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Genetic, Social, and Lifestyle Drivers of Healthy Aging and Longevity

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Abstract

Purpose of Review—"Healthy aging" is the state of the aging process in which a person can maintain physical, social, mental, and spiritual wellness. This literature review presents an overview of recent studies that explore how biological, social, and environmental factors contribute to healthy aging.

Recent Findings—A number of genome-wide association studies have been conducted recently for traits related to healthy aging, such as frailty index, healthspan, muscle strength, and parental longevity, leading to the discovery of dozens of genetic variants associated with these traits. In parallel, associations between healthy aging measures and multiple non-biological environmental elements have been identified as key moderators of the aging process, indirectly influencing day-to-day homeostatic processes.

Summary—Individual variations in lifespan and healthspan are influenced by genetic factors, with a heritability of ~ 25% in developed countries. Non-genetic risk variance is explained in part by social, cultural, and lifestyle conditions. Altogether, these factors contribute to a multifaceted state of wellness over time, shaping individual risk to frailty and resilience during the aging process. Notably, "Blue Zone" populations, which are characterized by an abundance in healthy lifestyles across generations, share some commonalities regarding determinants of health.

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Keywords

Healthy aging; Resilience; Frailty; Genetics; Environment

Introduction

The human body is a complex and dynamic system comprised of sub-systems and organs with specialized functions that work harmoniously to maintain allostasis and homeostasis [1, 2]. Allostasis is the process that keeps an organism alive and functioning by ensuring stability through change and promoting adaptation and coping [3], and homeostasis is the stable equilibrium reached through allostatic mechanisms [4]. *Healthy aging* can be conceptualized as the state of the aging process in which the person's allostatic responses can readily maintain physical, social, mental, and spiritual wellness [5]. Every system in the body uses allostasis to respond to external lifestyle or environmental events or stressors, including socioeconomic status, psychosocial factors, education, nutrition, physical activity, smoking, alcohol consumption, infectious disease, and pollution, leading to adaptation and homeostasis maintenance [6-16]. Additionally, the physiological response to acute versus chronic stress may be different. For example, an acute threat activates the fight or flight response, evolutionarily designed to protect individual well-being, to allow immediate action. However, when the stress is repeated over many weeks and becomes chronic, it leads to different systemic alterations that, ultimately, can result in adverse outcomes [3].

Aging occurs when the body's efficiency to maintain allostasis and homeostasis declines progressively over time [1]. At least nine *biological hallmarks* have been implicated in aging: (1) genomic instability, (2) loss of proteostasis, (3) telomere attrition, (4) epigenetic alterations, (5) deregulated nutrient-sensing, (6) mitochondrial dysfunction, (7) cellular senescence, (8) altered intercellular communication, and (9) stem cell exhaustion [1, 17]. However, the ways these processes become disrupted while contending against stressors are not understood [18].

Individuals become more vulnerable to environmental challenges if their allostatic responses are overused or inefficiently managed. This condition, known as *frailty*, increases a person's odds for adverse health outcomes and death. Conversely, when the allostatic response achieves a positive outcome in the face of adversity, the individual is considered to be in a state of *resilience* [19]. The determinants and mechanisms of resilience and frailty are yet to be elucidated.

The multifaceted state of healthy aging is influenced by genetic factors and the accumulation of experiences over the lifespan that promote an individual's resilience and contribute to risk for frailty. Our understanding of the genetic, social, and lifestyle determinants of healthy aging, longevity, frailty, and resilience has advanced considerably in recent years, thanks to a surge in the number of cohort studies, data collection efforts, and novel methodological approaches. However, there is no universal definition for healthy aging, as the meaning of wellness varies across different cultures [20]. In this context, we will review recent studies and provide an overview of the current understanding of the biological, environmental, and lifestyle factors that play a role in healthy aging worldwide.

Genetic and Other Biological Factors

One of the first genes implicated in longevity was the apolipoprotein (*APOE*) gene [21]. However, over time, it also became known as a "frailty gene" due to its role in dementia risk. Carriers of the ε4 isoform present an elevated risk of cardiovascular mortality at younger ages, shortening their lifespan and affecting their healthspan. Interestingly, a study found that carriers of the *APOE-ε4* isoform were extremely rare in Japanese centenarians aged 105 years or older [22]. Low allele frequencies for *APOE-ε4* were also observed in Canadians aged over 85 who had never been diagnosed with cardiovascular disease, dementia, diabetes, cancer, or chronic pulmonary disease. These observations suggest that individuals who do not carry the *APOE-ε4* allele have lower probabilities of presenting adverse health outcomes [23].

A classic example of a gene that promotes resilience is *FOXO3*. The *G* allele of SNP *rs2802292* in the *FOXO3* gene reduces mortality risk from coronary disease [24, 25]. The *HSF1* transcription factor binds to the enhancer sequence created by the *G* allele of *rs2802292* in *FOXO3* intron 2, conferring *resilience* to stress [26]. Recently, the same protective allele was associated with negligible age-related telomere attrition in a population in Okinawa, Japan, which may also explain its strong association to longevity [27].

In recent years, genome-wide association studies (GWAS) have enabled the screening of the entire genome for variants associated with frailty and related phenotypes. Atkins et al. [28] performed a GWAS of the *frailty index* in 164,610 European ancestry individuals aged 60–70 years from the UK Biobank. Their *frailty index* calculation was based on 49 self-reported items on symptoms, disabilities, and diagnosed diseases. They identified 26 independent genetic signals at 24 loci associated with *frailty index* across the genome. Most of those loci had previously been reported in genetic studies of traits such as body mass index, cardiovascular disease, smoking, depression, and neuroticism; however, the study also identified three reliable novel associations, implicating the *CSMD3, ANK3*, and *TMOD3* genes. The GWAS approach has also been used to study other related traits such as handgrip strength [29••], muscle weakness [30], cognitive resilience [31], age at the end of the healthspan [32•], and parental lifespan [33], described below.

Maximal handgrip strength is an element of the *frailty phenotype* [34]. It can predict a range of morbidities and all-cause mortality. Willems et al. [29••] analyzed data from 195,180 individuals and reported 16 loci associated with grip strength. Interestingly, the authors reported that common genetic variation in *ACVR2B*, the principal receptor of myostatin and activin in skeletal muscle, was associated with population-level variation in grip strength. Mendelian randomization analyses did not find evidence supporting a causal role of muscular strength in mortality risk nor the risk of cardiovascular events. A separate study [30] investigated the genetics of dynapenia (age-related loss of muscle strength) in 256,523 European ancestry individuals aged 60 years and over from 22 cohorts and identified 15 loci associated with muscle weakness. Some of the identified loci included genes implicated in autoimmune disease, arthritis, cell cycle control, transcriptional regulation, and others involved in developing and maintaining the musculoskeletal system. Taken together, this

body of literature suggests that muscle strength may serve as a measure of healthy aging rather than a contributor to it.

Regarding the healthspan, Zenin et al. [32•] built a risk model to predict age at the end of the healthspan, adjusting for gender and genetic background. Using data from 300,447 British individuals, they identified 12 loci associated with healthspan. At the whole-genome level, healthspan showed negative genetic correlations with stroke, congestive heart failure, myocardial infarction, chronic obstructive pulmonary disease, diabetes, cancer, and overall mortality. In other words, genetic risk for these age-related diseases is correlated with reduced healthspan.

Other factors, such as parental longevity, have been associated with longevity and cognitive resilience. A GWAS conducted in offspring of long-lived parents found a genome-wide significant loci for longevity near the *SMAD7* locus on chromosome 18 [35]. Furthermore, Joshi et al. [36] used data from 1 million parent lifespans from the UK Biobank and 26 independent European-ancestry population cohorts to carry out a GWAS of parental survival, which was quantified using Cox models. The study identified 11 novel loci associated with lifespan and replicated six previously discovered loci, with most lead SNPs previously implicated in autoimmune, cardiometabolic, neuropsychiatric, or smoking-related disease. In addition, Fitzgerald et al. [31] conducted a GWAS of cognitive resilience within the UK Biobank, using several proxy phenotypes. Notably, the study's authors modeled the heritable effects of educational attainment using genomic structural equation modeling. Thirteen independent genetic loci associated with resilience were identified. At the genome-wide level, resilience was correlated with multiple cognitive phenotypes, brain imaging measures, and brain disorders [31].

Both genetic and environmental factors also contribute to healthy aging and frailty. A recent twin study in the UK [37] examined the contribution of genetic and environmental factors to frailty using the *frailty index* in 3375 adult twins (840 monozygotic and 802 dizygotic full twin-pairs and 91 singletons) aged 40–84. Approximately 45% of the inter-individual variation in the *frailty index* was attributable to additive genetic factors, and 52% was due to the individual's unique environment. More studies are needed to elucidate the potential mechanisms that mediate the relationship between genes and environmental factors, for instance, whether or not they induce epigenetic modifications related to healthy aging.

Social Determinants of Healthy Aging

Socioeconomic status (SES) and education are associated with lifestyle choices that are important for healthy aging [12]. For instance, both SES and education affect the place a person lives and the number of chronic stressors that will challenge their allostatic load regularly [38]. They also impact access to healthcare and quality of care when dealing with illness (described in more detail below) [39]. Individuals with higher SES are more likely to live in mentally and physically stimulating environments. That is important because cultural resources may impact cognitive and social function, and green spaces and exercise facilities may enhance physical activity and help maintain physical capability. All of these factors contribute to significantly better health and lower risk for developing chronic illness. In

contrast, individuals on lower SES experience more neighborhood insecurities and economic instability, are less likely to afford healthy diets, and have access to fewer recreational options. These circumstances can lead to unhealthy lifestyle behaviors and higher morbidity, disability, and mortality rates than their counterparts at the higher end of the SES spectrum, ultimately contributing to health disparities [40].

People in vulnerable situations experience greater chronic, survival-related stress. Over time, it is detrimental to mental and physical health. Longitudinal studies have revealed strong associations between the stress-activated physiological pathways of chronic disease and SES-related measures [41, 42]. A lower income is correlated with elevated levels of cortisol throughout the lifespan [43-45]. High cortisol levels can contribute to other metabolic alterations, including changes in high-density lipoprotein (HDL), low-density lipoprotein (LDL), and fasting insulin and glucose levels, as well as cardiovascular disease incidence and risk factors (body mass index and waist circumference). All of these are widely used measures to assess the relationship between SES and cardiometabolic dysregulation. Acute-phase proteins such as C-reactive protein—a protein linked to inflammation, infection, and developing tissue damage and heart disease—are among the most common inflammation markers studied in association with SES [46]. The Chicago Community Adult Health Study showed that low neighborhood density and high neighborhood walkability were associated with lower C-reactive protein concentrations in adults of all ages [47]. These results suggest that aspects of densely populated neighborhoods (e.g., sleep-disturbing noise, pollution) may impact health over time [47]. This study also found that neighborhood affluence is associated with fewer biological risk factors for chronic diseases, such as high blood pressure and elevated cholesterol levels, after adjusting for individual-level social and economic background, suggesting the environment an individual currently lives in impacts health the most [48].

Social inequalities, including education, SES, and living environment, have arisen among historically disadvantaged groups. The aftermath of violence against specific racial and ethnic groups, namely colonization and slavery, continues to have long-term political, social, and economic effects on these populations. Black and brown individuals of Indigenous and African descent, primarily those residing in countries with a history of racial and ethnic discrimination, have worse health access and worse health outcomes in comparison to those whose ancestors were unaffected or benefitted from these violent historical events. Despite changes in political structures set in place to prevent racial discrimination; racial bias, microaggressions, and even overt racism perpetuate health disparities in Black and indigenous communities. Continuous exposure to racial discrimination has been associated with a decreased overall estimated life expectancy. Research has shown that the additive effects of stress caused by perceived racial discrimination may elicit epigenetic aging acceleration measured by DNA methylation [49, 50]. Beyond daily life stress associated with social class, discrimination, and resource scarcity, exposure to traumatic events during early life may trigger similar stress responses detrimental to a person’s health through adulthood. *Adverse childhood experiences (ACEs)* are characterized by traumatic events occurring during childhood; these may include verbal, physical, and sexual abuse inflicted on the individual or a parental figure, parental substance abuse, incarceration of a household member, and parental separation. Adults who have reported having three or more ACEs

are estimated to have approximately a 9-year reduction in quality-adjusted life expectancy (QALE) [51]. Also, ACEs increase the likelihood of developing alcohol and substance abuse and other mental illnesses later in life [52].

Older adults with higher *education* levels tend to be in better health, more frequently report higher life satisfaction and interest in life and well-being, and are more socially engaged [53]. In many world regions, obstacles to access basic education persist. Women suffer these educational disparities more than men and still struggle to attain a basic education level [54, 55]. A direct relationship between vulnerability and educational attainment has been controversial since education is also associated with income, self-efficacy, and comorbidities [56, 57]. Pendersen et al. [58] reported that one unit increase of education was associated with lower C-reactive protein (CPR), suggesting that having more education may reduce the allostatic load. Also, the occupational prestige gained with education was associated with lower CRP. On the other hand, the Coronary Artery Risk Development in Young Adults (*CARDIA*) study showed that lower educational levels are associated with higher cortisol levels in middle life [44]. These allostatic load changes related to education could mediate an individual's vulnerability to disease later in life.

Recent work by Huibregtse et al. [59••] studied 7064 participants from the Health and Retirement Study. The authors showed a strong negative association between educational attainment polygenic scores (EA-PRSs) and two indices of frailty, a deficit accumulation model and a physical phenotype. The association of EA-PRS exists above and beyond actual years of completed education and becomes weaker as older adults approach their 80 s. In a separate study, Atkins et al. [28] used Mendelian randomization to show that a higher educational attainment genetic risk score was causally associated with a lower risk of frailty. Furthermore, educational attainment has been linked to telomere length as a proxy for cellular aging. Data from the *Health, Aging, and Body Composition Study* in the USA showed that individuals with high school education had significantly shorter mean telomere length than those with post-high school education [60]. Individuals with shorter telomeres are more vulnerable to adverse outcomes and less likely to age healthily. The direction of causality for this relationship is not known and it should be investigated.

Lifetime *healthcare access* contributes to healthy aging by preserving an individual's function and increasing resilience. Adequate medical care can prevent adverse outcomes and sequelae that could increase the individual's vulnerability over time [61]. Also, access to prevention and rehabilitation services is essential to promote optimal human functioning and healthy aging [62]. Reduced access to healthcare leads to increased morbidity, which leads to decreased ability to work and increased poverty, which further reduces access to care [63], exacerbating vulnerability to adverse outcomes, including death. Conversely, even for individuals who have a high morbidity burden, the cumulative effect of having good access to healthcare and reasonable disease control increases the individual's resilience and the possibility of healthy aging [61].

Lifestyle Factors

A crucial element for healthy aging is a healthy lifestyle. Individuals living healthy not only survive longer but live longer in better health, with less disability and morbidity [53, 64]. Nutrition and exercise modulate the aging process and risk for age-related diseases. Research in this area has been challenging because of the lack of reliable dietary and exercise assessment methods, especially in elderly and diverse populations. Biological hallmarks such as telomere length, epigenetic clocks, and dysregulated nutrition sensing have helped us look at the relationship between nutrition and aging through a new lens [19].

The molecular “epigenetic clock” has shown that chronological age profoundly affects DNA methylation levels [65]. Epigenetic age acceleration is broadly defined as the epigenetic age left unexplained by chronological age. The terms intrinsic and extrinsic denote additional modifications to this concept depending on whether the measurement is affected by blood cell counts or not, respectively. Quach et al. studied extrinsic and intrinsic epigenetic age acceleration in more than 4000 subjects from the Women’s Health Initiative and the InCHIANTI Italian cohort. Intrinsic epigenetic age acceleration was negatively associated with fish intake, moderate alcohol consumption, and blood carotenoid levels—an indicator of fruit and vegetable consumption. Extrinsic epigenetic age acceleration showed a positive correlation with BMI [66]. An elevated BMI [67], insulin resistance [68], and cardiovascular disease [69] are related to oxidative stress and inflammation that affect telomerase activity, shortening the lifespan. These results show that food could influence healthy aging through the type of food and the consumed amount. Notably, radical interventions to lose weight, such as bariatric surgery, can cause recovery in telomere length [70].

Some of the recommended dietary interventions that aim to prevent disease and allow healthy aging might be more successful in individuals with specific genotypes. The Coronary Diet Intervention with Olive Oil and Cardiovascular Prevention (CORDIOPREV) study showed that the telomerase RNA component (TERC) rs12696304 interacts with monounsaturated fatty acids, modulating inflammation and telomere attrition related to coronary heart disease. Among individuals with monounsaturated fatty acid levels above the median at baseline, those with the C/C genotype had higher lymphocyte telomere length and lower high-sensitivity C-reactive protein levels than G allele carriers. Also, habitual consumption of a Mediterranean diet in individuals with the C/C genotype had a more significant decrease in high-sensitivity C-reactive protein than G allele carriers [71]. In addition to telomere length, other Mediterranean diet contents such as lower content of animal protein and lower glycemic index might modulate the insulin/IGF-1 or the mTOR pathways leading to the activation of FOXO3A and, consequently, to the transcription of homeostatic genes that favor longevity. Also, downregulation of both IGF-1 and mTORC1 induces an anti-inflammatory effect [72].

Physical activity triggers the activation of metabolic pathways, has protective properties against several age-related diseases, and is associated with increased quality of life. In contrast, a lack of physical activity or sedentary behavior is a significant risk factor for chronic illnesses. Individuals who engage in physical activity have lower mortality rates than those who are sedentary. In a meta-analysis of 23 longitudinal cohorts, Daskalopoulou et al.

[73] found a positive association between physical activity and healthy aging. Individuals engaging in physical activity had higher odds of living a healthy life in older age than less active participants. One of the responsible mechanisms might be related to the endothelium-derived hyperpolarizing factors, which act through K^+ channels, regulate blood flow, and are essential to vascular health. Healthy active older adults have enhanced K^+ channel–dependent endothelial vasodilatory mechanisms, suggesting increased responsiveness to endothelium-derived hyperpolarizing factors [74].

Sleep is also a part of the lifestyle factors that decrease frailty improving healthy aging. A study in the Rugao Longevity and Aging Study (RuLAS) in Jiangsu, China, investigated associations between sleep disturbances with frailty and pre-frailty states in 1726 people aged 70–87 [75]. Low *sleep quality* was associated with higher odds of frailty (*OR* = 1.78, 95% *CI* 1.19–2.66). Interestingly, longer sleep duration (> 9 h per night) was also associated with frailty and pre-frailty states [75]. A study in Ashkenazi Jewish centenarians from the Longevity Genes Project studied sleep patterns in 348 centenarians with preserved cognition, their offspring (513 adults, median age 69 years), and 199 controls age-matched to the offspring [76]. At age 70, centenarians were more likely to have slept more than 8 h (55%) and have napped (28%) than offspring and controls. Interestingly, they observed no association between sleep patterns and health outcomes among centenarians. Although the authors reported no significant differences in sleep patterns between offspring and controls, children of centenarians were less likely to present age-related diseases, suggesting inheritance of resilience genotypes from their centenarian parents [76].

Mental Health and Psychological Factors

Subjective well-being (SWB) is the practice by which people evaluate their own life experiences [77]. In recent years, research in psychology has prompted a paradigm shift where there has been a growing interest in understanding social and environmental factors influencing wellness [78]. Traditionally, psychology has focused on understanding pathological features of mental illness. However, a new wave of research centering on possible avenues for preventative care interventions has urged interdisciplinary approaches to understand the many domains by which subjective well-being is defined. Furthermore, biological and epidemiological studies have identified associations between SWB and different biomarkers of the aging body, suggesting SWB as an important element for healthy aging [79-82].

SWB can be divided into two main categories, hedonic (HWB) and eudaimonic (EWB) well-being. HWB refers to feelings surrounding the absence of pain and pleasure attainment, while EWB relates to feelings associated with self-realization, meaning, and purpose [83, 84]. These two features of SWB have been associated with biological mechanisms believed to contribute to overall physiological wellness. Positive affectivity elements from HWB show an association with mortality measured by day-to-day positive mood levels, where those with higher positive affect can show up to 50% mortality risk reduction [85]. Under eudaimonic well-being, a sense of *purpose in life* is hypothesized to act as a modulator for stress activation response, promoting faster recovery after exposure to stress [86]. Among

older adults, those with a high self-reported sense of *purpose in life* show a reduced risk of developing Alzheimer's disease than those at the lower ends of the spectrum [87].

There is substantial evidence that individuals who have clinical diagnoses across the entire spectrum of mental disorders have a shorter life expectancy than the general population [88]. Suicide accounts for 17% of mortality due to unnatural causes in this group [89, 90], but most of the years of life lost in people with mental illness are related to poor physical health, in particular, due to comorbid chronic and infectious diseases [91-95].

Frailty and *depression* in late life are highly correlated. Lohman et al. [96] used data from the 2010 Health and Retirement Study, which included 3453 community-dwelling participants aged 65 and older, to estimate correlations between depression and frailty. Three alternative conceptual models were used to index frailty: (a) biological syndrome, (b) frailty index, and (c) functional domains. The correlations between depression and frailty ranged from 0.61 to 0.70 and between 0.45 and 0.56 after accounting for shared symptoms between depression and frailty models. Stress and depression have also been implicated in telomere biology, accelerated aging, and associated age-related diseases, including metabolic disorders and dementia. Boccardi and Boccardi recently published a mini literature review on conceptual models of healthy and active aging and their relationship with telomere biology and mental health [97].

Older people with chronic illnesses show increased levels of depressed mood and impaired well-being [82]. Subjective well-being and physical health are related bidirectionally and affect the aging process, with better well-being having a protective role in health maintenance [82]. The role of individual components of well-being such as life satisfaction, positive affect, and negative affect has been studied in relation to longevity. Gana et al. [98] used longitudinal data from 3777 people aged 62–101 from the PAQUID cohort to identify longevity predictors. Only positive affect was associated with longevity, even after adjusting for prior medical conditions, functional status, and self-rated health.

From developmental stages to older age, intrapersonal interactions are crucial for survival. Social connections can influence health-altering lifestyle behaviors, impact mental health, and provide safety from environmental threats. Meta-analytic reports have shown significantly increased survival rates among those with strong social relationships across all ages [99]. Similarly, *loneliness*, defined by a lack of social interactions, has also been linked to morbidity and mortality rates in adult populations, showing an increased risk of death and chronic illness among lonely people [100]. Although there is not a precise biological mechanism by which loneliness affects physical health, a higher cortical amyloid burden has been detected among lonely older adults in a previous study [101].

Taken together, the above evidence suggests that subjective well-being, depression, loneliness, and having a life purpose may influence healthy aging and longevity. However, the precise mechanisms are yet to be elucidated.

Blue Zone Populations

Blue Zones are global regions where people reach age 100 at ten times greater than the US average. People in these areas not only live longer but also healthier lives. These areas are Loma Linda, CA, USA; Nicoya, Costa Rica; Sardinia, Italy; Ikaria, Greece; and Okinawa, Japan. These populations share some commonalities regarding social determinants of health. The environment in which healthy agers spend about 90% of their lives is within 5 miles of their home. In these areas, known as the "Life Radius," individuals are at a walkable distance from the places where they work, get food, socialize, and exercise their faith. These environments enable the possibility to walk wherever is needed, keeping inhabitants of these regions continuously moving without them having to think about it [18, 102]. Inhabitants of Blue Zone populations have a strong sense of purpose in life. For example, Okinawans have the concept of *ikigai*, a sense of purpose that results in personal fulfillment and is embodied by the sense of "having a reason to jump out of bed each morning." In addition, it is also crucial for long-lived, healthy agers to have a sense of belonging to a community, satisfactory family bonds, and strong, long-lasting friendships and support networks.

Despite overall healthy aging, disparities within Blue Zone populations do exist. For example, studies showed that Sardinian and Ikarian men had fewer depressive symptoms and better mental well-being than women [18, 102, 103]. Cultural reasons could explain these gender effects. For example, for Sardinians, overcoming societal pressure to control impulsive emotional expression was crucial for developing resilience in women. Conversely, the development of prosocial behaviors curbing aggression was crucial in men [103]. Of notice, all Blue Zone populations are very homogeneous societies. As a result, there are reduced opportunities for being discriminated against due to racial, SES, or religious reasons. Socialization and routines that shed life stress for the inhabitants of Blue Zones are important. Okinawans take a few moments each day to remember their ancestors; Adventists in Loma Linda pray; Ikarians take a nap; and Sardinians do happy hour [18, 102]. Regarding diet, there are two rules. The first rule is to eat 80% of the amount that makes them feel full during the day, and eat their smallest meal in the late afternoon or early evening [18, 102]. The second rule is that the diet is mostly plant-based. The dominant dietary model among the elderly of Nicoya and Sardinia is a plant-based diet (cereals followed by legumes and fruit), complemented by a non-negligible consumption of animal products (pork meat) and dairy products. More than 85% of the Nicoyans and more than 75% of the Sardinians drink coffee daily [104]. Coffee and tea drinking, fruit intake, and exclusive olive oil use were inversely associated with CVD and death in the Ikarian population [105]. Also, moderate wine drinkers outlive nondrinkers and reduced the number of cardiovascular diseases [18, 102].

Conclusions

In summary, healthy aging represents the life-long ability to physiologically adapt to intrinsic and external stressors to minimize frailty in aging and maximize resilience in older age. The continuum of allostatic load represents a combination of genetic and environmental factors that can, in some cases, have life-long consequences. There are numerous molecular, physical, objective, and subjective measures of healthy aging and well-being, though

whether these play causal roles versus merely proxy underlying biological phenomenon contributing to optimal homeostasis during aging remains to be determined. Healthy aging, epitomized by Blue Zone populations, is observed globally; these populations share common traits including strong life purpose, daily physical and social activity, life-long community engagement, and diets rich in plant products. However, another commonality of Blue Zone populations is homogeneity, since discrimination and exclusion are less likely in these contexts. That is in stark contrast to environments with long-standing social inequities across racial, ethnic, gender, lifestyle, religious, or political groupings, where disparities are exacerbated by additional social determinants of health, including reduced access to education and employment, lower SES, greater chronic stress due to discrimination, food scarcity, environmental hazards, pollution, and adverse childhood events. Chronic stressors increase the allostatic load, reducing overall resilience and increasing the risk for mental illness and age-related disease. Thus, to promote healthy aging across all global populations, it is paramount that we enhance our biological understanding of the drivers of resilience while simultaneously undoing the social barriers that underlie chronic stress leading to frailty.

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