause and cause-specific mortality (730). For example, the determination of the adipose-free muscle volume and the percentage of intramuscular fat in the thigh muscle by MRI can be compared to reference values and provides predictive data on health (731), or, at least in certain populations, on brain volume (732). Adipose distribution however can also be estimated by the much cheaper and simpler waist-to-hip circumference ratio, with good correlation to morbidity and mortality risks (733), which can develop in different trajectories compared to the BMI (734). Other parameters that should improve on the use of BMI have been proposed, including the Weight-adjusted Waist circumference Index (WWI, calculated by dividing waist circumference by the square root of body mass) (735, 736), the Body Roundness Index (BRI, calculated as $364.2 - 365.5 \times \sqrt{(1 - [\text{waist circumference in centimeters} / 2\pi]^2 / [0.5 \times \text{height in centimeters}]^2)}$) (737), or height-normalized abdominal body composition (738). The combination of muscle strength reduction and fat mass gain, as observed in sarcopenic obesity, might constitute an additional burden on health and mortality (739, 740), for example for the risk of dementia (741). Regardless of the method used, it is undisputed that strong associations of body composition with aging and health exist (742, 743), e.g. in terms of risk for frailty in sarcopenic obese and pre-sarcopenic individuals (744), in health and pathologies, for example non-alcoholic fatty liver disease (NAFLD) patients (745, 746). Notably, the genetic contribution to muscle mass and function are estimated at 30%-50%, implying a majority of the variations to be modifiable by environmental factors (747). Nevertheless, despite the recent arrival of new anti-obesity drugs, the rising rates in overweight and obesity are observed world-wide, accompanied by the corresponding obesity-related pathologies, necessitating effective and aggressive measures targeting environmental and lifestyle factors (748).

6.3 Muscle strength and power

6.3.1 Muscle force trumps mass: In recent years, it has become clear that an exclusive focus on muscle mass is insufficient to describe sarcopenia (muscle wasting in the aging process) and other diseases (749). In fact, the term dynapenia (or powerpenia) has been proposed to describe the functional loss of skeletal muscle, which can be dissociated

from changes in body or muscle mass (750–753). In aging, the loss in power is greater than in strength, and both are disproportionally larger than the reduction of muscle mass (754–756). Chronologically, the decline in power, strength and mass is accordingly found in this order (756). It therefore is no surprise that the decrease in muscle quality, a measure of strength or functionality relative to muscle mass, strongly correlates with mortality and health in aging (757–759). As a consequence, therapies that only ameliorate muscle mass, but not functional aspects, will most likely be suboptimal (760–762). Indeed, muscle strength (maximal force, expressed in N, sometimes reported as torque expressed in Nm to describe force application for rotational movement of a joint) (763–771) and power (scalar product of the vectors of force and shortening/lengthening velocity of the muscle (772, 773), revealing force production over time or speed of force production, expressed in Watt) (774–776) have been closely associated in an inverse manner with all-cause mortality (678, 751, 777–781) not only in healthy individuals, but also patients such as those suffering from diabetes (782).

6.3.2 Methods to determine muscle strength and power: hand grip and more:

The determination of handgrip strength with corresponding dynamometers is one of the most common methods, facilitated by the ease of use, and the availability of ample normative data (Figure 6), for which values are often expressed in relation to body height and mass, handedness and other anthropometric measures, with strong correlation with future morbidity and mortality (783–792) as well as potentially a number of sociodemographic, anthropometric behavioral and psychological factors (793).

Intriguingly, handgrip strength has predictive power for processes beyond muscle status, e.g. extending to frailty (794), glycemic measures (795), hypertension (796), brain (791, 797) and cardiovascular health (798), bone mineral density in women (799), or self-assessed quality of life (800), and associates with a wide variety of anthropometric, morphological and functional factors (801), or the risk for falls (802). The values obtained with hand grip dynamometers can be approximated with simple tests such as polyethylene terephthalate (PET) bottle opening or newspaper tear-off in old populations, albeit in the absence of broad, normative datasets (803). However, the measurement of a single strength component might be insufficient to capture more complex or different tasks, for example those related to activities that involve both upper and lower body functions (804, 805). Therefore, specialized, mostly isokinetic dynamometric equipment is used to measure the strength or power of single joint movements (e.g. knee extension), or multi-joint and -muscle involvement such as acquired with mechanographical force/power plates in plyometric exercises. Furthermore, standard isotonic gym equipment can be leveraged to assess parameters such as the one-repetition maximum (1RM), maximum voluntary isometric contraction (MVIC), muscular endurance (isometric or velocity loss with increasing number of repetitions), dynamic strength index (bar velocity related to force production), reactive strength index (RSI, divide drop jump height by ground contact time) and others. In a frail population, sit-to-stand tests (for example timing of 5 repetitions of sit-to-stand-to-sit movements without the use of arms and hands, or number of sit-to-stand repetitions in a 30 s window) or similar interventions might already be sufficient to estimate strength of the trunk and lower extremities. These measurements can be combined with electromyography (EMG)

to obtain additional information on neuronal activation, action potential transmission, motor unit recruitment and fatigue (806, 807). Moreover, clinical relevance can be expanded by the utilization of tensiomyography (speed of muscle contraction under isometric conditions) and myotonometry (measurement of reaction to a short mechanical impulse), providing data on muscle composition, architecture and viscoelastic properties (e.g. muscle tone, stiffness and elasticity), respectively (808). Such approaches might be complemented and expanded with wearable super-resolution myographic sensors in the future (809). Of note, integrated approaches, for example assessment of muscle mass and strength, potentially combined with other parameters such as a nutritional score, might increase the predictive power, e.g. for cancer mortality (810).

6.4 Step count, leisure time physical activity and sedentary behavior

6.4.1 Occupational and leisure-time physical activity in the modern world:

The evolution of humankind as persistent hunters is not reflected in the engagement in physical activity in modern societies, with various detrimental consequences on health (264, 296). The amount of physical activity is profoundly different between professions, which can result in beneficial outcomes, e.g. the lower incidence of coronary heart disease in conductors, constantly climbing and descending stairs, compared to the sedentary drivers of double-decker buses in London (811–814). Overall, ~80% of jobs in the USA are estimated to be predominantly sedentary (815).

Discrepancies also exist for non-occupational leisure time activity and a big proportion of the general population do not meet the current WHO guidelines recommending at least 150-300 min of moderate aerobic activity and regular muscle-strengthening exercises (816–821). For example, only 22.8% out of 2’629’508 adults adhering to muscle-strengthening exercise guidelines (822), or less than 52%, 35% and 28% of the general USA population met endurance, resistance, and combined endurance and resistance training recommendations, respectively, in the year 2018 (823). Reaching the activity levels defined by these guidelines confers substantial health benefits and lowers mortality risks (824–827), e.g. up to 31% on all-cause mortality in elderly individuals (828), independent of cardiorespiratory fitness (829, 830). Importantly, even relatively small shifts towards physical activity behavior can elicit beneficial effects (831), which can extend to non-muscle tissues and functions, e.g. cognition in acutely hospitalized older adults (832) or cancer (833). In fact, all aspects of resilience (834) and intrinsic capacity (835, 836), comprising locomotor (837), cognitive (838), psychological, sensory, and vitality capacity (839), are positively affected by physical activity (840). However, while positive outcomes are already seen at lower doses, additional value can be achieved with higher intensity/volume/frequency (841), albeit with diminishing returns (842–844). Inversely, a negative association of leisure-time, non-occupational physical activity to morbidity as well as mortality has been demonstrated (845–857). For example, a strong correlation between leisure-time physical activity and the risk for a number of cancers has been found in large cohorts (858–861), with a potential involvement of the exercise-remodeled immune system in this context (862). Importantly, the impact of physical activity is seen regardless of the time-of-day of performance (863), indicating that activity can mitigate potential adverse effects of circadian timing (864). Similarly, physical activity can overcome other markers of low functionality,

e.g. ameliorating mortality risks in individuals with low handgrip strength, or preventing cardiovascular disease incident across all handgrip strength levels (865).

Of note, sedentary behavior (as in time sitting), which is on the rise in many societies, should be independently assessed from other forms of inactivity, due to the marked negative effects of time sitting on health and disease risk that can be distinct from those arising from minimal physical activity (866–869). Accordingly, sedentary behavior can increase mortality risks, e.g. those for all-cause and cardiovascular diseases (870–874), which at least in part can be blunted by physical activity, in particular when performed at high intensity (875–881).

6.4.2 Methods to measure leisure-time physical activity: from step count to more sophisticated wearables:

Leisure-time physical activity and sedentary behavior data are often collected by self-reporting, with the corresponding limitations on data accuracy and standardization. More recently, advances in the use of wearable devices have helped to acquire such behavioral data in a more objective and quantifiable manner, and have confirmed the positive effect of physical activity on mortality risks (866, 881–885). Daily step count is the simplest parameter for which a good association with morbidity and mortality has been demonstrated (886–895), e.g. on incident risk of dementia (896) or of depression (897). More sophisticated accelerometers however allow a detailed and fine-grained acquisition of different types of activity (or sedentary behavior) in relationship to health and mortality (866, 898–900). For example, the personalized activity intelligence score assesses the cumulative fluctuations of heart rate of the most recent 7 days as a measure of relative intensity and energy expenditure of weekly physical activity, shown correlate with mortality risks (901, 902). Such refined manners of acquisition of behaviors are of particular importance to quantify time sitting (903). At the moment, wearables-based assessment of physical activity is widely deployed to capture endurance training-type of activities, using actigraphy, accelerometry, GPS tracking and heart rate measurements besides other sensors, even though issues with heterogeneity, accuracy and standardization still exist (904). However, strong health and mortality benefits also arise from resistance training (905–921), even at lower intensities/volumes (922), for which corresponding wearables that objectively and accurately quantify the work performed and actual (non-resting) exercise time are still under development (923). In fact, muscle strength and cardiovascular fitness are independent predictors of mortality, with best outcomes when performed in combination (924–927).

6.5 Gait speed/frailty parameters

6.5.1 Neurodegeneration and sarcopenia are the major drivers of loss-of-independence, morbidity and mortality:

In the absence of any debilitating disease, neurodegeneration (928, 929) and sarcopenia (257, 930–933) are two of the main factors that precipitate loss-of-independence, decreased quality of life, morbidity and mortality in aging (934). The effects caused by these two processes are exacerbated by compromised cardiovascular function (935–938) and loss of bone mass and mineral density (939). Osteopenia/osteoporosis is a prominent issue in postmenopausal women (940), but should not be overlooked in men (941). Of note, bone mineral density correlates with lean

body mass and muscle strength (747), and can be improved by exercise, in particular in combination with the intake of dairy products (942). Similarly, neurodegeneration and sarcopenia (and inversely physical activity) are mutually linked (943, 944), e.g. in the reduction in vestibular and proprioceptive abilities, leading to altered gait, and decreased senses of balance and motor coordination. With the progressive loss of the functional capacity caused by these events, a vicious cycle is initiated and fueled (945), in which insecurities in gait and balance reduce the drive for physical activity (and social interactions), which, in turn, accelerates neuronal and muscle degeneration (Figure 7). In the worst case, falls occur (946), with the risk of fractures, immobilization and hospitalization, further promoting this cycle through a "catabolic crisis" (947–950), ultimately culminating in a broad hospital-associated deconditioning (951) and hospital-acquired complications (952).

6.5.2 Gait speed and other tests for frailty and neuromuscular functionality:

Based on the deterioration of the neuromuscular system, it is of little surprise that functional capacity parameters depending on neuromuscular functionality are predictors of an independent lifestyle, morbidity and mortality, as seen in the example of gait speed (283, 953–961). Gait speed, representing voluntary locomotion, can easily be assessed with a stop watch, pedometers, or accelerometers (962). Additional information can be derived from a more sophisticated analysis of gait, in which for example speed, cadence, stride length, step width and other parameters describing footprint and gait dynamics are acquired, and collectively allow a more comprehensive assessment of aging-related alterations in gait (963, 964). Such data can be obtained with different methods, including pressure measurements, motion capture or wearable sensors (965). Gait speed trials often are combined with other tests of frailty, for example cognitive and sensory function, psychological and social aspects, balance and motor coordination, mobility and flexibility, muscle strength and endurance, muscle and body mass loss, fatigability/exhaustion, and integrated tasks of gross and fine motor skills (966–969). Such compound frailty assessments are predictive of mortality, as well as incident disability, falls, hospitalization and health care-dependence (970–973), even in long-term trajectories (974). For example, strength, balance and gait speed can be used to predict the risk of incident dementia (967, 975). However, even simple tests such as sit-to-stand time (976), sit and rise from the floor (977), or 10-second one-legged stance performance (978) can be used to estimate frailty, functional capacity, mortality and survival. Stair descendence phenotypes can reveal deficits in balance, coordination, muscular agility and strength, and thereby help to predict the risk of incident falls (979). A myriad of test batteries and protocols have been established, aiming for a test coverage of a broad and representative range of frailty, impinging on vulnerability to adverse events, reduced resilience towards stressors, and loss of functional capacity (956, 970, 971, 980), all of which clearly associate with the process of (advanced) aging (981, 982).

7 Classification of biomarkers of aging

The aforementioned physiological parameters belong to a group of biomarkers of aging, some of which, e.g. the 6 min walk test, have already been accepted by the FDA as surrogate in clinical trials (571). In terms of application, physiological biomarkers fulfill the

criteria of multiple categories (507). 1.) Predictive biomarkers: the physiological biomarkers have a strong and independent predictive power for all-cause mortality, and various disease-specific risks. 2.) Prognostic biomarkers: for most of the functional/physiological biomarkers, predictive power is not only limited to healthy individuals, but extends to patients in very diverse settings, for example as a measure for fitness for and outcome of surgery (983–988), clinical outcomes in heart failure (989), coronary bypass grafting (990), intensive care unit hospitalization (991, 992), frailty (971, 993–996), cancer mortality (997, 998), sarcopenia (999), biliary sepsis (1000), liver transplantation (1001), hospitalization secondary to COVID-19 or other infectious diseases (1002), potentially linked to reduced respiratory function (1003), or cognitive impairment and dementia (1004). Notably, the corresponding interventions, in particular exercise training, can be used in a prognostic manner in prehabilitation to mitigate loss of muscle mass and function, increase resilience, reduce adverse outcomes and shorten the duration of hospital stays (1005). 3.) Response biomarkers: the physiological biomarkers not only predict morbidity and mortality, but also react to interventions that improve prospects, first and foremost physical activity, the most robust intervention known to date to promote healthy aging. 4.) Surrogate endpoints markers: due to the extraordinary correlation between physiological biomarkers, biological age, morbidity and mortality, interventions aimed at the aging process should be benchmarked against these measures, whenever possible in a comprehensive manner. For example, weight loss caused by caloric restriction is not expected to change absolute $\dot{V}O_{2max}$, even though oxygen consumption normalized to body mass can increase, or could lead to a reduction in lean body mass if performed in the absence of concomitant resistance training (1006, 1007). However, leisure-time activity, number of steps as well as gait speed and other frailty markers could improve, at least based on extrapolation of data from mice. 5.) Discovery biomarkers: physiological biomarkers describe the integrated function of various tissues, organs and cell types, and thus reflect the multifactorial processes and complexity of aging. However, the underlying mechanistic principles are still poorly understood, and therefore harbor an enormous potential to reveal novel insights into the benefits of interventions that improve these biomarkers, as well as the patho-etiology of aging-linked processes.

7.1 Assessment of biomarkers of aging

Four main criteria for ideal biomarkers of aging have been put forward (507). The physiological biomarkers, in particular in combination, fulfill all of these. 1.) Measurement: the assessment of all of the physiological biomarkers is minimally invasive, and, maybe with the exception of self-reporting-based values, highly reliable. Therefore, longitudinal assessment, life-long, from young to very old age, is feasible. 2.) Aging relevance: the physiological biomarkers not only predict morbidity and mortality, but also provide a snapshot on functional capacity, resilience and (organ) health. 3.) Predictive power for functional aspects of aging: this is clearly provided by the physiological biomarkers, extending to practical and tangible aspects in daily life, e.g. impaired gait speed resulting in the inability to cross roads (1008). 4.) Responsiveness to longevity interventions: all of the physiological biomarkers are pliable, thus, responsive to interventions, in particular those with most benefits on the aging process (1009).

7.1.1 Feasibility and validity: The determination of physiological biomarkers, including $\dot{V}O_{2max}$, muscle mass and strength/power, gait speed, locomotor activity and frailty are minimally invasive, and non-lethal in model organisms, at least in higher vertebrates. A longitudinal assessment therefore is possible, even desirable to monitor trajectories over time, facilitated by the short time and ease of acquisition. Importantly, these measurements are non-age-accelerating – in fact, the tests, at least in some cases like $\dot{V}O_{2max}$, muscle strength/power, or gait speed represent the intervention, and therefore contribute to the beneficial effects. Then, physiological biomarkers are age-sensitive, with high correlation with chronological age. However, in contrast to other molecular biomarkers for which accuracy for chronological age seems to come at the expense of predictive power for mortality and age-associated health outcomes, physiological biomarkers have been demonstrated repeatedly to provide very accurate prediction of morbidity and mortality, and possibly “biological age” (Figure 8).

Importantly, in contrast to most contemporary molecular biomarkers, extensive epidemiological, prospective, longitudinal and cross-sectional data in humans exist for the physiological biomarkers in that regard. Thus, age-sensitive criteria are fulfilled: good prediction of all-cause mortality, as well as correlation with multiple age-sensitive features, i.e. age-associated morbidities, by providing information about functional aspects of multiple systems, integrating different signals, and incorporating heterogeneous aspects. Two types of information are provided: integrity and resilience of tissue/organ function, as well as, in the case of longitudinal assessment, rates of progression of deterioration (or mitigation/reversion by interventions).

7.1.2 Mechanistic criteria and biologic plausibility: In the absence of confounding age-associated diseases, inevitable neurodegeneration, sarcopenia, and functional decline in the cardiovascular system are the main drivers for elderly individuals to lose independence, being admitted to nursing homes, and experience increased morbidity and mortality (1010). Collectively, these processes promote an inactive lifestyle due to increased perception of effort, insecurities (e.g. related to a decline in balance and motor coordination), leading to a vicious, self-reinforcing cycle. In the worst case, elderly individuals fall, and the ensuing fracture, facilitated by osteopenia/osteoporosis (in osteosarcopenia) (1011), potentially exacerbated by osteoarthritis (in musculoskeletal failure) (1012), leads to immobilization and hospitalization. Inversely, an active lifestyle, in particular when enriched by endurance, resistance, balance/agility and flexibility training (1013), is the best, indeed so far only intervention to mitigate sarcopenia and neurodegeneration (1014), and one of the best to counteract osteopenia/osteoporosis and boost cardiovascular function. In fact, endurance, strength and flexibility training have all been shown to improve mortality risks (1015, 1016). Fall risks are reduced by strength and balance training affecting posture, gait and coordination, resistance training improving sarcopenia and join mobility, and cognitive exercises boosting spatial awareness and attention (1017). Thus, a clear anti-aging effect has been demonstrated, impinging on various deleterious processes that affect health- and lifespan.

The aforementioned physiological biomarkers exhibit a well-described deterioration with "biological age", e.g. in terms of muscle mass and strength, cardiorespiratory function, gait speed or frailty. While the latter are primarily affected in old age, the former exhibit an association starting at younger ages. Thus, even though the pathways and molecular underpinnings of, and the potential health-benefits elicited by interventions aimed at these biomarkers are still only poorly understood, a strong biologic plausibility exists that links functional resilience of the cardiorespiratory and neuromuscular systems to aging, morbidity and mortality, and most likely impinge on fundamental aspects of aging. Of note, the effects of the interventions that are directly related to these biomarkers transcend health and function of the primary target tissues. Thus, exercise-based interventions not only improve muscle and cardiovascular function, but affect almost every organ and system in the human body in a clinically relevant manner (297, 303, 1018, 1019). For example, muscle mass and strength, as well as the amount of physical activity are negatively associated with the relative risk for dementia and a decline in cognitive function, brain structure, neurodegeneration and mental health (1004, 1020–1031), even when performed in an irregular manner, e.g. in "weekend warriors" (943, 1027, 1032–1034). Such activity patterns, concentrated at one or two days per week, also confer health benefits in other domains, for example cardiovascular disease incident rates (1035). More regular exercise-based interventions obviously also mitigate these risks (1036), potentially even changing life-long trajectories if initiated early in life (380, 1004, 1037–1039). Such youth-specific programs could affect life history and thereby influence health aging (1040, 1041).

7.1.3 Generalizability: Most of the proposed physiological biomarkers can be assessed in model organisms, and at least some show a remarkable similarity to humans, e.g. pliability of $\dot{V}O_{2max}$ (1042), association of $\dot{V}O_{2max}$ with longevity (1043), or deterioration of balance and gait in mice, amenable to amelioration by exercise (1044), if certain biological and methodological issues are considered (97, 1045). Thus, these biomarkers can be studied mechanistically in multiple species, with a high translatable potential (1046). In humans, importantly, these biomarkers have been validated in different clinical populations and demographics (573, 792, 889, 1047), even across different age groups (573, 774, 1048). For example, cardiorespiratory fitness in youth predicts age-associated diseases at old age, e.g. for site-specific cancer (1049). Similarly, mid-life grip strength correlates with functional capacity and resilience at old age (1048), or youth sport participation with sarcopenia (1050). Furthermore, these parameters, and the corresponding interventions, are equally valid from the youngest (1051) to the oldest of the old (767, 954, 955, 1052–1062), as exemplified by a case study of a 71-years-old world champion powerlifter who started resistance exercise at the age of 63 years (1063), or a late bloomer octogenarian triathlete (1064). Of note, benefits are found even in suboptimal conditions, e.g. obesity (609, 1065), Alzheimer's disease (1066), schizophrenia (1067), poor sleep (352, 1068, 1069), hospitalization (1070), rheumatoid arthritis (1071), hypertension (1072–1074), pulmonary hypertension (1075, 1076), heart failure (1077) and cardiac rehabilitation (1078), chronic obstructive pulmonary disorder (COPD) (1079–1081), diabetes (1082), chronic kidney disease (1083, 1084), depression (1085, 1086), or even multimorbidity (1087). At the moment, very few pathological context contraindicate the use of physical activity, for example as hotly debated in myalgic encephalomyelitis/chronic fatigue syndrome (ME/

CFS), in which patients can experience a post-exertional malaise lasting for several days (1088). Nevertheless, physical activity levels are directly correlated with all-cause mortality even in individuals with other risk factors, such as cigarette smoking or early parental death (1089, 1090). Inversely, physiological biomarkers can be uncoupled from the genetic background, and accordingly are pliable even between monozygotic twins (1091–1094). Moreover, consensus is emerging that absolute non-responders to physical activity do not exist, inasmuch such individuals might respond to different training paradigms, intensities or volume, or might have been misclassified as non-responders due to measurement and other technical errors (296, 1095–1099). This extreme clinical generalizability is different from many of the proposed pre-clinical interventions aimed at life- and/or healthspan extension, many of which only work in specific mouse strains (e.g. caloric restriction (212)), sex (e.g. the majority of pharmacological approaches (129)), or experimental conditions (e.g. pharmacological approaches (38, 476) or caloric restriction (83, 208–210, 219)).

At a glance, some of the existing data on physiological biomarkers seem counterintuitive and suffering from similar drawbacks: for example, even though women have markedly lower $\dot{V}O_{2max}$ (Figure 5B) or grip strength (Figure 6) than men, the former outlive the latter in most societies in terms of average and maximal life expectancy (1100). Surprisingly, opposite to this improved survival, frailty is more common in women than men, suggesting a sex-based frailty-mortality (or health-survival) paradox (1101–1106). Biological differences certainly contribute to these observations, e.g. in terms of immune system function or the prevalence of life-threatening vs. non-life-threatening chronic conditions (1107). Similarly, considerable sex-based differences in the exercise response and performance exist (1108). However, psychosocial, societal, socioeconomic (1109) and educational factors should not be neglected, for example sex differences in the number of doctor visits, inclusion in clinical trials, risk aversion, or engagement in healthy nutritional and other lifestyle behaviors. Indeed, at least in some countries, the survival gap between women and men is narrowing (1110), potentially driven by behavioral changes, socioeconomic factors and education (1111). Curiously, women also derive greater benefits from equivalent doses of leisure-time physical activity than men, at least in terms of reduction of mortality (1112). Even though this interesting phenomenon still is only rudimentarily understood at the moment, it is important to note that physiological biomarkers predict mortality not only in sex-separated, but also in mixed groups. In the future, this predictive power might be further elevated by leveraging group-stratified data or individualized trajectories, making use of a combination of physiological biomarkers that integrate aspects of health, resilience and deterioration representative of different organs and systems. At the same time, a more personalized approach, based on sex amongst other factors, in determining functional aspects, health and well-being, coupled to the design of early and late preventative as well as therapeutic measures, seems necessary.

7.1.4 Response criteria: The physiological biomarkers of aging reflect accelerated and decelerated aging inasmuch they accurately predict morbidity and mortality. More importantly, the interventions aimed at these biomarkers, physical activity and exercise, are powerful geroprotectors (37, 38, 264, 925, 1018, 1113).

7.1.5 Cost considerations: Most molecular biomarkers and clocks rely on invasive sample acquisition, specialized equipment, prohibitive costs, and extensive data analysis, precluding population-wide application, at least at the moment. In contrast, the measurement of most physiological biomarkers is easy and relatively cheap, e.g. to measure step count, grip strength, sit-to-stand tasks or gait speed. For others, most expense will arise from the initial investments for the acquisition of the corresponding instruments (e.g. gas analyzers for the determination of $\dot{V}O_{2max}$, and dual energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), magnetic resonance imaging (MRI) or computed tomography (CT) instruments for the determination of (segmental) body composition, lean and muscle mass, respectively). Importantly, these instruments can be re-used, even re-purposed for additional applications, and require minimal continuing investment. Indeed, large-scale, longitudinal imaging programs with MRI, DEXA and carotid ultrasound have been successfully initiated with 30’000-100’000 of participants (1114, 1115). The notion of cardiorespiratory fitness tests being unduly demanding in resources and costs pales in light of the tremendous significance on predicting health and mortality risks, and strongly favors a broad and routine implementation of such tests in clinical practice (1116–1118). Thus, in general, physiological biomarkers can be cost-effectively collected in large cohorts and longitudinal studies. Moreover, some parameters can even be determined with self-monitoring, e.g. daily steps, gait speed, or sit-to-stand time.

7.1.6 Invasiveness and safety: In general, the physiological biomarkers can be measured in a low-risk, non-invasive manner. The determination of cardiorespiratory fitness via $\dot{V}O_{2max}$ is the only biomarkers that necessitates higher intensities and could thus be more problematic in some cohorts. Standardized guidelines for the determination of cardiorespiratory fitness have been established to implement testing in the clinical setting (1119–1123). Adequate safety measures should be considered, e.g. pre-participation health screening, and the concomitant acquisition of electrocardiographic data and/or blood pressure (1124–1129). Such measurements provide additional clinical insights into cardiovascular health and potentially masked hypertension. Notably, $\dot{V}O_{2max}$ can also be estimated in submaximal tests (1125, 1130).

Cautionary findings have also been reported for exercise-based interventions, in particular at very high intensities (581, 582, 1131). For example, a U-shaped association between exercise intensity and the occurrence of atrial fibrillation has been reported (1132, 1133), however diametrically opposed to the clear negative correlation of the risk for atrial fibrillation with cardiorespiratory fitness levels (1134, 1135). A potential “exercise toxicity” could also be inferred from reversed J-type (or U-shaped) mortality curves in other studies, with an increase of the relative risks at very high intensities (1136–1138). Of note, the confidence intervals for these specific groups are large, due to the low number of participants training at such intensities, and the relative risk still is markedly below that of sedentary individuals (1136). Besides atrial fibrillation, excessive endurance training has also been linked to a higher occurrence of arterial plaques and myocardial fibrosis (1139), even though the association with intensity (1140) or volume (1141) seems complicated (1142), and associations are not seen consistently across studies (1143). For example, a reduction in plaques was seen in an exclusive female Master endurance athlete cohort

(1144). At the moment, it is not clear whether these changes indeed are pathological, if they are induced by other factors and risk behaviors (e.g. former smoking habits), or represent non-conventional pathophysiology (e.g. calcified vs. non-calcified plaques, and/or stabilization of plaques). Indeed, follow-up studies of endurance athletes with increased pathophysiological symptoms revealed no increase in all-cause or cardiovascular mortality (1139), regardless of coronary artery calcification load (1145) or elevated genetic risk for cardiovascular diseases (1146).

In contrast to these cautionary findings, no upper threshold for the mortality benefit of cardiorespiratory fitness was found up to very high levels (573, 600, 1147, 1148). In fact, structural analysis revealed no cardiac changes beyond the normal range, even in individuals with very high engagement in physical activity (1149). Indeed, many studies report “L”-type mortality curves, with no added benefit, but also no drawbacks of very high intensity exercise (1065, 1150). Thus, at some point, increased training load might have a very small additional impact on health parameters (1151, 1152), but, based on most available data, should also not confer pathological outcomes on the cohort level (926, 1153, 1154), even though individuals with unfavorable genetic predisposition and/or morphological, anatomical or functional abnormalities might be at higher risk (1155). As a case in point, even athletes with enormous training loads, e.g. participants of Olympic Games, the Tour de France, the first sub-4 minutes per mile male runners or other former athletes, have better morbidity and mortality scores compared to the general population, or even their non-competing siblings (296, 1156–1170). This is irrespective of country of origin, medal or type of sport (1171), and to a large extent driven by improved cardiovascular and cancer mortality (1157, 1172, 1173). In fact, even epigenetic aging seems decelerated in Olympic champions compared to non-champions, with hypo-methylation of genes involves in synaptic health, glycosylation, metal ion transfer and force generation, as well as hyper-methylation of genes associated with cancer promotion (1174). Obviously, none of these effects can be completely dissociated from a selection bias based on other health beneficial habits that could distinguish this group from their non-elite athlete peers (1175, 1176). However, improved survival is also found in non-elite athletes, e.g. in a study of 546’876 participants of Dutch running, cycling and walking events that has revealed that even in the short term (7 days), no increase in mortality odds were observed, while a 30% lower risk of death ensued in a 3.3 year follow-up (1177). Benefits most likely persist and could confer life-long health advantages, e.g. as reported in the case study of a 77-year-old former world-record-holding marathoner (1178). Importantly, low incidence rates of cardiac arrest were also reported during long-distance events including half-marathon (0.27 per 100’000 participants), marathon (1.01 per 100’000) (1179) or triathlon (1.74 per 100’000) (1180). Indeed, the estimated rates of sudden cardiac death in athletes that range from 1:40’000 to 1:300’000 are much lower than those observed in the general population at 1:2’000 (97, 1181).

In summary, in the absence of adverse pathologies, exercise is an extremely safe intervention, with proven benefits, and thus should be broadly recommended (97), even in old (1182), frail or otherwise pathological cohorts when certain measures are taken, for example people with heart failure (581, 582, 1183, 1184). Thus, appropriate pre-participation screening, design and monitoring of training programs as well as clinical

follow-up of vulnerable populations, including the aforementioned potential cardiovascular events associated with high-intensity/volume endurance exercise in veteran athletes, should help to prevent and mitigate any adverse outcomes (581, 582, 1185–1192). Thus, for most people, the risks and potential adverse effects of physical activity are dwarfed by the benefits (1188). Importantly, such benefits can even arise from small efforts (1193–1198) such as walking (1199–1202) or non-exercise-related activities in daily life (1203), and can be long-lasting when following appropriate protocols, e.g. up to 4 years in volunteers of retirement age undergoing resistance training (1204). The overall accumulation of time of physical activity seems more important than individual bout lengths (1205–1207), at least when performed at moderate to vigorous intensity (1208). Notably however, additional effects can be achieved by higher engagement, e.g. in structured high-intensity interval training (HIIT) compared to moderate intensity continuous training (MICT), or unstructured activity that meet the national guidelines (1209).

7.2 Validation of biomarkers of aging

7.2.1 Analytical validation: Most physiological biomarkers are quantifiable and easy to measure using well-established methods for data acquisition and interpretation, and their assessment is accurate, reliable, repeatable and reproducible, e.g. $\dot{V}O_{2max}$, muscle mass, strength/power or step count. They circumvent issues of many molecular biomarkers in terms of signal-to-noise in the differentiation of positive and negative results. Similarly, drawbacks in invasive sample acquisition, preparation, storage, and assay do not exist. However, some of the physiological biomarkers can rely on self-reporting and questionnaires, for example the amount of leisure-time activity, or individual assessment of fatigue and well-being in frailty scores. Importantly, with the increasing use of wearable sensors, these drawbacks might be overcome in the future, providing more quantitative, accurate and reproducible data on these parameters (296, 1210, 1211). For example, physical activity can be precisely measured with accelerometers, and correlation with health benefits has been demonstrated (1203, 1212–1214). Machine learning-based methods can help in the interpretation, and activity- or risk-recognition can be based on the wearables data (1215). In fact, the use of wearables extends to the improvement of adherence and compliance to physical activity interventions, with clear, long-term clinical benefits (1212, 1216). Bluetooth low energy sensors, or similar techniques, could extend the usability to the tracking of indoor location and even social interactions (1217). Obviously, issues of validity, reliability, accuracy, reproducibility, standardization, transparency in used algorithms, data privacy, usage and ownership will have to be resolved before deployment of such instruments (1218). If successful, such applications would further increase the objective quantitation of physiological biomarkers (1219–1221).

7.2.2 Clinical validation: In contrast to most molecular biomarkers, physiological biomarkers have an extended history of clinical validation regarding morbidity and mortality as predictive, prognostic and response biomarkers in various cohorts and populations. Moreover, at least some of these parameters help in clinical decision making in different patient populations, e.g. in the prediction of postoperative outcomes (983, 997, 1222). In fact, clinical exercise testing, in particular cardiorespiratory fitness measurements, have been promoted as key tests to stratify patient risk profiles, and encourage healthy lifestyle choices

(1121). Moreover, the higher the adoption of standardized tests, e.g. for cardiopulmonary exercise testing (1223), the better normative reference values for different ethnicities, sexes, age groups, healthy vs. clinical populations, and other demographic parameters will be obtained (1224–1232). To achieve such ambitious goals, national and global registries and multicenter databases for cardiorespiratory fitness values with sufficient representation of various populations, from pediatric to geriatric, have been proposed, including normative as well as criterion-based standards (1233, 1234). Similar datasets should be acquired for the other physiological biomarkers of health and aging. A number of the proposed physiological biomarkers have already been used in longitudinal aging studies such as the English Longitudinal Study of Ageing (ELSA), Health and Retirement Study (HRS) or Longitudinal Aging Study Amsterdam (LASA). For example, reduced function of lower extremities assessed by gait speed and balance is associated with a two to three times higher risk of incident dementia over 15 years (975). Furthermore, an improvement in one score in the Short Physical Performance Battery (SPPB), evaluating gait speed, balance and repeated sit-to-stand, is associated with 8% lower odds of falling over a 14-year period together with a lower risk for other mobility impairments (1235). Similarly, one score increase in the physical performance test (including a walking, sit-to-stand and balance test) or the gain in one kg handgrip strength reduces the 6-years fracture risk in men by ~10% and ~5%, respectively (1236).

7.2.3 Translation of biomarkers: For many molecular biomarkers, translation to a clinical setting is hampered by several challenges, of which six key barriers have recently proposed (135). Here, the current position of the physiological biomarkers is discussed in this framework. *1. Data sharing for development and validation*. Open and free access to publication and data is a problem that is not unique to the field of biomarkers of aging, but extends to all of scientific research. It thus is as imperative for the physiological as it is for the molecular biomarkers of aging that the FAIR (findable, accessible, interoperable and reusable) principles are followed. For some biomarkers, e.g. cardiorespiratory fitness, such attempts currently are ongoing (1119). *2. Relative importance of criteria*. Even though evaluation criteria for biomarkers of aging have been proposed (507), the relative importance of these is unclear, and arguments for and against can be formulated. For example, as first of the eight criteria discussed (135), the correlation of a biomarker with chronological age is important, but, if to rigid, might not be modifiable by geroprotectors or other factors that affect age trajectories. Of note, physiological biomarkers exhibit both, change with chronological age as well as pliability. Second, strong predictive power of all-cause mortality exists, while, at the same time, specific risks for sub- and various clinical populations have been found. Third, some of the tests, e.g. gait speed and other frailty assessments, predict functional capacity primarily in older individuals. Others however, e.g. $\dot{V}O_{2max}$, are also applicable and valid in younger subpopulations. Fourth, the risk for many age-related diseases can be assessed from physiological biomarkers, and in many cases, direct causality proposed, for example linking suboptimal cardiorespiratory fitness to cardiovascular pathologies. Fifth, the physiological biomarkers reflect causal aspects of aging, represented by the universal decline in muscle, neuronal and bone tissue mass and function. Sixth, the response to factors that accelerate aging, or, better, increase the risk of morbidities and mortality, is given, at least for those with a clear effect such as a

sedentary lifestyle (306). Seventh, inversely, the proven geroprotectors, e.g. physical activity, have likewise a positive effect on physiological biomarkers. Finally, the physiological biomarkers have been tested and validated in large and diverse populations. *3. Age range for application*. With the exception of frailty markers mainly relevant in geriatric populations, physiological biomarkers can be assessed and longitudinally monitored starting at young age, and help to reveal healthy or unhealthy trajectories that are central for the aging process. Importantly, the determination of these factors is safe and non-invasive. *4. Minimal criteria for clinical use and implementation*. As the physiological biomarkers are already used in clinical practice, such criteria have been met. *5. Positioning of biomarkers of aging in the current disease-specific healthcare setting*. Physiological biomarkers are being used for patient stratification, treatment monitoring, disease prevention or targeted interventions, thus providing clear actionable insights. *6. Connecting biomarkers of aging with actionable insights in healthcare and preventative settings*. Physiological biomarkers are excellent measures for individual health monitoring. However, only some are easily implementable on an individual level that does not require access to specialized equipment and facilities. A subset such as step counters and other wearables can be, and are, already widely used, with meaningful outcomes for health and mortality.

In summary, the physiological biomarkers of aging have already overcome most of the challenges that are faced by new molecular biomarkers for clinical translation. Nevertheless, further improvements are still desirable, including open science principles, or accessible and affordable infrastructure for the longitudinal monitoring of large populations.

8 Challenges and perspectives

The validity of physiological biomarkers to predict morbidity and mortality in the human aging process is well-established. Similarly, the effects of exercise as geroprotector, and as highly efficacious intervention for the prevention and treatment of many pathologies, most of which are chronic and age-associated in nature, are undisputed, as is the acceptance of a sedentary lifestyle as strong and independent risk factor for many different diseases (264, 303, 306). It therefore is mysterious why this knowledge is not leveraged to a greater extent in predicting health, the aging process, morbidity and mortality in pre-clinical and human studies. As outlined, the determination of these parameters is non-invasive, non-age accelerating, easy, precise and reproducible, in particular with improvements based on wearables data. Moreover, even a wide-spread screening of large cohorts is relatively cost-efficient once initial investments in instruments have been done.

8.1 A potential action plan for health monitoring in from young to old

A comprehensive, longitudinal assessment of health and aging trajectories would optimally be done in a systematic, multicomponent manner (Figure 9A).

Currently, such biomarker assessments have to be stratified by the strength of clinical evidence. Thus, first and foremost, the physiological biomarkers, as discussed in Section 6, would provide the basis of screening at the current time. The validity might however be further amplified by expanding such screenings with other indices of health and co-morbidities (1187, 1188), including blood biomarkers for disease risk (1189–1191) and

composite markers for different domains, e.g. endocrine and immune function or cognitive and physical functional capacity (1192). An integration of the physiological biomarkers with the determination of other attributes of functional capacity (1237) (cognition, psychology, hearing, vision and vitality/nutrition), e.g. used in the WHO Integrated Care for Older People (ICOPE) program to assess intrinsic functional capacity (1238–1240), reproduced in the INSPIRE animal cohort, could further boost the predictive power and reflect the multidimensional aspects of aging, functional capacity and resilience (980). Similarly, additional tests of (micro)vascular health, e.g. assessed non-invasively in the retina, could complement $\dot{V}O_{2max}$ data on cardiovascular health and function (1241), maybe combined with other retinal features (1242, 1243). Moreover, wearable-based acquisition of sleep-related parameters (342, 1244), and app-based inventory of nutrition (1245) would cover other important aspects related to the aging process, even provide compositional insights, e.g. on sleep and activity (1246). Improvements in acquisition of such data, in particular in regards to nutrition, would have to be made, since self-reporting, as in other areas, is of limited reliability (335, 336, 1247). At the moment, disease risk and outbreak is mostly monitored with general health screenings, even though the corresponding benefits often are questionable (382). Along the same lines, pharmacological interventions such as broad administration of polypills, and some wearables data, for example those claiming to predict atrial fibrillation (1248) and continuous glucose monitoring in non-diabetic patients (1249, 1250), will have to be rigorously tested since clinical use of these in healthy individuals and in aging is still under debate. Little to no data currently exists for proposed pharmacological and interventional “anti-aging” strategies as discussed in Sections 2 and 3, as well as the molecular biomarkers of aging. Nevertheless, once positive steps to clinical validation in humans have been achieved, these could also be included in a health screening. Finally, other molecular, morphological and functional screening tools might be considered and tested in the future, e.g. aimed at estimating immune system function, intestinal or other microbiomes, or blood and urinary biomarkers (1251).

Optimally, a personalized health pass based on such data would be initiated at young age, and updated in a longitudinal manner throughout life (Figure 9B). Thereby, favorable or unfavorable trajectories could be identified (573, 1049, 1050, 1252, 1253) and appropriate measures initiated in early stages of deterioration. Moreover, the impact of detrimental events, e.g. hospitalization, as well as the benefits of interventions could be quantified. Finally, personalized diagnosis, e.g. of sarcopenia, could overcome prevailing issues with cross-sectional and population data (1254), and might enable early detection and initiation of preventative measures on the individual and/or community levels (1255). Thus, a better integration of these physiological biomarkers in fundamental aging studies in model organisms and humans, population-wide health screening and clinical trials is one challenge to overcome, even though hurdles to do so are low (1256).

8.2 How can the adoption of a healthy lifestyle be increased?

A much larger challenge than the implementation of many of these biomarkers and screenings is the poor compliance and adherence of many people to life style-based interventions despite the obvious health benefits (1257, 1258). In this section, physical activity will be used as an example, but analogous conclusions and recommendations could

also be made for the better adaptation of other factors discussed in Section 3. Certainly, various reasons contribute to differences in active and sedentary behavior, including socio-economic aspects, availability of time, access to facilities, or fatigue (296). However, to a significant extent, human (and murine) activity behavior is controlled by innate, genetic factors (1259). Therefore, vague recommendations to increase leisure-time activity, or to simply overcome lack of willpower, often fall short, even in patient populations with high risks and clear benefit of exercise (1260). In recent years, factors that decisively contribute to adherence and compliance have been studied and quantified (1261–1267), helping to overcome the intention-behavior gap (1268, 1269). Even the WHO initiated the "Global Action Plan on Physical Activity 2018-2030" with the vision of "more active people for a healthier world", aiming for a 15% relative reduction in the global prevalence of physical inactivity by 2030 (1270). In many regards, promoting physical activity (and other behaviors with health benefits) can be attributed to four levels (1264, 1271–1273): Political framework, health care systems, health care professionals and individuals (Figure 10).

1.) Political framework: for example, the reduction of individualized, motorized vehicles, which is strongly linked to sedentary behavior and unhealthy lifestyles (1274–1277), in favor of biking, walking, or public transportation and other infrastructural aspects (e.g. central, easily accessible, and attractive staircases instead of elevators and escalators, parks and recreational areas, urban/jungle gyms, walking/running tracks) promotes an active lifestyle. These efforts also include expanding walking and cycling networks and improving pedestrian and cyclist safety (1270).Notably, walkability confers clear benefits on physical activity behavior in healthy individuals (1278) and cancer survivors (1279). Additionally, fostering an active society can involve offering free activities in parks and public open spaces or the temporary/permanent closure of roads to motorized vehicles to facilitate activities such as cycling, inline skating, and walking (1270). Other interventions include reducing adverse behaviors such as usage of tobacco, alcohol or sugar-sweetened beverages and other unhealthy food and drinks through taxation, and the reduction/elimination of subsidies for fossil fuels (to curb anthropomorphic climate change and promote more active ways of mobility), all of which will liberate funds for the promotion of healthy lifestyles (233). The conversion of Paris with the Plan Vélo 2021-2026 shows the feasibility even in large metropolitan areas, provided the political will and financial investments. As a side-effect, other potentially detrimental factors on healthy aging, e.g. air pollution, noise emissions or insufficient sun exposure, would also be mitigated by such infrastructural changes. Importantly, research and surveillance of healthy lifestyle habits and interventions should be promoted, as should public awareness.

2.) Health care systems: a shift of the emphasis from treatment, care and rehabilitation to prevention (primary and secondary) should be promoted (Figure 11).

Financial relief, e.g. on health care costs, certainly belong to the strongest incentives. Moreover, the establishment of science-based, individualized, structured and guided exercise programs, including aspects of behavior change and habit formation, would ensure the highest adherence and compliance (1261, 1262, 1268, 1280, 1281). This could be facilitated if general practitioners were able to issue physical activity or lifestyle prescriptions for

inactive individuals, covered by the health insurance. In most countries, this is usually only possible for individuals with existing physical impairments, thus in rehabilitation or secondary prevention, rather than for primary prevention in those who are still healthy but inactive. The prevailing reactive health care system, focused on treatment and rehabilitation, leads to high costs, and patient relapse (Figure 11A). Programs for secondary prevention that go beyond rehabilitation often do not exist, but would help to minimize relapse by aiming at achieving functional capacity levels that surpass those that initially contributed to an incident or disease in these patients (Figure 11B). Optimally, proactive programs would be established for the primary prevention in healthy individuals to reach a level of functional capacity and resilience that minimize such incidents before they even occur (Figure 11C).

3.) Health care professionals: it is clear that a general recommendation of "being more active and eat a balanced diet" are insufficient (1282). Therefore, personalized physical activity or lifestyle counselling should be accessible for individuals with an unhealthy lifestyle, tailored for different populations such a geriatric individuals (1283, 1284). The recognition of the importance of physical activity is very divergent amongst health care professionals. For example, there is a large variation in exercise prescription by physicians depending on their own physical activity level (1282). In fact, physically active physicians provide almost twice as many daily physical activity consultations compared to their inactive colleagues. One of the major barriers for primary care physicians to prescribe physical activity to patients include a lack of education. Accordingly, medical curricula should much more strongly emphasize the importance of physical activity, which in many diseases is on par with pharmacological and other interventions (303). This should help health care professionals to incorporate routine fitness testing and exercise interventions in the clinic, and guide patients towards structured programs (1285).

4.) Individuals: the education about the strong benefits of an active lifestyle has to be massively expanded, starting at young age, notably in an accessible and understandable manner to minimize misunderstanding and misinformation (1286). Often, such aspects are the first to be removed from already overloaded school curricula. Moreover, extracurricular activities, such as walk- or cycle-to-school programs, should also be strengthened, including the integration of road safety education (1270). Second, social safety nets, which reduce the work time of socio-economically disadvantaged cohorts, would lessen time pressure and fatigue, and increase motivation to engage in exercise (1287, 1288). The goal of the educational measures on different levels should be clear guidance for the design and application of personalized, evidence-based, safe and efficacious training paradigms (1289, 1290), nutrition (1291), and other interventions.

8.3 Who is going to pay for this?

Obviously, any of these measures are associated with considerable financial investments, at least in the short-term, which might dampen the enthusiasm for such political and societal initiatives, e.g. in politicians who think in 2, 4, or 6 years election cycles. It however is important to point out that in the long run, better public health will yield enormous savings, even in the context of an aging population (233). For example, various studies estimate an average saving of USD 3 to 4 for each dollar invested in measures that promote

physical activity alone (1292, 1293). Each increase in one metabolic equivalent (MET) in cardiorespiratory function leads to an individual annual reduction in health care costs between USD 1025 and 5193 in different populations (thus approx. 5-10% of total costs) (1294, 1295), a decrease in all-cause sickness absence days (1296), improved work ability, and less doctor and hospital visits (1118). Further return of investment can be expected from other changes, e.g. healthy diet (1297), for example by lowering the annual costs of GBP 2.68 billion caused by unhealthy food in the UK (1298), cycling infrastructure (1299), or adequate sleep (1300). In Canada, the economic burden of low cardiorespiratory fitness is estimated at CAD 3.6 billion, with savings of CAD 644 million per year with a 10% reduction in the prevalence of low cardiorespiratory fitness (1301), and similar numbers for low muscle strength (CAD 3 billion total costs and CAD 546 million savings with 10% improvement) (1302). Along these lines, a reduction in the incidents of fatal and non-fatal falls would save costs in the millions, if not billions of USD even only within the United States (1303). Finally, risk factors such as elevated BMI or waist circumference significantly drive health care costs, for example, by 15.4% more with an increase in waist circumference by 10 cm (1304). Thus, while finding a true “anti-aging” drug or intervention could mean a lot of money to be gained (for a handful of individuals or companies), engaging in proven lifestyle- and behavior-associated interventions with certainty leads to a lot of money saved (for a society).

8.4 Conclusion and outlook

All of these arguments should not be taken as a vote against current research into molecular clocks, epigenetic reprogramming and rejuvenation, and other cutting-edge topics in aging research. Hopefully, future insights in these fields will synergize with those obtained in research areas focused on the basic biology of the physiological biomarkers, and together, provide mechanistic and causal data on healthy and unhealthy aging. Moreover, potential age-reversal-age-extension (ARAE) paradoxical effects between pharmacological geroprotectors and lifestyle interventions, e.g. the attenuating effect of metformin, resveratrol or rapamycin on training adaptation (37, 38, 476, 1305), could be overcome with a better understanding of the respective systems. Importantly, assessment and leverage of the physiological biomarkers (1306), the knowledge of proven drivers of unhealthy aging and of interventions promoting healthy aging are available now, and could (should!) be applied immediately in an effort that would benefit all to attain a healthier, longer and happier life (1307) (“a high tide lifts all boats”), instead of waiting for potential future breakthroughs, many of which might only be accessible to a handful of millionaires. Indeed, a three-round Delphi study recently came to the overwhelming conclusion that the physiological biomarkers are currently by far the best tools to monitor and assess interventional studies aimed at aging and longevity (1308). Until other biomarkers and interventions, e.g. those based on molecular criteria, reach the same level of maturity, it thus is important that, despite the heightened interest and the massive influx of money for basic research, biotechnological and clinical application, with the hope of immense return of investment (1309), hype of premature, preliminary and not yet reproduced results should be avoided to temper inflated expectations in scientists, funders, the media and the lay public alike (1310).

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Clinical Highlights

1. Aging is the strongest risk factor for many (chronic) diseases, frailty, morbidity and mortality.
2. At the moment, the molecular underpinnings of aging are still only poorly understood and accordingly, pharmacological interventions that directly target aging elusive.
3. The molecular biomarkers of aging exhibit a large variability, with very few attempts of validation in humans.
4. Physiological biomarkers of aging, centered on functional, anthropogenic and morphological aspects, are well-established in large human populations, with very high predictive value for disease risks, frailty, morbidity and mortality.
5. The physiological biomarkers however are somewhat underappreciated, even though they could be used in young and old, healthy and clinical populations right now.
6. Lifestyle, behavioral and environmental factors have a significant effect on human health and mortality, while many pharmacological and interventional approaches found in pre-clinical models still await human translation.
7. These factors with proven benefits should be encouraged and promoted on the individual and societal levels.

Box 1

Proposed framework and criteria of aging biomarkers. Adapted from ref. 507

Classification	How can the biomarker be used? **1.)** Predictive (e.g. for aging trajectories, identification of individuals that respond to interventions) **2.)** Prognostic (e.g. trajectories and treatment of age-associated diseases) **3.)** Response (e.g. biological reaction to aging or interventions) **4.)** Surrogate endpoint (e.g. to substitute for direct measurement of aging)
Assessment	How can the biomarker be measured? **1.)** Feasibility and validity of measurements (e.g. prerequisites for sample acquisition, processing and data interpretation, age-sensitivity, non-age-accelerating) **2.)** Mechanistic underpinnings and biological plausibility (e.g. reflection of underlying mechanisms involved in the aging process) **3.)** Generalizability (e.g. narrow vs. broad applicability from model organisms to humans, usage in different ethnicities, sexes, age groups and other demographics and populations) **4.)** Response to aging and interventions (e.g. reflecting improvement or deterioration in the aging process and inversely, promotion of geroprotective effects) **5.)** Costs (e.g. application in large-scale settings and life-long longitudinal assessments) **6.)** Invasiveness and safety (e.g. minimally invasive, devoid of adverse effects, safe to test from the young to the oldest of the old)
Validation	Has the biomarker been validated in terms of measurement methods and clinical application? **1.)** Analytical validation (e.g. quantifiable, accurate, reliable, repeatable and reproducible measurement, standardized procedures) **2.)** Clinical validation (e.g. validity in different human cohorts, statistically relevant reference values for broad demographics and populations)

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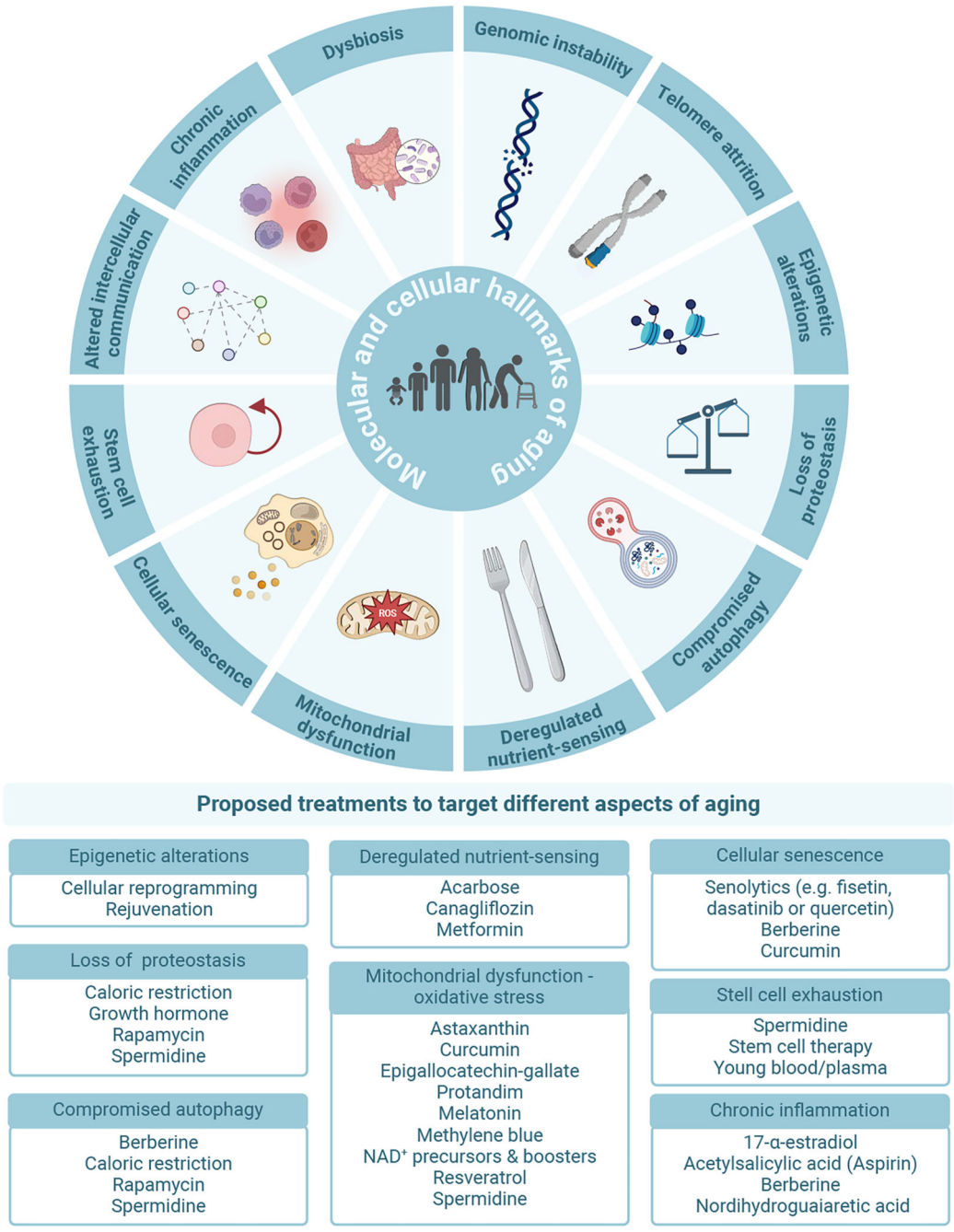

Figure 1. The molecular and cellular hallmarks of the aging process and potential anti-aging compounds.

A number of molecular cellular alterations have been proposed to be associated with the aging processes, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, compromised autophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis (see ref. 110). Various treatments have been suggested to target some of these processes (examples shown) and might thereby have the potential for anti-aging drug effects (see refs. 38, 110, 113–128). However, at the moment, no

evidence for efficacy (and safety) for the application of any of these pharmacological and interventional factors on the human aging process exists. Figure created with BioRender.com.

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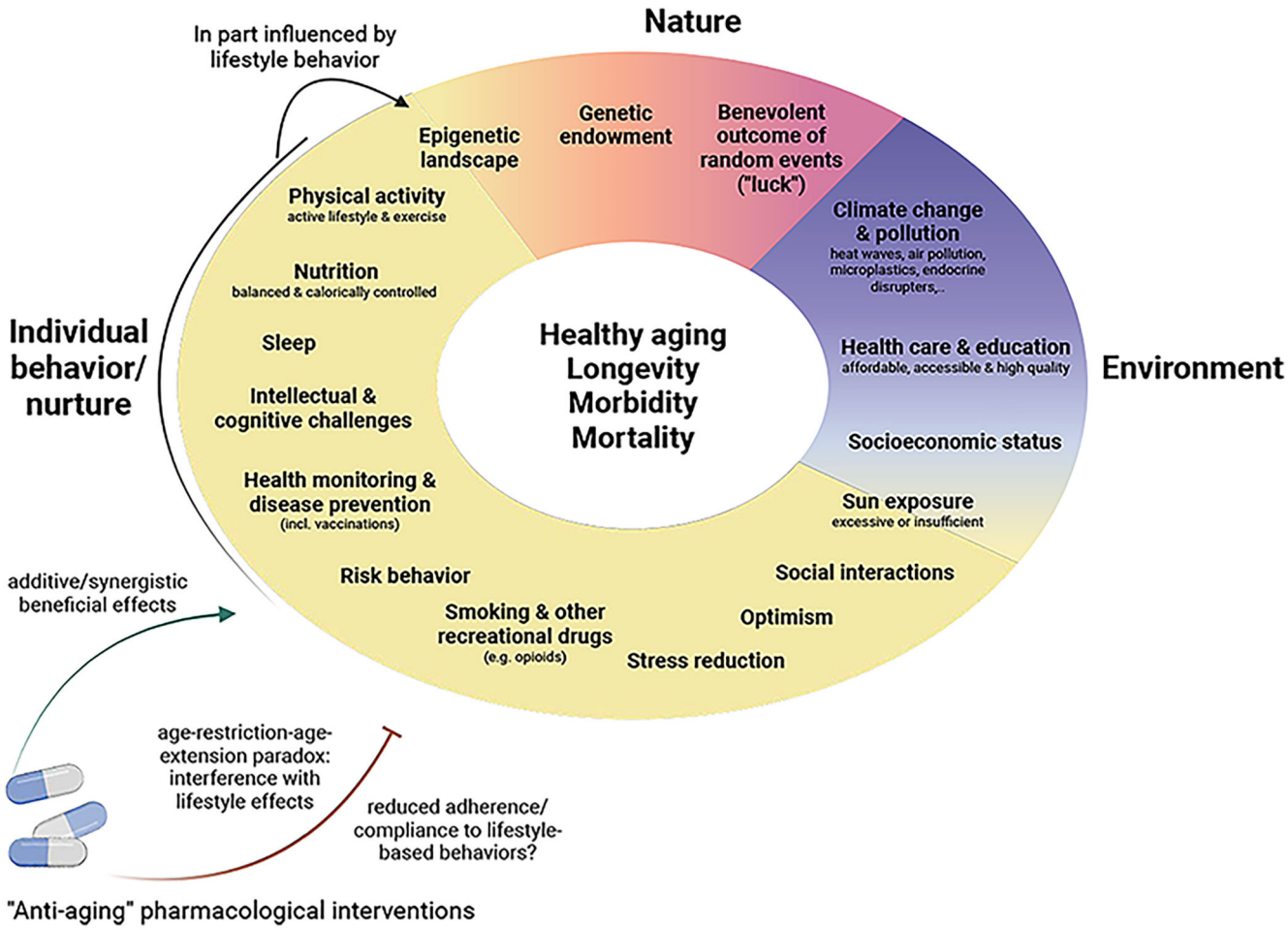

Figure 2. Factors and interventions affecting healthy aging, health- and lifespan, morbidity and mortality.

Nature: The genetic endowment and the benevolent outcome of random events cannot be influenced. Nurture: Lifestyle-associated behaviors can, to a large extent, be influenced on an individual level, extending to the modulation of some epigenetic modifications. Environment: Other significant factors, e.g. socio-economic status, health care and education, are determined by the prevailing political and societal landscape. For all of these factors, solid epidemiological and/or observational data for a significant influence on morbidity and mortality in humans exist. Yet to be identified “anti-aging” drugs with validated efficacy in humans could add to or synergize with the effect of these factors. Inversely however, they could also interfere, both on a psychological level, e.g. intake of a pill replacing exercise as an easier “substitute”, or on a mechanistic level, e.g. as described for resveratrol, metformin or rapamycin. Thus, at the moment, efforts should center on improving the adoption and promotion of the proven factors shown here. Figure created with BioRender.com.

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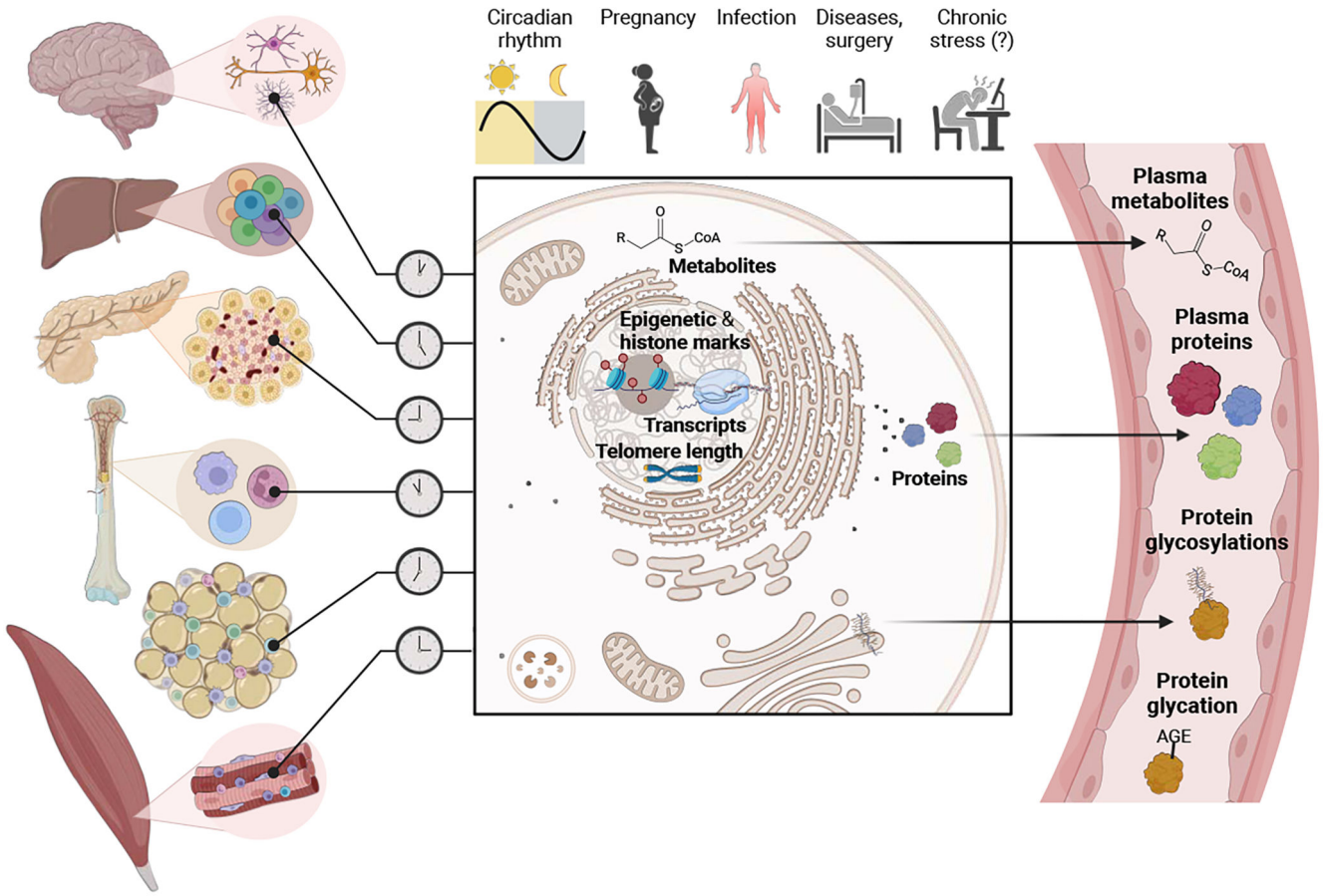

Figure 3. Molecular biomarkers and aging clocks.

The age-dependency of several molecular events is leveraged to predict whether “biological age” deviates from chronological age. Processes that are monitored range from telomere length to epigenetic marks, most notably DNA methylation events. Specific fingerprints of transcripts, proteins, metabolites and protein glycosylations and glycation have likewise been proposed as biomarkers for aging. Most of these age-dependent molecular changes occur in all cells, tissues and organs of the body. However, significant differences exist between individual tissues/organs, cell types, or even between cells of the same type based on spatial organization within an organ. One way to avoid potential confounding effects of cell heterogeneity is to define plasma metabolite or plasma protein profiles that are associated with aging. Of note, some of these clocks are affected by circadian rhythms or external perturbations such as pregnancy, infection, diseases and potentially other factors such as chronic stress. Abbreviation: AGE, advanced glycation end product. Figure created with BioRender.com.

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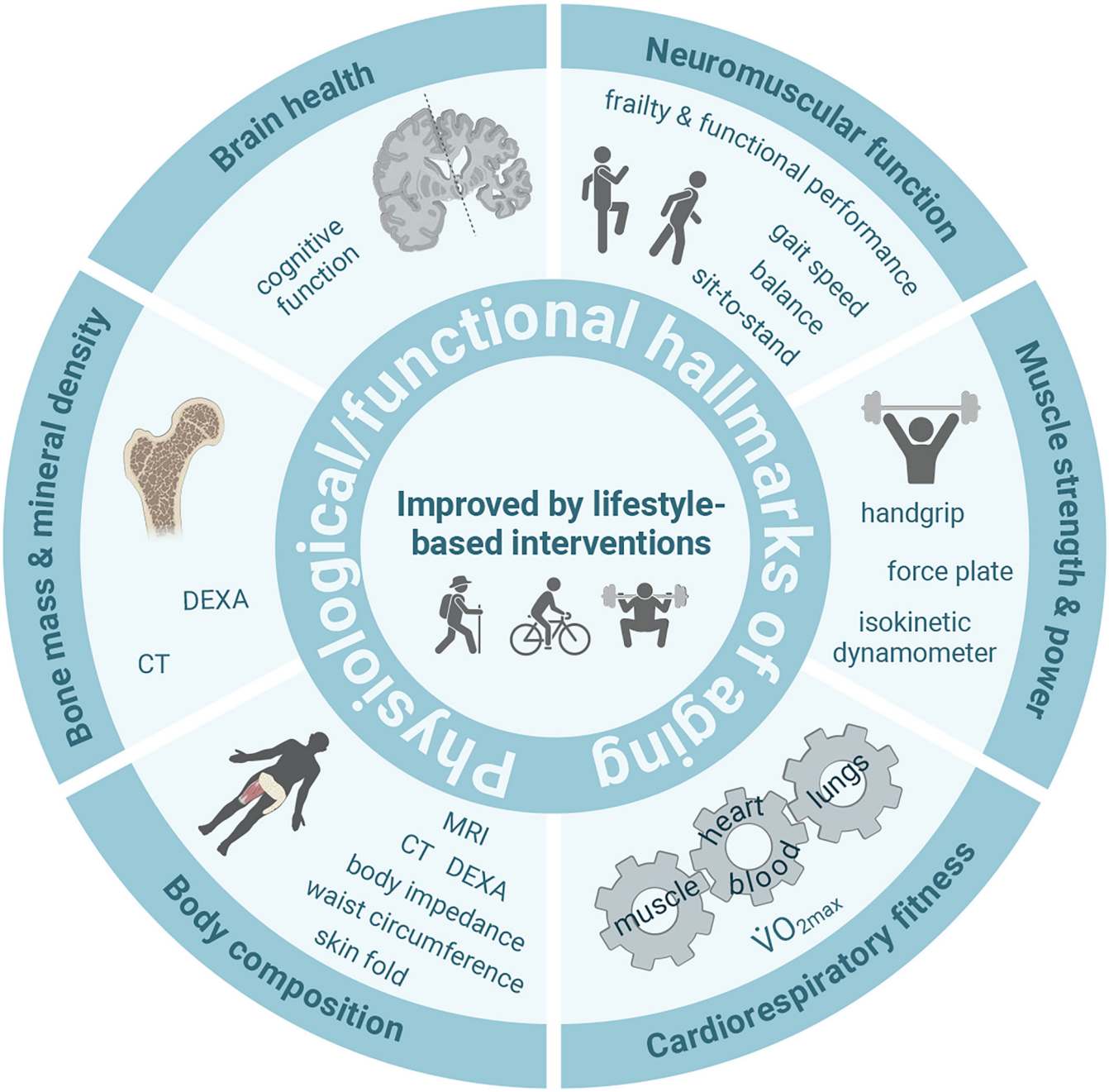

Figure 4. Physiological/functional hallmarks of aging.

The loss in muscle mass, often associated with a change in fat mass and distribution, reduced cardiorespiratory function, impaired muscle strength/power and neuromuscular deficiencies associated with frailty are age-related processes that are observed universally, all of which are measured with the physiological biomarkers of aging. In addition, reduced brain health, in particular driven by neurodegeneration, and a loss in bone mass and mineral density occur. Most of these hallmarks of aging can be determined by the proposed physiological biomarkers. Of note, all of these hallmarks of aging are ameliorated by the lifestyle- and behavior-based interventions, most importantly exercise training.

Abbreviation: CT, computed tomography; DEXA, dual energy X-ray absorptiometry; MRI, magnetic resonance imaging. Figure created with BioRender.com.

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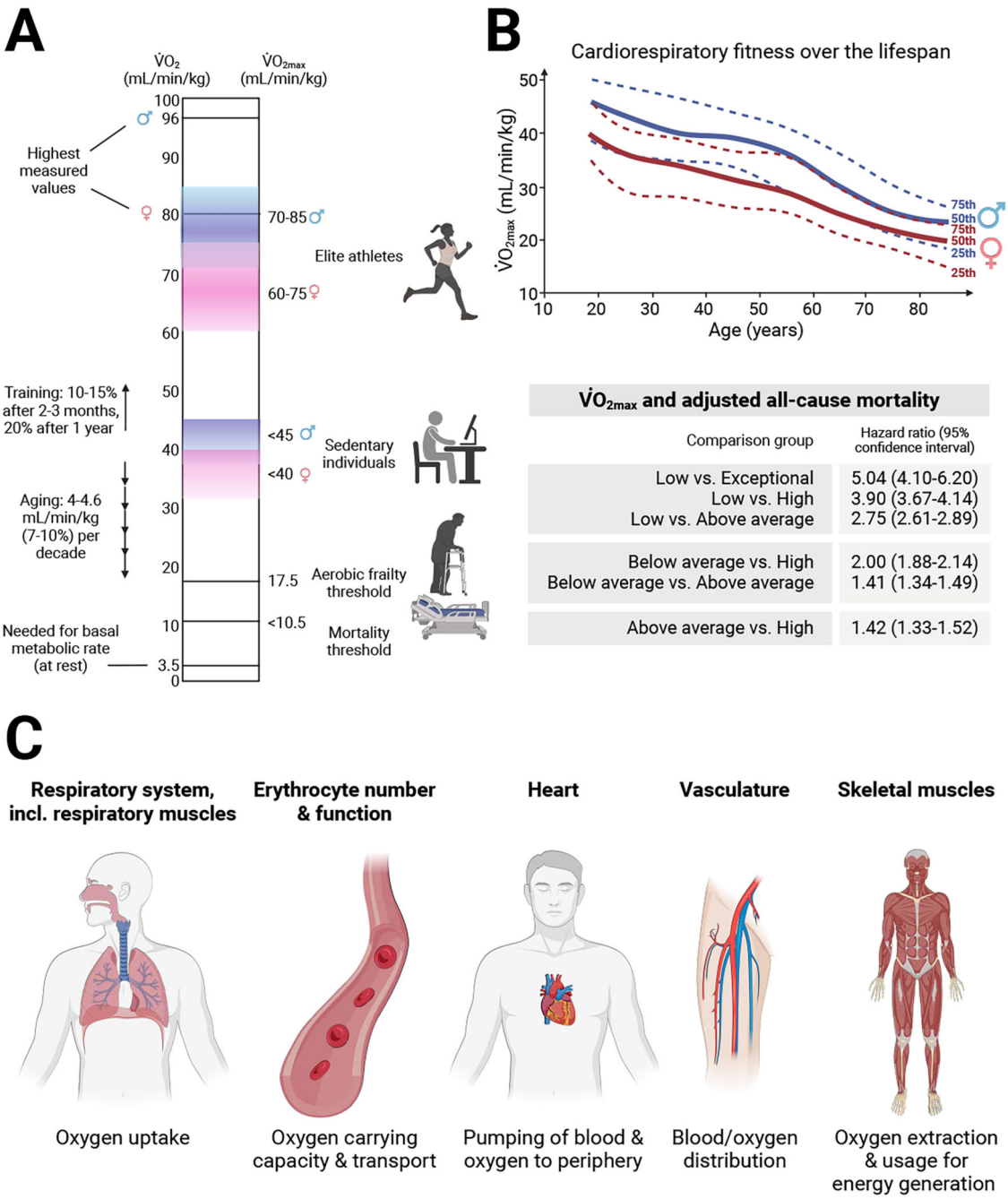

Figure 5. $\dot{V}O_{2max}$ is a strong predictor of health, morbidity and mortality.

A, $\dot{V}O_{2max}$ represents a multisystem readout of cardiorespiratory fitness, which is highly pliable by exercise. The age-associated decrease of up to 10% per decade can meet an aerobic frailty threshold, leading to disability and loss-of-independence. $\dot{V}O_{2max}$ is substantially higher in elite athletes, with measures approx. 2-fold above those of the general population. **B**, Age-related $\dot{V}O_{2max}$ in a cross-sectional patient study of different ages and sexes (n=122’007; men: n=72’173; women: n=49’904), acquired over 24 years, tested by treadmill running. The 25th, 50th and 75th percentiles for each sex are indicated

by solid (50^{th}) and dashed (25^{th} and 75^{th}) lines. Adjusted all-cause mortality hazard risk ratios between groups (pooled over all age groups and both sexes) are all significant ($p<0.001$). Groups: Low ($<25^{th}$), below average (25^{th}-49^{th}), above average (50^{th}-74^{th}), high (75^{th}-97.6^{th}), exceptional ($>97.7^{th}$). Values from ref. 600. **C**, Examples of organs, tissues and cell types that contribute to and determine $\dot{V}O_{2max}$. Figure created with BioRender.com.

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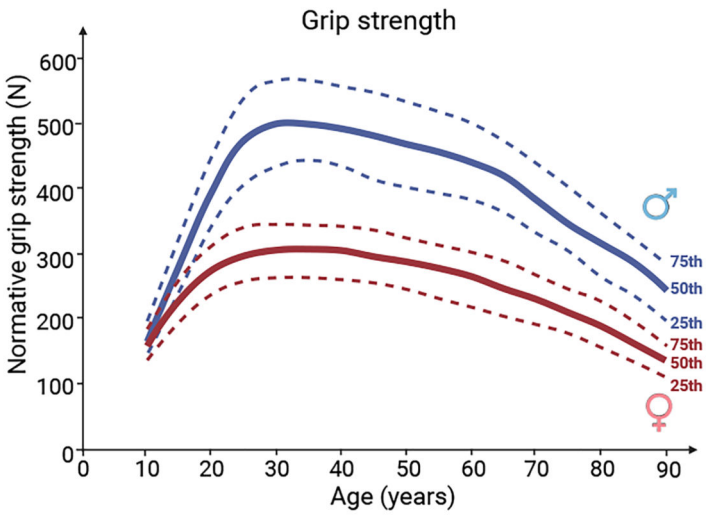

For every 49 N (5 kg) decrease in grip strength	Hazard ratio (95% confidence interval)
All-cause mortality	1.16 (1.13-1.20)
Cardiovascular mortality	1.17 (1.11-1.24)
Myocardial infarction	1.07 (1.02-1.11)
Stroke	1.09 (1.05-1.15)

Lowest vs. highest strength quintiles	Hazard ratio (95% confidence interval)
Dementia incidence	1.72 (1.55-1.92)
Dementia mortality	1.87 (1.55-2.26)

Figure 6. Physiological biomarker grip strength.

Age trajectories of grip strength in men and women. Grip strength data from ref. 785 (n=49’964 participants; men: n=23’277; women: n=26’687). Adjusted hazard risk ratios from refs. 792 and 789. Figure created with BioRender.com.

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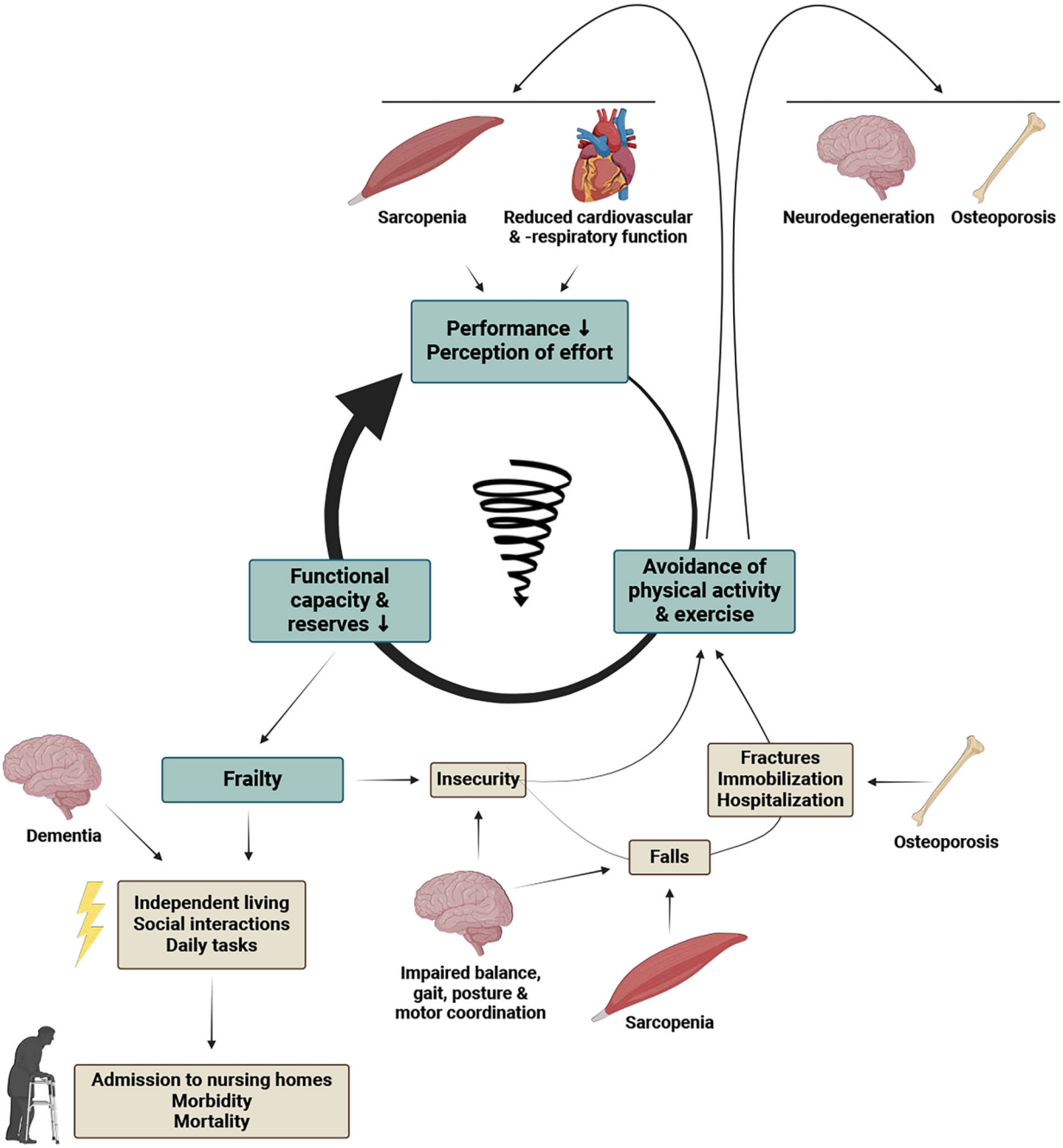

Figure 7. Age-associated degeneration of skeletal muscle, neuronal tissue, bone and the cardiovascular system drive a vicious cycle leading to loss-of-independence, morbidity and mortality.

Sarcopenia (loss of muscle mass and function), together with reduced cardiovascular and – respiratory function (leading to decreased endurance and increased fatigability) reduce physical performance and increase the perception of effort for exercise- and daily task-related endeavors. As a consequence, such activities are being increasingly avoided, further depleting functional capacity and reserves. The lack of adequate levels of these lead to frailty, which, in turn exacerbates sarcopenia, cardiovascular dysfunction, neurodegeneration

and osteoporosis, thereby fueling a vicious cycle. Together with neurodegenerative events, e.g. linked to dementia, this constitute the major driver for the inability to perform daily tasks (e.g. carrying groceries, cleaning the apartment, walking up- and downstairs or across pedestrian crossings), enjoy social interactions, and independent living, thus leading to admission to nursing homes, increasing the risk for (co-)morbidities and elevating mortality risks. Neuromuscular deterioration, e.g. in balance, motor coordination and gait, promotes insecurity and, exacerbated by muscle weakness, also the risk for incident falls, which, in the worst case, lead to fractures (facilitated by reduced bone mass and mineral density), immobilization and hospitalization. All of these factors contribute to the avoidance of physical activity and exercise, thus further fueling this vicious cycle. Figure created with BioRender.com.

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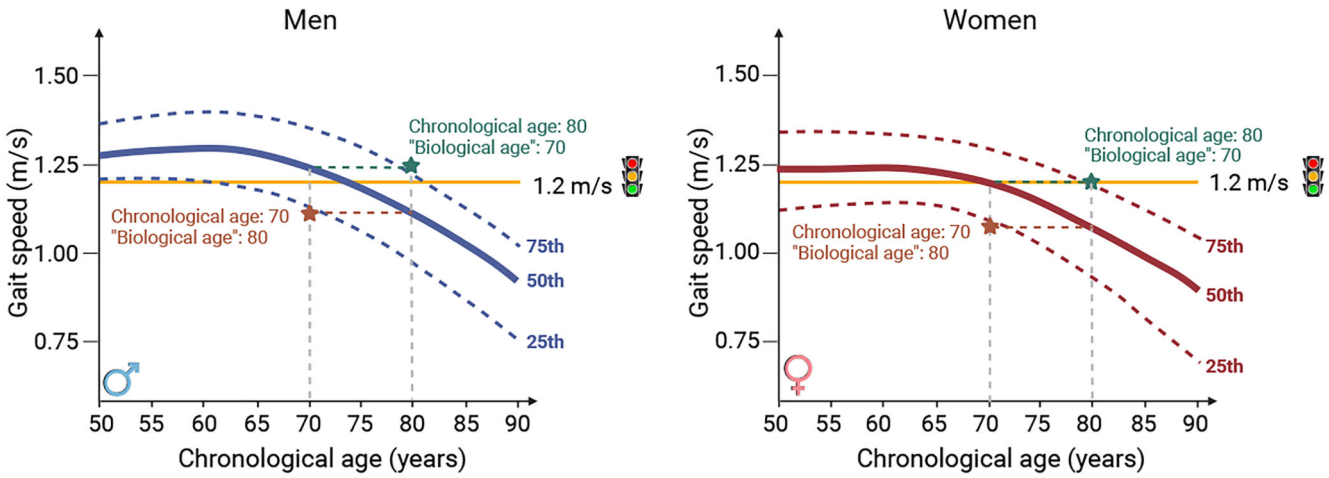

Figure 8. Physiological aging biomarkers associate with chronological age, while also predicting "biological age".

In this figure, the decline of gait speed with chronological age in men and women is shown from which a "biological age" can be inferred. In the examples, the green star represents an individual of chronological age 80, who however has a gait speed representing the mean of 70 years of age. In contrast, the slow gait speed of the 70-years old red star is equivalent to that of 80-years old individuals. In these examples, the 80-years old would still sequester above the threshold of 1.2 m/s gait speed needed to walk across many pedestrian crossings (indicated by the yellow line) (see ref. 1311), while the 70-years old individuals would fail to succeed in this task. The figure is based on data presented in ref. 1312 (men: n=2'087; women: n=2'569). Figure created with BioRender.com.

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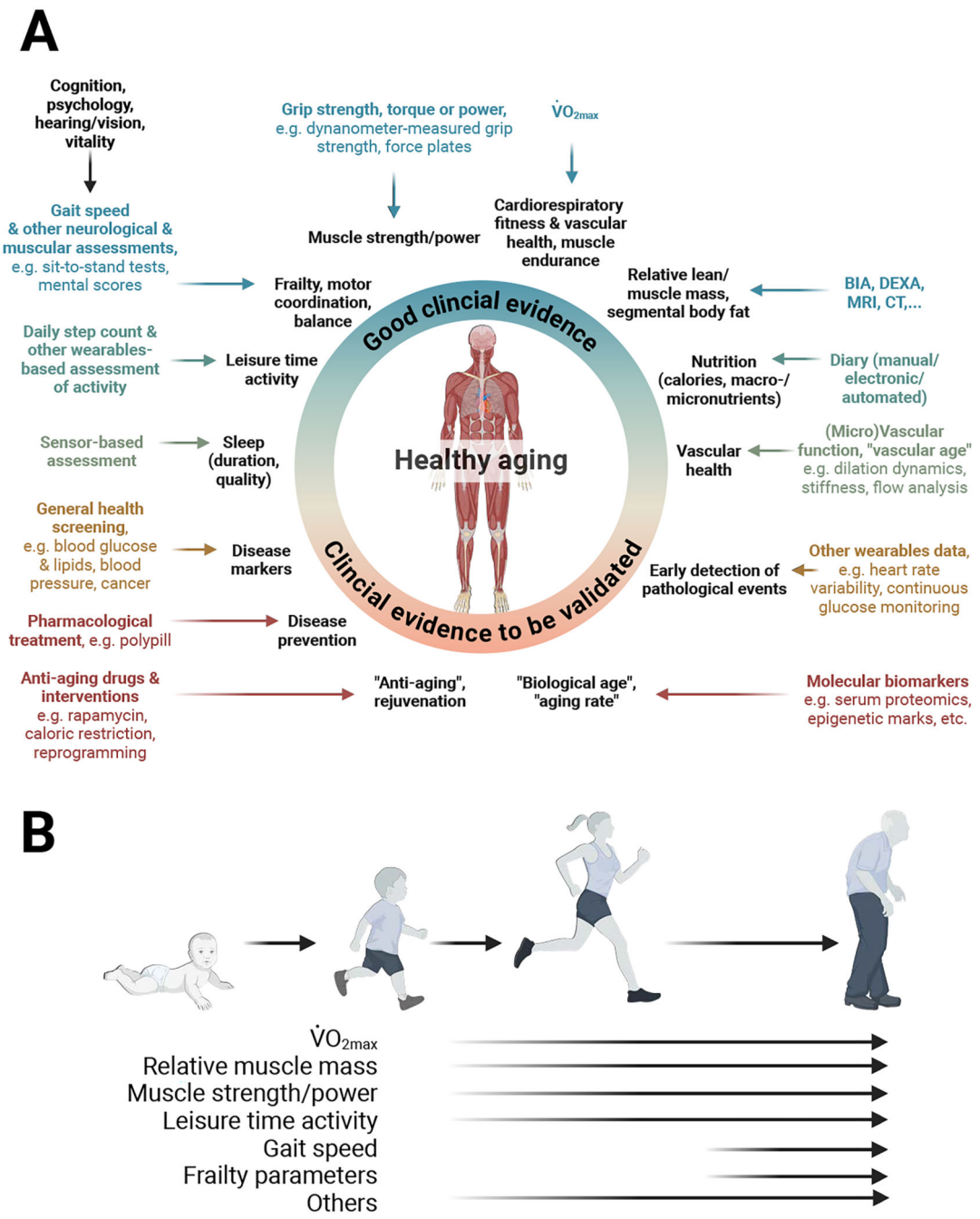

Figure 9. Comprehensive assessment of physiological and other biomarkers of aging.

A, Gait speed, grip strength, leisure time activity, $\dot{V}O_{2max}$, relative muscle mass and related parameters are clinically proven biomarkers of aging. A longitudinal assessment throughout lifetime could provide information on aging and health trajectories, efficacy of interventions and treatment, and detrimental outcome of pathological events. Data on sleep and nutrition, wearable- and/or app-based, could likewise be included. Moreover, specific assessment of vascular function (and “vascular age”), based on blood flow, stiffness and dilation dynamics, assessed in a non-invasive manner, for example in the retinal vasculature, helps to predict

vascular health. Such an individual “health/aging” pass, consisting of a combination of these markers, could further be combined with general health screening, pharmacological preventative interventions (e.g. a polypill) or wearables data, even though the benefits of these measures are currently questionable. In the future, molecular biomarkers of aging, as well as potential pharmacological and interventional means could be included in such a strategy, if valid clinical data on efficacy and safety in the human aging process can be shown. **B**, A personalized health pass covering various domains should be based on the proposed biomarkers and obtained in a longitudinal manner from young to old age. Thereby, favorable or unfavorable trajectories could be identified early on, and appropriate measures prescribed. Abbreviations: BIA, bioelectric impedance analysis; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging. Figure created with BioRender.com.

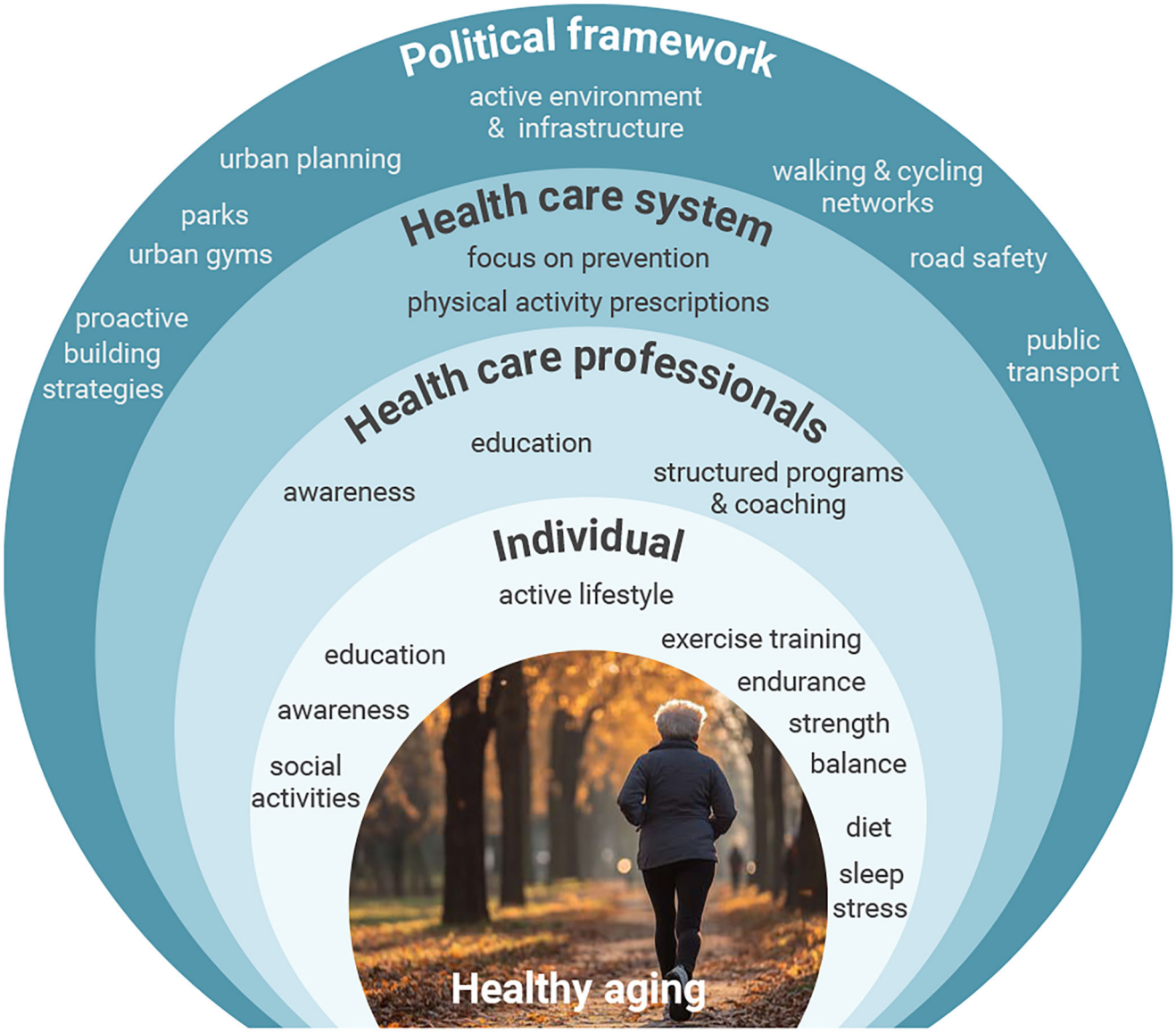

Figure 10. A four-level approach to promote physical activity.

Physical activity, exercise training and calorically-controlled, balanced diet have proven benefits on the aging process, morbidity and mortality. These lifestyle-based behaviors should therefore be promoted on different levels, from a political framework that supports the corresponding infrastructural adaptations, to health care system investing in prevention, health care professionals monitoring and prescribing guided, structured programs, and eventually the individual who will have to initiate and maintain behavioral changes for long-lasting effects. Various examples of measures are shown. Figure created with BioRender.com and Adobe Stock Photos.

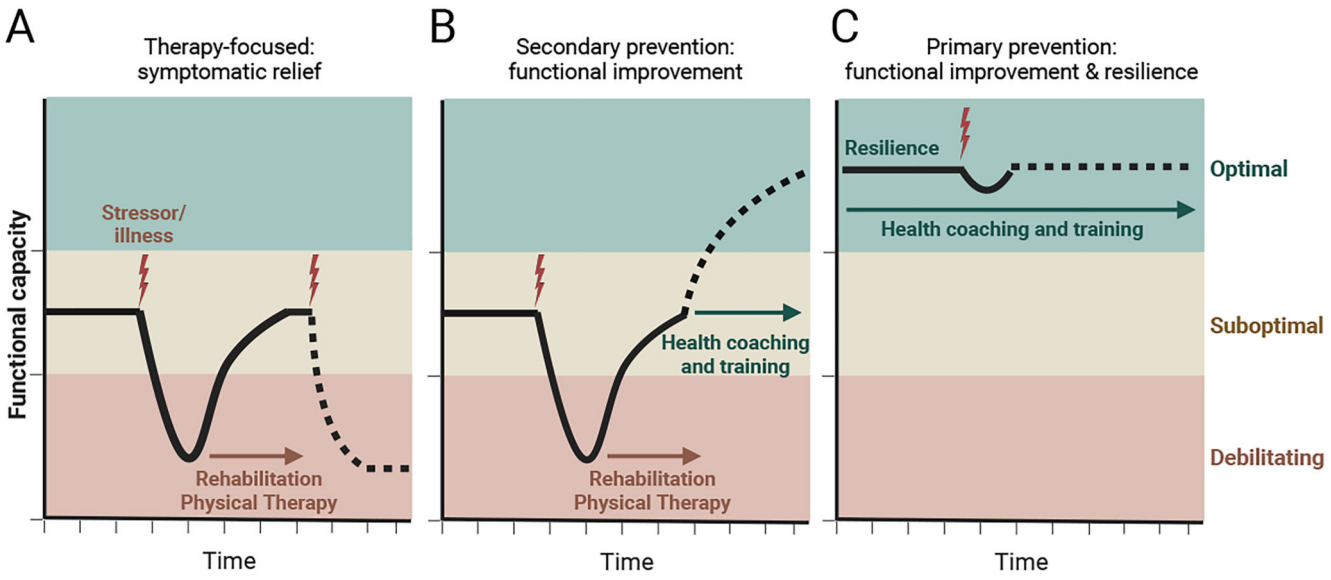

Figure 11. Focus on prevention rather than treatment.

A, Impaired functional capacity is a major driving force for incident morbidity, accidents or wear and tear, potentially leading to dependence on medical intervention and hospitalization and the corresponding debilitation. The prevailing model of a reactive, therapy-focused system with high costs, and high relapse if rehabilitation is aimed at bringing back patients to the initial baseline of functional capacity, which, often remains in a suboptimal range, thus potentially setting up patients for relapses. **B**, Additional programs that boost functional capacity to an optimal level, e.g. with health coaching and guided, structured training programs, could help in a more pro-active manner in secondary prevention. Thereby, a more optimal state of functional capacity could be achieved, preventing or at least mitigating the risk for relapses. **C**, In the best case scenario, programs aimed at health individuals in primary prevention would improve functional capacity to an optimal range before the onset of an incidence, thereby conferring resilience to avoid or reduce pathological events and health care system dependence. Figure created with BioRender.com.