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Longevity and aging: An integrative perspective on genetic, epigenetic, microbial, and lifestyle interactions

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Aging is a multifactorial biological process influenced by genetic, epigenetic, environmental, and lifestyle factors. Despite advances in biomedical research, the mechanisms determining human longevity and healthy aging remain insufficiently understood. This review aims to analyze key biological mechanisms of aging in relation to lifestyle, environmental, and socio-cultural factors that contribute to lifespan regulation. This narrative review summarizes current data on the nine established hallmarks of aging proposed by López-Otín et al. and their systemic manifestations across major organ systems. Particular attention is given to sex-related differences in aging trajectories, including hormonal, metabolic, and immune characteristics. The influence of modifiable lifestyle factors is assessed, with emphasis on physical activity and dietary patterns associated with increased longevity. A comparative analysis of the Mediterranean, Okinawan, and Azerbaijani diets reveals common protective features, including anti-inflammatory properties, a balanced micronutrient composition, and metabolic resilience. Additionally, emerging evidence on the role of the gut microbiome in aging processes is briefly discussed. The integrated analysis presented in this review highlights the importance of combining biological and lifestyle-based approaches in the development of strategies aimed at promoting healthy aging and extending healthspan.

Keywords: *Aging, longevity, epigenetics, gut microbiome, oxidative stress, gene–environment interaction*

1. INTRODUCTION

The global demographic shift toward an aging population has brought unprecedented attention to the biological, social, and environmental determinants of aging and longevity. As life expectancy continues to increase, understanding the mechanisms that promote not only lifespan but also healthspan has become a key priority in biomedical research. Aging is a complex, multidimensional process that affects all levels of biological organization from molecular pathways to systemic physiology and is further modulated by cultural and environmental contexts (Li et al., 2024; Moskalev et al., 2017).

The study of longevity, particularly exceptional longevity (individuals aged 95 and older), poses unique challenges and opportunities. Recent advances in molecular biology, genetics, and systems medicine have provided insights into the cellular and biochemical foundations of aging. However, longevity is not solely the product of genetics; it results from a dynamic interplay between inherited traits, epigenetic modifications, gut microbiome composition, lifestyle behaviors, and broader sociocultural factors (Anstey et al., 1993; Berger, 2005). This variability is reflected in the biological age differences observed among individuals with similar chronological ages.

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This review aims to provide a comprehensive overview of the current understanding of human aging, integrating findings from molecular biology, genetics, epigenetics, microbiome studies, and population-based research. By highlighting both universal mechanisms and population-specific patterns, we emphasize the necessity of an interdisciplinary, personalized approach to studying aging and promoting healthy longevity.

1.1. Objective of the review

The primary aim of this review is to provide an integrative overview of the current understanding of human aging and longevity by synthesizing insights from molecular biology, genetics, epigenetics, microbiome science, and population-level studies. The review seeks to highlight both universal and population-specific mechanisms of aging and to advocate for personalized approaches to healthspan extension. Special focus is placed on the impact of diet, the gut microbiome, sex-specific biology, and cultural practices on healthy longevity.

1.2. Methodology

This review is based on a comprehensive analysis of interdisciplinary literature published over the past decade (2014-2024) from databases such as PubMed, Scopus, Web of Science, and Google Scholar. The sources include original research articles, systematic reviews, meta-analyses, and official reports from the World Health Organization (WHO). The following areas were prioritized:

- Molecular and cellular mechanisms of aging;
- Genetic and epigenetic determinants of longevity;
- Structure and function of the gut microbiome;
- Traditional dietary patterns (Mediterranean, Okinawan, Azerbaijani);
- Sex-based differences in aging;
- Psychosocial and cultural contributors to healthy aging.

Additionally, the review incorporates data from longitudinal cohort studies (e.g., Long Life Family Study, Danish Twin Study) and research on centenarian populations from Sardinia, Okinawa, and the South Caucasus, especially rural Azerbaijan. The methodology emphasizes an interdisciplinary and comparative approach to uncovering common and divergent pathways to exceptional longevity.

2. MECHANISMS OF AGING

2.1. Primary and secondary aging

Aging has traditionally been conceptualized as comprising two interrelated processes: primary aging, which refers to intrinsic, genetically programmed biological changes; and secondary aging, which results from the interaction of these intrinsic changes with environmental exposures, lifestyle, nutrition, and disease processes. This distinction was first articulated by Busse et al. in 1969 and has since evolved into more nuanced frameworks. For instance, the World Health Organization (2019) differentiates between intrinsic capacity the biological trajectory shaped by primary aging and functional ability, which reflects the role of external influences on aging outcomes (Levant et al., 2015).

2.2. The hallmarks of aging

A major milestone in the conceptualization of aging at the cellular level was the proposal of the nine hallmarks of aging by López-Otín et al. in 2013. These hallmarks represent a set of interconnected biological processes that collectively drive age-related functional decline:

1. Genomic instability
2. Telomere attrition
3. Epigenetic alterations
4. Loss of proteostasis
5. Deregulated nutrient sensing
6. Mitochondrial dysfunction
7. Cellular senescence
8. Stem cell exhaustion
9. Altered intercellular communication

Building upon this framework, Andrew Steele (2020) and David Sinclair (2019) have further expanded the concept by emphasizing the role of the gut microbiome as a tenth hallmark, recognizing its influence on immune modulation, metabolic regulation, and neuroinflammatory processes (National Institutes of Health, 2011; National Council on Aging, 2019; National Institutes of Health, 2016; National Institute of

Arthritis and Musculoskeletal and Skin Diseases, 2014; Shokri-Kojori et al., 2018; Strine et al., 2005; Remond et al., 2015; Christina et al., 2021).

These hallmarks serve not only as descriptors of aging but also as potential targets for intervention. Understanding and modulating these mechanisms through diet, pharmacological agents, or lifestyle modifications holds the key to delaying aging and preventing age-related diseases.

3. SYSTEMIC PHYSIOLOGICAL CHANGES IN AGING

Aging is accompanied by progressive functional decline across multiple organ systems, driven by cumulative molecular and cellular damage. These changes are not uniform and are influenced by both intrinsic genetic factors and extrinsic environmental exposures. Below, we summarize key age-related physiological alterations by system.

3.1. Digestive system (Liu et al., 2023; Ogrodnik et al., 2024)

With advancing age, the gastrointestinal (GI) system undergoes structural and functional modifications. Gastric acid secretion and production of digestive enzymes such as pepsin decrease, impairing protein digestion and absorption of micronutrients like vitamin B12, iron, and calcium. Mucosal atrophy in the stomach and intestines reduces nutrient absorption, while decreased GI motility contributes to constipation, dyspepsia, and gastroesophageal reflux disease (GERD). Altered neuromuscular coordination and reduced sensitivity of baroreceptors further slow peristalsis. Importantly, the aging gut microbiome becomes less diverse and more prone to dysbiosis, promoting inflammation and compromising intestinal barrier integrity.

3.2. Immune system (Ghosh et al., 2022; Lee et al., 2022)

Aging is associated with immunosenescence, characterized by diminished function of T and B lymphocytes, reduced antibody production, and impaired immune memory. Concomitantly, inflammaging a state of chronic, low-grade systemic inflammation emerges due to overactivation of innate immunity and elevated levels of pro-inflammatory cytokines such as IL-6, TNF-α, and CRP. This inflammatory milieu contributes to increased susceptibility to infections, decreased vaccine efficacy, and higher risk of cardiovascular disease, type 2 diabetes, cancer, and neurodegenerative disorders. Additional impairments include reduced interferon signaling, diminished macrophage phagocytosis, and decreased activity of natural killer (NK) cells.

3.3. Gut microbiome (Blinkouskaya et al., 2021)

The gut microbiota plays a central role in metabolic regulation, immune homeostasis, and gut-brain communication. Aging is accompanied by a decline in microbial diversity and an increase in pathobionts, particularly Proteobacteria. These changes reduce the production of short-chain fatty acids (SCFAs) such as butyrate, which are crucial for maintaining anti-inflammatory tone and gut barrier integrity. Aged microbiomes also exhibit reduced abundance of bacteria involved in vitamin B12 and vitamin K synthesis, further impairing host nutrient status. Disruptions in gut-brain and gut-liver axes contribute to cognitive decline, mood disorders, and systemic metabolic disturbances.

3.4. Central Nervous System (CNS) (Yilmaz et al., 2024; Spanoudaki et al., 2023)

Aging of the CNS includes brain atrophy, reduction in neuronal and synaptic density, and deterioration of dendritic architecture. Neurotransmitter signaling slows, particularly in the dopaminergic and cholinergic systems, contributing to memory deficits, reduced processing speed, and attentional impairments. Myelin integrity diminishes, and cerebral perfusion declines. Structural changes are most pronounced in the hippocampus, prefrontal cortex, and cerebellum. Chronic neuroinflammation, along with accumulation of β-amyloid and tau protein, increases the risk for Alzheimer's disease. Nevertheless, neuroplasticity and cognitive stimulation offer potential for slowing age-related cognitive deterioration.

3.5. Musculoskeletal system (Donato et al., 2018; Ahmed et al., 2024)

Key features of musculoskeletal aging include sarcopenia the progressive loss of muscle mass and strength alongside osteoporosis and osteoarthritis. Sarcopenia results from reduced muscle fiber size and number, anabolic resistance to dietary protein, and declines in growth hormone (GH), IGF-1, and testosterone. These changes compromise mobility, increase fall risk, and reduce quality of life. Bone demineralization due to vitamin D deficiency, decreased calcium absorption, and physical inactivity leads to fragility fractures. Osteoarthritis involves cartilage degradation, joint inflammation, and pain, further limiting mobility and independence.

3.6. Cardiovascular system (Allshouse et al., 2018; Bin-Jumah et al., 2022)

Aging-related cardiovascular changes include arterial stiffening, endothelial dysfunction, and increased vascular resistance. These changes result in elevated systolic and reduced diastolic blood pressure. Endothelial cells produce less nitric oxide (NO), impairing vasodilation and promoting smooth muscle proliferation factors that facilitate atherosclerosis. The aging myocardium becomes more fibrotic and exhibits reduced β-adrenergic responsiveness, compromising both systolic and diastolic function. Cardiac reserve decreases, and risks of heart failure, ischemic heart disease, and arrhythmias (particularly atrial fibrillation) increase substantially with age.

3.7. Reproductive system (Singh et al., 2019)

In women, reproductive aging culminates in menopause, marked by cessation of ovulation and a steep decline in estrogen and progesterone levels. This hormonal shift leads to ovarian atrophy, loss of bone density, dyslipidemia, and elevated risk of cardiovascular disease. Estrogen deficiency also alters vaginal microbiota, increasing susceptibility to urogenital infections and mucosal dryness. In men, a gradual decline in testosterone levels termed andropause leads to decreased libido, erectile dysfunction, muscle atrophy, and reduced bone mineral density. Aging also affects sperm quality, including motility and morphology, potentially reflecting both hormonal and epigenetic alterations.

4. GENETICS AND GENE–ENVIRONMENT INTERACTIONS IN LONGEVITY (Ang et al., 2008; Passarino et al., 2016; Aguado et al., 2020; Cisneros et al., 2022; Pemmasani et al., 2024; Wang et al., 2022; Evangelina et al., 2025)

4.1. Heritability and genetic architecture of longevity

Human longevity has a moderate genetic component, with heritability estimates ranging from 20% to 30%, increasing in cases of exceptional longevity (individuals ≥95 years). Large-scale family-based studies, such as the Long-Life Family Study (LLFS), have shown that offspring of long-lived individuals have lower rates of age-related diseases and improved metabolic profiles compared to age-matched controls. These findings support the notion that genetic predisposition plays a significant role in healthy aging.

Genetic variants associated with longevity include polymorphisms in genes related to lipid metabolism (e.g., APOE, CETP), insulin/IGF-1 signaling (e.g., FOXO3A), DNA repair, inflammation, and oxidative stress resistance. For example, FOXO3A, a transcription factor involved in stress resistance and metabolic homeostasis, is one of the most consistently replicated longevity-associated loci across populations.

4.2. Assortative mating and genetic nurture

Beyond traditional inheritance, assortative mating the tendency of individuals to select partners with similar cognitive, behavioral, and health-related traits may contribute to the enrichment of longevity-promoting alleles within families. These shared traits may be partially heritable and influenced by common environments, leading to cumulative effects on offspring health.

The concept of genetic nurture further complicates the genetic landscape. It suggests that even non-transmitted alleles in parents can influence offspring development via the environment they create, such as diet, education, or health behaviors. This highlights the need to consider both genetic and environmental

transmission in studies of heritability.

4.3. Population-specific genetic pathways

Comparative studies across populations have demonstrated that the molecular pathways underlying longevity may vary between groups, even when the phenotypic outcome is similar. For example, while FOXO3A is associated with longevity in both Japanese and European populations, other variants appear to be population-specific. Studies in Sardinia, Okinawa, and China have identified distinct longevity-associated loci, shaped by demographic history, migration patterns, and local adaptation.

This supports the concept of "convergent phenotypes" similar longevity outcomes achieved through different genetic and environmental mechanisms. One compelling example is the TCF7L2 polymorphism, associated with increased type 2 diabetes risk, whose effects are attenuated by adherence to a Mediterranean diet an illustration of gene-environment (G×E) interaction.

4.4. Early-life environment and epigenetic inheritance

Socioeconomic conditions during early life can profoundly influence lifespan, in part through epigenetic modifications such as changes in DNA methylation and histone modification patterns. These environmentally induced epigenetic marks can persist into adulthood and even be transmitted across generations.

For instance, famine exposure during prenatal development such as in the Dutch Hunger Winter or Korean War famine cohorts has been linked to increased risk of metabolic diseases and shorter lifespan in subsequent generations. Similarly, data from Estonia show that social inequality modulates the expression of cognitive and behavioral traits, demonstrating the plasticity of gene expression in response to cultural context.

5. EPIGENETICS AND THE GUT MICROBIOME IN THE REGULATION OF LONGEVITY

5.1. Epigenetic regulation of aging (La Torre et al., 2023; Wilmanski et al., 2021; Dattani et al., 2023)

Epigenetics refers to heritable but reversible modifications of gene expression that do not alter the DNA sequence. Key epigenetic mechanisms involved in aging include DNA methylation, histone modifications, and non-coding RNA regulation, all of which contribute to the control of gene expression programs related to inflammation, metabolism, and cellular stress responses.

Recent studies have led to the development of epigenetic clocks, such as those proposed by Horvath and Hannum, which measure biological age based on DNA methylation patterns. These clocks often predict biological aging and mortality risk more accurately than chronological age, highlighting their utility in geroscience and precision medicine.

Importantly, environmental exposures such as nutrition, stress, pollution, and physical activity can influence the epigenome, making it a powerful interface for gene–environment interactions. For instance, caloric restriction and polyphenol-rich diets have been shown to delay epigenetic aging in both animal models and humans.

Furthermore, because epigenetic modifications are reversible, they offer a promising target for therapeutic interventions aimed at modulating aging trajectories and reducing the risk of age-related diseases.

5.2. The aging gut microbiome (Austad et al., 2016; Zarulli et al., 2024)

The gut microbiome is a dynamic and complex ecosystem that plays a critical role in maintaining immune homeostasis, metabolic function, and neurological signaling. With age, the microbiota undergoes a shift characterized by reduced diversity, lower abundance of beneficial commensals, and increased pro-inflammatory taxa, such as members of the phylum Proteobacteria.

These compositional changes lead to:

- decreased production of short-chain fatty acids (SCFAs) like butyrate, essential for colonocyte energy metabolism and anti-inflammatory signaling;
- compromised gut barrier integrity and increased intestinal permeability (“leaky

gut");
- disruption of the gut-brain axis and gut-liver axis, with consequences for mood, cognition, and systemic inflammation.

Remarkably, centenarians and other long-lived individuals have been found to possess unique microbiome profiles, often enriched in SCFA-producing bacteria such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*. These profiles are associated with lower systemic inflammation and better metabolic resilience.

Lifestyle factors such as diet, exercise, prebiotic/probiotic intake, and exposure to antibiotics significantly shape the microbiome. Longitudinal studies suggest that microbiota stability and diversity in old age are associated with improved physical and cognitive function, further reinforcing its role as a modifiable factor in healthy aging.

6. SEX DIFFERENCES IN LONGEVITY (Aithken, 2023; Kaufman et al., 2019)

Across virtually all human populations, women consistently outlive men, both in average and exceptional longevity. While environmental improvements and behavioral factors have contributed to this disparity, biological sex differences play a central role in shaping the trajectories of aging and disease susceptibility.

6.1. Hormonal protection and oxidative stress

One of the most well-studied biological mechanisms behind female longevity is the protective effect of estrogens. Estrogens enhance the expression of antioxidant genes, improve mitochondrial efficiency, and reduce reactive oxygen species (ROS) production. In contrast, men experience greater mitochondrial oxidative stress, contributing to accelerated aging of various tissues.

Estrogens also modulate both innate and adaptive immunity, enhancing humoral responses and suppressing pro-inflammatory cytokine production. These immunomodulatory effects contribute to lower susceptibility to infectious and inflammatory diseases in premenopausal women.

6.2. Menopause and post-reproductive aging

Despite their longevity advantage, women undergo a sharp hormonal transition at menopause, which marks the end of reproductive capacity and leads to a range of physiological changes. Estrogen deficiency following menopause contributes to:

- loss of bone mineral density (osteoporosis);
- dysregulation of lipid metabolism, increasing cardiovascular risk;
- urogenital atrophy and increased susceptibility to infections;
- changes in the vaginal and gut microbiome.

Given that women in developed countries now spend up to 50% of their lives postmenopause, understanding the long-term effects of sex hormones on aging is essential for developing gender-specific health interventions.

6.3. Male reproductive aging (Kassis et al., 2023)

In contrast to the abrupt cessation of female reproductive function, male aging is characterized by a gradual decline in testosterone levels, termed late-onset hypogonadism. This leads to reductions in muscle mass, bone density, libido, and spermatogenesis. Aging sperm exhibits increased DNA fragmentation and epigenetic alterations, which may affect offspring health and development.

Testosterone also plays a role in immune modulation, typically favoring pro-inflammatory pathways, which may contribute to higher male mortality from infections and cardiovascular diseases.

6.4. Behavioral and sociocultural factors

While biology accounts for a significant portion of the sex gap in longevity, lifestyle differences have historically widened this disparity. Men have been more likely to engage in risky behaviors, smoking, alcohol abuse, and occupational hazards, all of which elevate mortality risk.

In recent decades, as gender roles have shifted, some of these behavioral differences have diminished. Nevertheless, biological sex remains a critical variable in aging research and must be

considered in both basic and clinical studies.

7. LIFESTYLE, CULTURE, AND DIET IN AGING

A growing body of evidence highlights the modifiability of aging through lifestyle choices. Key behavioral factors including diet, physical activity, smoking, and alcohol consumption directly influence systemic inflammation, metabolic homeostasis, and cellular stress responses. Healthy lifestyle patterns are strongly associated with both increased healthspan and reduced risk of chronic diseases.

7.1. Caloric restriction and nutrient sensing

Experimental models have shown that caloric restriction (CR) especially protein restriction activates protective molecular cascades such as IGF-1, mTOR, FOXO, and AMPK pathways, enhancing cellular repair and reducing oxidative damage. These effects are conserved across species and are believed to delay aging and extend lifespan.

In human populations, CR-like effects are achieved through plant-rich, low-protein diets, particularly those high in fibers, polyphenols, omega-3 fatty acids, and complex carbohydrates.

7.2. The Mediterranean and Okinawan Diets

The Mediterranean diet, traditionally consumed in Southern Europe, is rich in olive oil, vegetables, legumes, nuts, whole grains, and includes moderate consumption of red wine (rich in resveratrol). This dietary pattern has been associated with reduced incidence of cardiovascular disease, metabolic syndrome, and cognitive decline.

Similarly, the Okinawan diet is low in calories and animal protein, but high in sweet potatoes, seaweed, soy-based products, and green tea. Okinawans also follow hara hachi bu a cultural practice of eating until 80% full which may contribute to metabolic efficiency and longevity.

7.3. Azerbaijani cuisine and cultural longevity

The Azerbaijani traditional diet, especially in rural and mountainous regions (e.g., Lankaran, Lerik), features several characteristics aligned with healthy aging:

- High consumption of fresh vegetables and herbs (parsley, coriander, dill, mint) rich in polyphenols and antioxidants;
- Frequent use of fermented dairy products, such as qatiq and ayran, which support gut microbiome diversity;
- Moderate intake of lean lamb and fish, alongside legumes (lentils, chickpeas) and grains (bulgur, rice);
- Traditional dishes like dovga (yogurt-herb soup) and plov (rice with vegetables, fruits, and herbs) combine complex carbs, fiber, and plant bioactives;
- Use of spices like turmeric and sumac, which have anti-inflammatory properties;
- Limited intake of refined sugars and processed foods, particularly in older generations.

Importantly, food in Azerbaijan is closely tied to social rituals, seasonal cycles, and family structures, all of which support mental well-being and community belonging factors also shown to protect against age-related decline.

Although comprehensive epidemiological studies are limited, observational reports from regions like Lerik, known for high numbers of centenarians, suggest a potential link between traditional dietary practices and healthy longevity. These findings warrant further scientific investigation within a cultural-longevity framework.

7.4. Physical activity and psychosocial factors

Regular physical activity, particularly low-intensity endurance exercise and resistance training, is associated with improved cardiovascular fitness, muscle mass preservation, and cognitive function in older adults. Populations with exceptional longevity often engage in daily physical labor, walking, gardening, and household activities well into advanced age.

Psychosocial factors such as purpose in life, social cohesion, and spirituality also significantly

impact aging. Cultures that promote intergenerational support, ritualized mealtimes, and respect for elders (as in Azerbaijan, Japan, and parts of the Mediterranean) provide psychological resilience and a sense of meaning, which are independently associated with lower mortality and cognitive decline.

8. CONCLUSION AND FUTURE DIRECTIONS

Human longevity is a complex, multifactorial phenotype shaped by the dynamic interaction of genetic, epigenetic, microbial, behavioral, and cultural factors. While intrinsic biological mechanisms such as genomic stability, mitochondrial function, and nutrient sensing underpin the aging process, it is the modulation of these mechanisms by environmental inputs that ultimately determines health outcomes in old age.

The concept of biological age, increasingly assessed through epigenetic clocks and microbiome composition, offers a powerful tool to move beyond chronological age as a predictor of health. Likewise, understanding gene–environment (G×E) interactions provide insight into why certain individuals or populations achieve exceptional longevity despite adverse conditions.

Evidence from global longevity hotspots including Sardinia, Okinawa, and traditional communities in Azerbaijan demonstrates that long life is often embedded in culturally coherent lifestyles, characterized by nutrient-rich diets, regular physical activity, strong social bonds, and psychological well-being. These findings highlight the need for population-specific, gender-sensitive, and culturally informed approaches in aging research and public health policy.

Future directions in the field of aging biology and longevity science include:

- Personalized geroprotective interventions based on individual genetic, epigenetic, and microbiome profiles;
- Development of epigenetic and metabolic biomarkers for early detection of age-related decline;
- Longitudinal studies exploring the impact of traditional dietary patterns and cultural environments on aging trajectories;
- Cross-cultural comparative research to better understand convergent longevity mechanisms across diverse populations.

Ultimately, extending healthspan the period of life free from major disease and disability requires a transdisciplinary effort that bridges molecular biology, population health, and cultural anthropology. As scientific knowledge continues to advance, integrating these dimensions will be crucial to designing effective strategies for active and healthy aging in diverse global contexts.

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CONFLICT OF INTEREST

The authors declare no conflict of interest related to this study.

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