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REVIEW

Factors involved in human healthy aging: insights from longevity individuals

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Abstract **The quest to decipher the determinants of human longevity has intensified with the rise in global life expectancy. Long-lived individuals (LLIs), who exceed the average life expectancy while delaying age-related diseases, serve as a unique model for studying human healthy aging and longevity. Longevity is a complex phenotype influenced by both genetic and non-genetic factors. This review paper delves into the genetic, epigenetic, metabolic, immune, and environmental factors underpinning the phenomenon of human longevity, with a particular focus on LLIs, such as centenarians. By integrating findings from human longevity studies, this review highlights a diverse array of factors influencing longevity, ranging from genetic polymorphisms and epigenetic modifications to the impacts of diet and physical activity. As life expectancy grows, understanding these factors is crucial for developing strategies that promote a healthier and longer life.**

Keywords longevity; centenarians; longevity factors; age-related diseases; long-lived individuals

Introduction

The pursuit of understanding and extending human longevity has been a cornerstone of biomedical research, driven by the global rise in life expectancy and the aging population. Over the past century, significant strides have been made in increasing the average lifespan, with a profound shift in the demographic landscape [1]. This increase in longevity is not merely a consequence of reduced early-life mortality; it also reflects a substantial reduction in age-related diseases and disabilities, particularly among individuals aged 70 years and above [2,3].

The complexity of aging and longevity is underscored by the intricate interplay of genetic, epigenetic, metabolic, immune, and environmental factors. This review paper delves into the biological underpinnings of aging, with a particular focus on the characteristics and factors associated with long-lived individuals (LLIs). These LLIs, who have surpassed the average life expectancy, offer a unique perspective for studying the phenomenon of healthy longevity [4–6].

LLIs, especially centenarians, demonstrate an exceptional capacity to delay the onset of age-related diseases and maintain higher levels of health, suggesting the presence of protective mechanisms that contribute to their longevity. This review synthesizes the current understanding of genetic polymorphisms, epigenetic modifications, metabolic profiles, immune responses, and environmental factors that have been associated with longevity (Fig. 1). Understanding the factors that contribute to longevity is not only academically intriguing but also has profound implications for public health and individual well-being. As we continue to unravel the mysteries of aging, the identification and validation of longevity-promoting factors hold the promise of enhancing healthy aging and extending the human health span.

Characteristics of LLIs

Definition of LLIs

Human longevity is characterized by an exceptional lifespan that exceeds the average life expectancy, which

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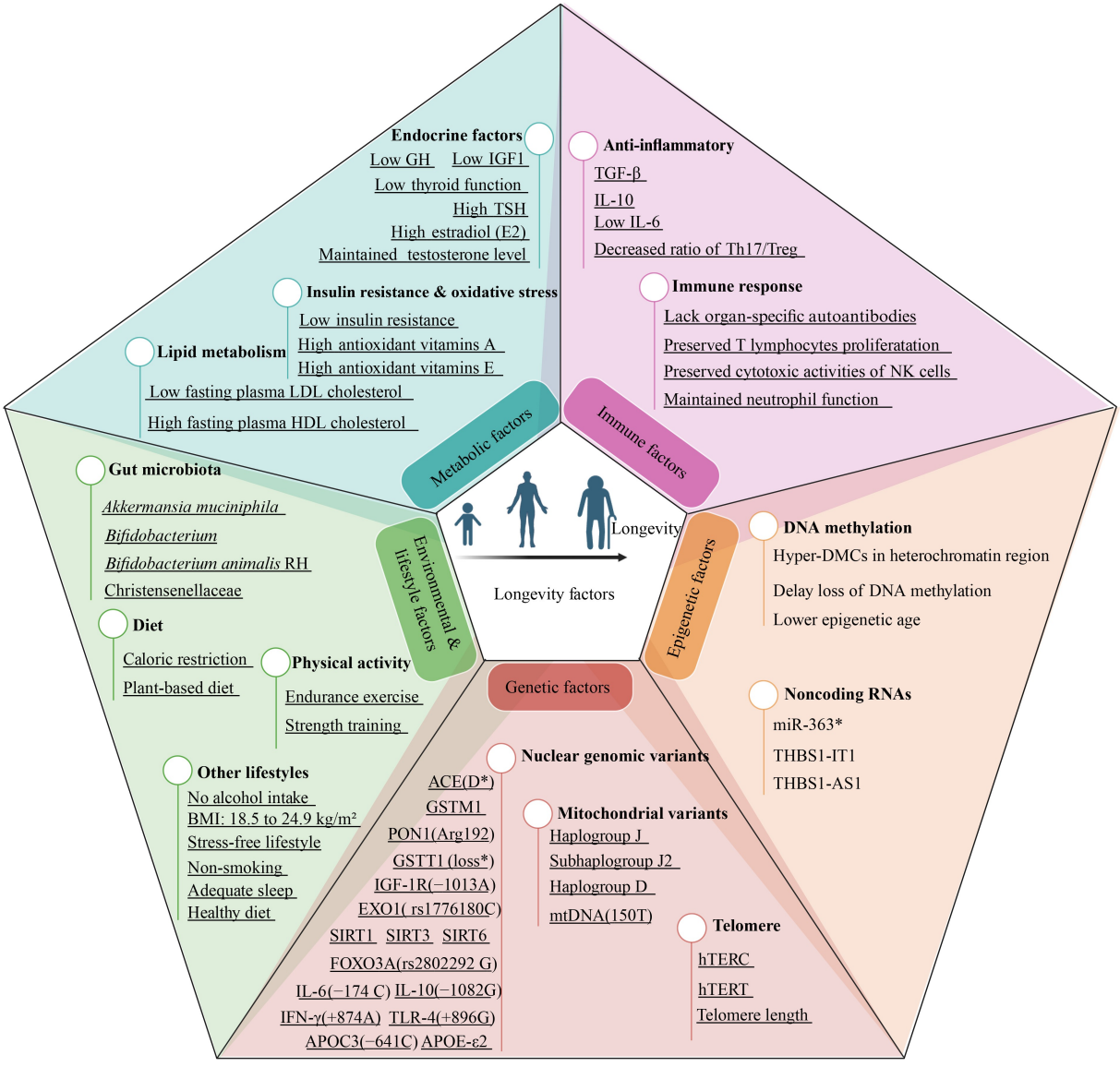

Fig. 1 A comprehensive overview of the multifactorial determinants of human longevity. This schematic diagram illustrates the complex list of genetic, epigenetic, metabolic, immune, environmental and lifestyle factors that contribute to human longevity based on studies of LLIs. ACE(D*) represents a deletion of 287 bp fragment in the ACE gene in chromosome 17. loss* represents alleles for loss of function in the corresponding gene. TGF-β, transforming growth factor β; IL, interleukin; Th17/Treg, T-helper 17/regulatory T cells; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TSH, thyroid-stimulating hormone; IGF1, insulin-like growth factor 1; GH, growth hormone; BMI, body mass index; NK, natural killer.

is approximately 71.8 years [7]. Generally, longevity is defined as survival to age 90 years or older [8,9]. Individuals aged 90+ years, often considered as representative of exceptional longevity, have been widely studied to identify genetic variants associated with longevity [10,11]. In academic discourse, terms like "long-lived people," "long-living individuals (LLIs)," and "oldest old" are often used interchangeably to denote human longevity. LLIs, which include nonagenarians (ages 90–100 years), centenarians (ages 100–104 years), semi-supercentenarians (ages 105–109 years), and supercentenarians (ages > 110 years), exemplify the upper limits of human lifespan. They represent a select group of survivors who have reached these extreme ages.

Distribution of LLIs

Globally, LLIs are not evenly distributed; they tend to cluster in areas known as longevity blue zones (LBZs) [12]. The concept of LBZs describes regions where populations sharing similar lifestyles and environments exhibit exceptionally high longevity. The most renowned LBZs include Okinawa (Japan), Nicoya Peninsula (Costa Rica), the Island of Ikaria (Greece), Sardinia (Italy), and Loma Linda in California [12]. Additionally, LLIs are often found within families [13,14], suggesting a genetic

predisposition to longevity. Offspring [15–21] and siblings [22–24] of centenarians have been shown to have a reduced risk for age-related diseases and better functional status compared to the general population.

LLI as a health aging model

LLIs, especially centenarians, serve as the best model for studying healthy aging and human longevity. Despite showing signs and characteristics of aging, many LLIs avoid or survive major diseases that typically affect older individuals [6], maintaining a lifelong healthy aging process [25,26]. This phenomenon aligns with the "compression of morbidity" hypothesis [27], which suggests that living to extreme ages is associated with a compression of morbidity [28] and disability [29]. Centenarians achieve exceptional longevity without loss of functioning [30–32] and spend less time in hospitals in their lifetime [5]. In the case of supercentenarians, health span even approximates their life span [33].

While LLIs experience extreme aging, they often differ significantly from individuals undergoing normal aging. Normal aging is frequently associated with a gradual decline in physiologic functions [34] and earlier onset of age-related diseases [35]. In contrast, most LLIs survive well with these age-related functional declines [30] and diseases [31,36]. Meanwhile, LLIs tend to delay or even escape the onset of common age-related diseases such as cancer [37–43], cardiovascular disease [44], insulin resistance and diabetes [45], Parkinson's disease [33], dementia [46–48], osteoporosis, stroke, and hypertension [49]. This delay contributes to a compression of morbidity, allowing LLIs maintaining physical and cognitive functionality until the very late stages of life [30–32]. Furthermore, LLIs are often genetically predisposed to enhanced health resilience [50], enabling them to either mitigate or escape many of the diseases that typically accompany aging, setting them apart from the general aging population.

In summary, longevity is associated with a compression of morbidity and disability, with some LLIs demonstrating resilience to age-related diseases or even escaping them altogether. This makes them an extraordinary and informative model for identifying the mechanisms behind healthy aging and human longevity.

Sex difference of longevity

Females generally outlive males and are overrepresented in the older population, particularly at advanced ages. This sex difference in life expectancy is a universal phenomenon, indicating that human longevity seems strongly sexually biased. The number of female centenarians is constantly higher than male centenarians, and the female/male (F/M) ratios range from 2:1 to over 8:1 [13,14,51–54]. Conversely, male centenarians suffer from fewer age-related diseases [55] and are often healthier than female centenarians [29,33,53].

Heterogeneity of longevity

Centenarians display a remarkable diversity in their health conditions. Motta *et al*. have delineated three distinct categories of health status among centenarians: Group A, characterized by good health; Group B, indicating intermediate health; and Group C, reflecting poor health [36,56]. An alternative classification [31] further divides centenarians into "survivors," who are diagnosed with age-related pathologies before reaching 80 years of age; "delayers," who receive such diagnoses between the ages of 80 and 99; and "escapers," who exhibit no history of common age-related diseases until reaching the age of 100. This stratification underscores the potential existence of various pathways to achieving exceptional longevity.

Longevity associated factors

The extension of human lifespan can be attributed not only to enhancements in economic and cultural conditions, along with improvements in social and healthcare systems, but also to the synergistic effects of these conditions with the genetic diversity present within human populations. Individuals who exhibit exceptional longevity offer a unique and valuable sample for investigating the protective factors that contribute to healthy aging. Empirical evidence suggests that a blend of genetic predispositions, environmental exposures, and stochastic factors collectively shape healthy longevity. Currently, there is a growing focus on pinpointing the genetic and non-genetic factors associated with longevity and healthy aging in humans. Identifying these factors is of paramount importance, as they may reveal potential targets for tailored interventions. Such interventions could be designed to enhance healthy aging and extend longevity, offering profound implications for individual and public health.

Longevity associated genetic factors

Longevity often clusters within families, implying a genetic predisposition. Relatives of LLIs not only show a significant survival advantage but also have a higher probability of reaching old age themselves [24,57]. They are also less likely to suffer from major age-related diseases [15,22]. For example, nonagenarian siblings exhibit a 41% reduced risk of mortality compared to nonagenarians without such siblings [58], underscoring the familial nature of longevity. These findings collectively suggest that longevity is a moderately

heritable trait.

Twin studies have provided valuable insights into the genetic basis of lifespan, estimating that 20% to 50% of the variation in human lifespan can be attributed to genetic factors [59–62]. However, population-based samples offer a slightly lower estimate, ranging from 4% to 29% [63], indicating a significant yet modest genetic contribution to human life span. Notably, the genetic influence on survival becomes increasingly prominent at advanced ages, particularly beyond 60 years [64].

The search for genetic variations linked to longevity has led to the investigation of numerous candidate genes and loci that may act as protective factors promoting longevity. Some of the most extensively studied and biologically plausible genetic factors are discussed below, including nuclear genomic variants, mitochondrial variants, and telomere maintenance mechanisms.

Nuclear genomic variants

Apolipoproteins (APOE, APOB, APOC1, and APOC3)

Lipid metabolism [65] and apolipoproteins [66] are crucial for longevity. Genome-wide association studies (GWAS) on long-lived subjects reported significant enrichment of genes involved in lipid metabolism pathways [67]. Apolipoproteins are soluble molecules present in plasma, and many genetic studies showed their role in longevity. Genetic variations in apolipoprotein E (APOE) are the most replicated region in many different populations associated with human longevity and lifespan [68,69]. The APOE gene's two polymorphisms (rs7412 C/T and rs429358 C/T) give rise to three haplotypes: ε2, ε3, and ε4. Studies show that a low frequency of the APOE-ε4 allele and an increased frequency of the APOE-ε2 allele contribute to longevity [68,70–72]. APOE-ε4 is a risk allele associated with Alzheimer's disease (AD) [73] and cardiovascular disease (CVD) [74], while APOE-ε2 is associated with longevity and reduced disease risk, exhibiting a protective role. Additionally, associations with longevity have been described for apolipoprotein B (APOB) gene 3′ variable number tandem repeat (APOB-VNTR) in Italian centenarians [75], for apolipoprotein C1 (APOC1) in the Bama populations [76], and for apolipoprotein C3 (APOC3) (−641C allele) in Ashkenazi Jewish centenarians [77]. These genetic variants likely influence lipoprotein profile, cardiovascular health, and insulin sensitivity to benefit longevity.

Insulin–IGF1 signaling pathway (GH, IGF1, IGF1R) and FOXO3A

Energy metabolism and longevity are intricately linked processes [78]. The insulin–insulin like growth factor 1 (IGF-1) signaling (IIS) pathway plays a crucial role in a wide range of functions related to metabolic regulation and energy management. IGF-1 and IIS pathway-related genes are some of the most conserved genetic determinants of longevity across a variety of model organisms [79]. Loss-of-function mutations in genes encoding components of the IIS result in the extension of lifespan in yeasts, worms, flies, and mice [80]. In humans, IGF-1 is involved in insulin and glucose metabolism, and elevated levels of growth hormone (GH) and IGF-1 are associated with cancers [81] and all-cause mortality [82]. Conversely, lower IGF-1 circulating levels are indicative of better life expectancy in LLIs [83], and IGF-1 circulating levels are notably lower in centenarians [84,85]. A single nucleotide polymorphism (SNP) in the IGF-1R gene, which leads to reduced levels of free-plasma IGF-1, has been significantly associated with longevity in LLIs [86]. Additionally, female Ashkenazi Jewish centenarians exhibit an overrepresentation of loss-of-function mutations in the IGF1R gene [87].

FOXO3A (Forkhead Box O3a), a downstream transcription factor negatively regulated by the insulin/IGF-1 signaling (IIS) pathway, plays a crucial role in regulating longevity across multiple species, from worms [88,89] to humans [90]. Extensive research has shown that genetic variability in FOXO3A is closely associated with human longevity. Notably, the rs2802292 G-allele (G > T) has been positively correlated with increased lifespan across diverse populations [91–94]. Additionally, homozygosity for this allele confers a significant protection against coronary heart disease (CHD) and cancer [91].

The IIS pathway regulates FOXO3A through AKT-mediated phosphorylation, which prevents FOXO3A from translocating into the nucleus and inhibits the activation of its downstream targets [95]. When IIS activity is reduced, FOXO3A becomes activated and regulates key targets such as superoxide dismutase (SOD2) and catalase, which neutralize reactive oxygen species (ROS) and mitigate oxidative damage [96]. Additionally, FOXO3A facilitates DNA repair by upregulating GADD45 [97] and drives autophagy through the regulation of LC3 and BNIP3 [98]. FOXO3A also promotes apoptosis by activating several apoptosis-related genes, including FasL, BIM, PUMA, TRAIL, and NOXA [99], ensuring the removal of damaged cells while maintaining mitochondrial health. Together, these mechanisms position FOXO3A as a central factor in human longevity, through regulating a variety of gene transcriptions involved in oxidative stress resistance, DNA repair, autophagy and apoptosis.

Sirtuins (SIRT1, SIRT3, SIRT6)

Sirtuins, a family of NAD^+-dependent protein deacylases,

play pivotal roles in cellular processes implicated in aging. These enzymes, particularly SIRT1–7 in mammals, regulate gene expression, DNA repair, apoptosis, and mitochondrial biogenesis, influencing overall cellular health and longevity pathways [100]. In organisms such as yeast [101], worms [102], and flies [103], the activity of sirtuins prolongs lifespan. In humans, SIRT1 expression was found to be 4-fold lower in lymphoblastoid cell lines (LCLs) from Alzheimer's disease patients and 2.2-fold higher in LCLs from centenarians compared to individuals aged 56–82 years [104]. This suggests that elevated SIRT1 levels may offer neuroprotection against dementia and contribute to increased longevity. Additionally, a study analyzing the genotype-specific survival function related to the G477T marker of SIRT3 found that in males, the TT genotype enhances survival in the elderly [105]. Furthermore, a novel VNTR enhancer within the SIRT3 gene has been associated with increased survival at the oldest ages [106]. These findings highlight the potential of SIRT1 and SIRT3 in promoting healthy aging and longevity.

For SIRT6, the SNP rs350845, located within an intron, has been identified as an eQTL for SIRT6 upregulation, suggesting that its increased expression may contribute to longevity [107]. Furthermore, two rare missense variants in perfect linkage, rs183444295 (A313S) and rs201141490 (N308K), collectively known as centSIRT6 (N308K/A313S), have been observed to enhance SIRT6 function by improving genome maintenance through increased mono-ADP-ribosyltransferase (mADPr) activity and interaction with lamin A/C (LMNA), thus contributing to human longevity [107]. These variants have also been shown to prevent nonalcoholic steatohepatitis (NASH) by altering the hepatocyte proteome and lipidome [108].

However, the role of the remaining human sirtuins — SIRT2, SIRT4, SIRT5, and SIRT7 — in longevity, particularly in LLIs such as nonagenarians and centenarians, has not yet been widely reported or established. This gap presents an opportunity for further research to explore their potential contributions to human longevity.

Inflammation (IL-6, TGF-β, and IL-10)

Chronic inflammation, often termed "inflammaging," is increasingly recognized as a fundamental biological mechanism contributing to the decline in physical function observed with aging [109]. Cytokines, critical regulators of inflammatory responses, have been extensively studied for their roles in this process [110]. Variations in genes encoding pro- and anti-inflammatory cytokines are influential in determining successful aging and longevity. Elevated plasma levels of the pro-inflammatory cytokine interleukin-6 (IL-6) have been consistently linked to increased disability, morbidity, and mortality in the elderly [111]. Thus, a strong inflammatory response is associated with a higher risk of life-threatening diseases, while longevity should correlate with the capability to maintain a low-intensity inflammatory response. A genetic polymorphism involving a C to G transition at nucleotide −174 in the IL-6 gene promoter (referred to as the −174 C/G locus) has been shown to influence IL-6 production levels. Specifically, the GG genotype at this locus is associated with increased IL-6 production in older individuals [112]. Conversely, a higher prevalence of the IL-6 −174 C allele has been noted among LLIs [113,114]. This genetic variant may exert a positive influence on longevity by potentially reducing IL-6 levels, suggesting a role in modulating inflammatory responses that could favor extended healthspan.

Anti-inflammatory cytokines, such as transforming growth factor β (TGF-β), have also been implicated in longevity. Plasma levels of TGF-β are reportedly higher in centenarians compared to younger individuals [115]. Another anti-inflammatory cytokine, IL-10, features a genetic polymorphism at position −1082 (G→A), with the GG genotype correlating with higher IL-10 production. An increased frequency of this homozygous genotype has been observed in Italian centenarian men [116], suggesting a contribution to an anti-inflammatory status that may enhance longevity.

Furthermore, the G allele of Toll-like receptor 4 (TLR-4), which is involved in innate immune defense, has been found to be more prevalent in male LLIs [117]. Similarly, the +874A allele of interferonγ (IFN-γ), a pro-inflammatory cytokine, is linked to reduced IFN-γ production and is associated with an overall anti-inflammatory status that may promote longevity [118].

DNA repair (TP53 and EXO1)

DNA damage can lead to cell cycle arrest, cell death, or mutation. Studies have shown that older organisms exhibit a higher load of DNA damage due to the reduced efficiency and increased error-proneness of DNA repair mechanisms with age [119,120]. This accumulation of DNA damage contributes significantly to the aging process and the development of age-related diseases. Research on centenarians, individuals who live to be 100 years or older, indicates that this population has enhanced DNA repair activity. They show significantly lower frequencies of genomic and cellular damage compared to younger individuals [121–123]. This suggests that superior DNA repair mechanisms may be crucial for achieving exceptional longevity. A functional promoter variant in the DNA repair gene exonuclease 1 (EXO1) has been associated with longevity, particularly in female centenarians [124]. EXO1 plays a critical role in DNA

mismatch repair, which is essential for maintaining genomic stability by correcting DNA replication errors.

The tumor protein P53 (TP53) gene is also vital for DNA repair and has significant antitumor activity, especially as organisms age. TP53 functions as a tumor suppressor by regulating the cell cycle and inducing apoptosis in response to DNA damage. A study found that a specific polymorphism, involving the replacement of arginine (Arg) with proline (Pro) at position 72 of human TP53, decreases its apoptotic potential. Carriers of the TP53 codon 72 Pro/Pro genotype have a 41% increased survival rate despite a higher risk of cancer [125]. This indicates a complex balance between enhanced survival and cancer risk mediated by TP53's role in DNA repair and apoptosis.

Overall, efficient DNA repair mechanisms, influenced by genetic factors such as EXO1 and TP53, appear to play a significant role in achieving exceptional longevity. Enhanced DNA repair helps maintain genomic integrity, reduces cellular damage, and potentially delays the onset of age-related diseases, thereby contributing to longer life spans.

Others (ACE, GST, and PON1)

The angiotensin-converting enzyme (ACE) is a key component of the renin-angiotensin system, which regulates blood pressure [126]. The D-allele of the ACE gene is positively associated with survival in older age [127,128] and exceptional longevity in centenarians [72]. Although the D-allele leads to higher ACE enzyme activity in the blood [129] and increases the risk of cardiovascular disease [130,131], it is still associated with exceptional longevity. This suggests that the ACE I/D polymorphism may exhibit pleiotropic age-dependent effects on longevity, where the D-allele increases disease risk earlier in life but provides a survival advantage later in life.

Glutathione S-transferases (GSTs) are a family of enzymes crucial for detoxification processes within cells, maintaining cellular homeostasis, and protecting against oxidative stress and toxic compounds [132]. Homozygosity for the GSTT1 functional gene is associated with significantly increased mortality in older subjects [133]. Studies have found that carriers of the GSTT1 non-functional allele are more frequent among Italian centenarians [134], suggesting that the deletion of GSTT1 may contribute to longevity. Conversely, a decreased frequency of the GSTM1 deletion genotype was observed in Japanese centenarians [135], indicating that the GSTM1 functional gene is a protective factor for longevity.

Human paraoxonase (PON1) is a high-density lipoprotein (HDL)-associated esterase that hydrolyzes lipid peroxides, counteracting oxidative stress [136]. PON1 has gained attention as a protective factor against peroxidative damage of low-density lipoprotein (LDL), playing an important role in preventing atherosclerosis [137]. The association between PON1 polymorphism and longevity has shown an increase in the arginine allele at codon 192 in Italian centenarians [138]. A pooled analysis of Italian and Irish LLIs [139] and a meta-analysis [140] revealed a survival advantage for LLIs carrying the Arg allele. These studies suggest that genetic variability at the PON1 locus can enhance paraoxonase activity, benefiting survival at extreme ages.

Mitochondrial variants

Mitochondria play crucial roles in oxidative phosphorylation, cell metabolism, and apoptosis, especially during aging. Mitochondrial loss of function is considered a hallmark of aging [141]. Mitochondrial DNA (mtDNA), which contains a genome of 16 569 base pairs, includes genes essential for mitochondrial functions. The variation in the mitochondrial genome's impact on health and longevity is suggested by the observation that age at death correlates more closely with the age at death of a person's mother than that of the father [142].

Associations between mitochondrial genome sequence variants or haplogroups (combinations of specific variants that correlate with specific populations) and healthy aging or longevity have been noted in many ethnic populations [143–147]. Haplogroup J has been identified to be associated with longevity in different European populations, with this haplogroup being more frequent in centenarians than in ethnically matched younger controls [143,146,147]. Similarly, the Asian haplogroup D, a mtDNA haplogroup predominantly found in East Asian populations, is overrepresented in Japanese centenarians [148]. However, these associations were not confirmed in studies conducted in different geographic areas [149,150], suggesting that the effect of mtDNA on longevity might be population-specific.

The C150T variant at the origin of replication of the mitochondrial heavy strand occurs at a much higher frequency in centenarians, either inherited or somatically acquired [151]. The higher frequency of C150T has also been confirmed in LLIs from Finland and Japan [152]. Additionally, C150T was shown to be associated with longevity in subhaplogroup J2, consistent with a specific study on mtDNA haplogroup J in centenarians [153]. Thus, available data suggest that mtDNA variants, such as the C150T polymorphism and haplogroup J or subhaplogroup J2, are associated with longevity in a population-specific manner. It is speculated that the C150T variant and/or J haplogroup may reduce oxidative phosphorylation efficiency and reactive oxygen species (ROS) production, thereby reducing oxidative stress and promoting longevity. However, more functional studies

are needed to investigate their precise biological role in longevity.

Telomere

Telomeres are the protective ends of chromosomes, consisting of repeated DNA sequences [154] that play a central role in maintaining chromosome stability and preventing the inappropriate activation of DNA damage pathways [155]. Telomeres shorten with each cell division, and their progressive shortening is a key mechanism underlying cellular aging and the onset of age-related diseases [156]. In worms, individuals with longer telomeres live longer than those with normal-length telomeres [157]. Telomere length varies among individuals of the same age group, and a possible association between telomere length and health in late life has been reported in human centenarians [158].

Studies have demonstrated that centenarians and their offspring maintain longer telomeres compared with age-matched controls [159]. Longer telomeres also are associated with protection from age-related diseases, better cognitive function, and healthier lipid profiles [159]. Telomere length is maintained by telomerase, a specialized ribonucleoprotein enzyme complex that adds telomere repeats to the ends of chromosomes. Telomerase has two essential components: a catalytic component encoded by the human telomerase reverse transcriptase (hTERT) gene and a human telomerase RNA component (hTERC). Sequence analysis of TERT and TERC in Ashkenazi centenarians showed overrepresentation of synonymous and intronic mutations among centenarians relative to controls, pinpointing a TERT haplotype linked to longer telomere length and exceptional longevity [159]. Additionally, single nucleotide polymorphisms (SNPs) located at SIRT1 [160] and TERC [161] are associated with both telomere length and longevity. Together, variations in human telomerase genes that promote better maintenance of telomere length appear to confer exceptional longevity in humans.

A brief summary for genetic factors

Over the past decades, efforts to identify genes influencing longevity through candidate gene and GWAS have shown limited success. GWAS have identified numerous gene polymorphisms involved in immune response, inflammation, oxidative stress response, and the insulin/IGF1 signaling pathway, among others, with varying frequencies in centenarians compared to controls. However, extensive GWAS and meta-analyses across multiple data sets have only consistently highlighted APOE and FOXO3 as the predominant genes associated with longevity across diverse populations [69,162–164]. The complexity of the longevity phenotype, influenced by environmental and dietary factors, contributes to the challenges in replicating and confirming genetic findings across studies. Therefore, genetic studies of longevity often exhibit population-specific differences that reflect diverse environmental contexts.

Longevity associated epigenetic factors

DNA methylation

Genetically identical twins exhibit significant differences in genome methylation patterns as they age, influencing gene expression and lifespan [165,166]. This underscores the role of epigenetics, which bridges the gap between genetics and environmental factors, in longevity. Epigenomic changes are increasingly recognized as integral to aging and its associated pathologies [167]. Age-related reductions in global DNA methylation have been documented in human bronchial epithelial cells [168] and leukocytes [169,170], particularly in repetitive elements like Alu sequences [171].

Conversely, offspring of centenarians show delayed loss of DNA methylation compared to offspring of shorter-lived parents [172]. Global DNA methylation and Alu element methylation are higher in centenarians' offspring, with hypermethylated CpG loci enriched in genes related to DNA/RNA synthesis, metabolism, and cellular signaling. Hypomethylated CpG sites are associated with processes related to signal transmission. Epigenetic clocks based on DNA methylation reveal that offspring of semi-supercentenarians have a younger epigenetic age [173], and centenarians themselves age slower than expected [173–176]. Genomic regions associated with a younger state are enriched for genes involved in cancer and cognitive function [177]. Recent studies in Chinese centenarians have identified centenarian-specific hyper-DMCs (hyper-differentially methylated CpG sites) in H3K9me3 regions, distinct from those associated with chronological age, likely contributing to healthy aging and longevity by stabilizing constitutive heterochromatin [178]. These findings underscore the existence of epigenetic factors in longevity, though their precise genomic locations remain undetermined.

Noncoding RNAs

Noncoding RNAs, including long noncoding RNAs (lncRNAs) and microRNAs (miRNAs), also play pivotal roles in the epigenetic regulation of aging. In a cross-sectional analysis, miR-363* expression, which typically declines with age, remains preserved in B cells of centenarians, potentially targeting longevity-associated genes such as phosphatase and tensin homolog (PTEN), BCL2 apoptosis regulator (BCL2), AKT serine/threonine

kinase 1 (AKT1), and insulin-like growth factor binding protein 5 (IGFBP5) [179]. Additionally, 11 centenarian-specific lncRNAs highly expressed in long-lived individuals have been identified [180]. Notably, overexpression of THBS1 intronic transcript 1 (THBS1-IT1) and THBS1 antisense RNA 1 (THBS1-AS1), two lncRNAs abundant in centenarians, significantly suppresses senescence-related markers like cyclin-dependent kinase inhibitor 2A (P16), cyclin-dependent kinase inhibitor 1A (P21), and β-galactosidase activity, suggesting their role as novel longevity factors by inhibiting cellular senescence.

Longevity associated metabolic factors

Lipid metabolism

Healthy centenarians typically have a less atherogenic plasma lipid profile, characterized by lower fasting plasma LDL cholesterol and higher fasting plasma HDL cholesterol [181]. Numerous genes associated with longevity are also involved in lipid metabolism and apolipoprotein. For example, the apolipoprotein CIII variant, APOC3 C(−641)V, correlates with favorable lipoprotein particle size [77], while ApoE, essential for the catabolism of triglyceride-rich lipoproteins, has been linked to lifespan in several cohorts [182,183]. A lower prevalence of hypertension in APOC3 −641C homozygotes suggests a protective effect against cardiovascular disease [77]. Other longevity genes involved in lipid metabolism include cholesteryl ester transfer protein (CETP) [184,185] and adiponectin, C1Q and collagen domain containing (ADIPOQ) [186]. Specific lipid species associated with aging diseases and longevity, such as ether phosphocholines PC (O-34:1) and PC (O-34:3), have also been identified [187]. Thus, LLIs maintain a beneficial lipid profile that promotes healthy aging.

Insulin resistance and oxidative stress

Aging is generally associated with a progressive rise in insulin resistance [188]. However, centenarians exhibit a low degree of insulin resistance. They have preserved glucose tolerance and insulin action compared to aged subjects [45]. Insulin resistance increases with age, peaking in individuals aged 80 to 90 years; however, individuals over 90 years old display a lower degree of insulin resistance [189]. The lack of insulin resistance in healthy centenarians suggests that successful metabolic remodeling contributes to their extreme lifespan. Although insulin regulation appears to play a role in human longevity, further studies are needed to elucidate the environmental or genetic factors that regulate insulin resistance in LLIs.

Aging is also associated with increased oxidative stress due to a decline in antioxidant activity and a rise in pro-oxidant factors like glucose and insulin [190,191]. Notably, extreme longevity, such as in centenarians, is linked to low oxidative stress and insulin resistance [189]. Centenarians also have higher plasma levels of antioxidant vitamins A and E compared to older controls [192]. Furthermore, chronic pharmacological doses of vitamin E have been shown to lower plasma free radical concentration and improve insulin action [193], suggesting that LLIs are better equipped with antioxidants to combat oxidative stress.

Longevity associated endocrine factors

Physiologic aging involves functional declines in the endocrine system, which is essential for maintaining homeostasis. Decreased or absent thyroid function is associated with extreme longevity in many animal models [194,195], suggesting a causal relationship between thyroid function and lifespan. A population-based study in the Netherlands found that individuals with low-normal thyroid function live up to 3.5 years longer than those with normal-high thyroid function [196]. Indeed, an association between low thyroid function and longevity has also been observed in humans [197]. Lower plasma levels of thyroid hormones [198] and higher plasma thyroid stimulating hormone (TSH) levels [199,200] have been noted in centenarians, indicating that increased serum TSH and decreased thyroid activity play a favorable role in healthy aging. From a genetic perspective, a heritable phenotype characterized by raised serum TSH is associated with human longevity [201], with carriers of rs12050077 and rs10149689 SNPs of TSHR in centenarians and their offspring exhibiting higher serum TSH, potentially contributing to decreased thyroid function and longevity.

The GH/IGF system is crucial in regulating lifespan and age-related diseases. Disruption of IIS in lower organisms such as nematodes, yeasts, flies, and mice has been associated with prolonged lifespan [80]. In humans, high IGF-1 levels are a risk factor for many types of cancers [202]. Conversely, GH [203] and IGF-1 [84,85] concentrations are lower in centenarians. Genetic mutations of IGF-1R have been identified in human centenarians [87], indicating lower IIS activity associated with human longevity. However, low IGF-1 is also linked to conditions like glucose intolerance [204], osteoporosis [205], poor cognitive function [206], and coronary heart disease [207]. These findings suggest a complex role for the IGF axis in overall longevity and functional decline of specific organs, warranting further investigation into the underlying biological mechanisms.

Additionally, while melatonin secretion decreases with age, it is maintained in centenarians [208,209]. As

melatonin plays a crucial role as both an endogenous synchronizer and a free radical scavenger, the persistence of physiologic circadian organization of melatonin secretion may be relevant for successful aging.

Longevity associated sex hormones

Sex hormones, including androgens and estrogens, are closely linked to aging and human longevity [210]. In women, studies reveal that centenarians generally exhibit significantly higher levels of estradiol (E2) —the most potent form of estrogen—when compared to women aged 80–99 years [211–213]. E2 plays a crucial role in regulating bone mass homeostasis [214], and its levels naturally decline with age [215]. However, in long-lived women, higher E2 levels may provide protective benefits for bone maintenance and overall longevity.

In men, testosterone levels begin to drop during middle age and continue to decline gradually with advancing age [216,217]. Notably, preserved hypothalamic-pituitary function is a characteristic of longevity in men. For instance, 94% of Ashkenazi Jewish men aged 90–106 years showed normal testosterone levels [218]. These highlights the critical roles of hormonal homeostasis in promoting longevity across genders.

Longevity associated immune factors

Immunosenescence refers to aging-related changes in the immune system, characterized by a decrease in immune competence, increased susceptibility to diseases, and higher morbidity and mortality due to infections and various age-related pathologies. It is proposed as a continuous adaptation to the exposure to low levels of internal and external damaging agents rather than a simple deterioration process [192]. Indicators of an aging immune system include increased sensitivity to infectious diseases and cancer, decreased antibody production to non-self antigens, increased levels of autoantibodies, defective natural killer (NK) cell activity, and decreased T lymphocyte proliferation [219]. However, healthy centenarians lack organ-specific autoantibodies, suggesting a lack of autoimmune responses in long-lived individuals [219]. Additionally, T lymphocytes from healthy centenarians can proliferate effectively [219]. Some immune responses, such as the cytotoxic activities of NK cells, remain efficient in centenarians [220]. Moreover, centenarians maintain good neutrophil function, similar to that of young adults, despite the progressive impairment typically seen with aging [221].

A major aspect of the aging immune system is the imbalance between inflammatory and anti-inflammatory networks, leading to a low-grade chronic pro-inflammatory state known as inflammaging. Interleukin-6 (IL-6), a pro-inflammatory cytokine, is usually tightly regulated and expressed at low levels, but its concentration increases with age [222,223]. Higher serum IL-6 levels are associated with disability [111] and mortality [224]. Genetic predisposition to low IL-6 levels throughout life appears to promote longevity in male centenarians [113]. Conversely, centenarians exhibit higher circulating levels of the pro-inflammatory cytokine IL-22, which is protective against infection and promotes longevity [225]. One other study also identified the −1082G genotype of IL-10, an anti-inflammatory cytokine, which is associated with increased IL-10 production and is highly represented among centenarian men [116]. Additionally, the anti-inflammatory response in centenarians can be elevated by decreasing the ratio of Th17 to Treg cells and shifting them to anti-inflammatory secretory phenotypes [226]. Together, these findings suggest that LLIs are genetically equipped with efficient mechanisms for balancing inflammatory and anti-inflammatory responses [227], potentially contributing to their longevity.

Longevity associated environmental or lifestyle factors

Over the past century, the average life expectancy has nearly doubled, increasing from approximately 50 years to a range of 75 to 80 years [1]. This significant increase is primarily attributed to a substantial decrease in early life mortality during the early twentieth century, followed by a less widely recognized but equally important reduction in mortality rates among individuals aged 70 and above in the subsequent 50 years [2,3]. These rapid changes on an evolutionary timescale suggest that non-genetic factors have played a significant role in increasing human lifespans. Families with multiple nonagenarian and centenarian siblings, who exhibit exceptional longevity and health-span, likely possess a combination of inherited genes that facilitate longevity. However, their nine decades of life experiences and behaviors also play a crucial role, interacting with their genetic makeup. Non-genetic factors such as diet, physical activity, health practices, and psychosocial elements are estimated to account for about 50% of the variability in human lifespan, with genetic differences explaining an additional 25% [228]. In this section, we examine various non-genetic, environmental factors that have been associated with promoting longevity in humans.

Gut microbiota

The study of gut microbiota (GM) in exceptionally long-lived individuals offers insights into how this symbiotic microbial community contributes to longevity. The GM is highly dynamic and sensitive to environmental stimuli, changing throughout the host's lifespan. During aging, microbial communities lose diversity, and the number of

pathogenic bacterial species increases [229,230]. The core GM, including dominant symbiotic bacterial taxa such as Ruminococcaceae, Lachnospiraceae, and Bacteroidaceae, loses diversity and abundance with age [231]. However, in extreme longevity, this decline is counterbalanced by an increase in longevity-adapted and health-promoting subdominant species, such as *Akkermansia*, *Bifidobacterium*, and Christensenellaceae [231].

Interestingly, centenarians have a specific gut microbiota composition characterized by increased diversity and richness in health-associated and young-specific bacteria [232]. For example, Spanish centenarians' microbiota contains an abundance of *Klebsiella*, *Lactobacillus*, *Parabacteroides*, and *Akkermansia* [233]. In Chinese centenarians, taxa such as *Bacteroides fragilis*, *Parabacteroides merdae*, *Ruminococcus gnavus*, and *Clostridium perfringens* may contribute to longevity [234]. Thus, LLIs readapt their GM to include new microbial components, establishing a new homeostasis that helps them reach extreme ages.

Probiotic supplementation with strains such as *Propionibacterium freudenreichii* [235] and *Lactobacillus gasseri* [236] has been shown to promote longevity by stimulating the innate immune response in *Caenorhabditis elegans*. Probiotic treatment with *Bifidobacterium animalis* subsp. *lactis* LKM512 increased longevity in mice, possibly due to the suppression of chronic low-grade inflammation in the colon [237]. Oral administration of purified exopolysaccharide fractions from *Bifidobacterium animalis* RH, isolated from the fecal samples of centenarians in Bama longevity villages (Guangxi, China), significantly increased the activity of superoxide dismutase, catalase, and total antioxidant capability in mice serum, potentially contributing to longevity [238].

Fecal microbiota transfer (FMT) studies also highlight the importance of microbiota in extending lifespan in various animal species. Transplanting microbiota from young to old fish significantly increases lifespan [239]. Moreover, microbiota transplantation from long-living humans to mice increases beneficial bacteria and reduces aging-related metabolites [240]. *Akkermansia muciniphila* transplantation extends lifespan in a mouse model of progeria by 13.5% in median lifespan and 9% in maximal survival [233]. Oral administration of *A. muciniphila* reduced age-related deterioration in intestinal barrier function, decreased proinflammatory cytokines in C57BL/6J mice, and increased intestinal concentrations of anti-aging metabolites, including bile acids, short-chain fatty acids (SCFAs), 2-hydroxybutyrate, and polyamines [241]. In the future, as more longevity-associated bacteria emerge from GM studies in centenarians, GM-based treatments could soon be exploited for anti-aging therapy.

Caloric restriction

Caloric restriction (CR) is the only intervention consistently shown to slow aging and increase lifespan in short-lived species. CR involves reducing total caloric intake by 20%–60% without causing malnutrition or a reduction in essential nutrients. This strategy improves health span and lifespan in flies [242], mice [243,244], rats [245], and nonhuman primates [246,247]. Epidemiological studies suggest that CR also benefits human longevity. For example, the inhabitants of Okinawa, Japan, consume fewer calories, and in this older cohort (aged 65+), mortality from coronary heart disease and cancer is markedly lower than in the average mainland Japanese and US populations [248–250]. Consequently, Okinawa has one of the highest numbers of centenarians in the world, with approximately 50 per 100 000 inhabitants. Similarly, CR is associated with the diet habits of Italian centenarians [251]. The phenotype of centenarians is remarkably similar to that observed in adult volunteers following different CR regimens [232]. Moreover, CR also contrasts age-related diseases, including cardiovascular disease [252–254], cancers [255], diabetes [256], and neurodegenerative diseases [257]. Thus, the benefits of CR partly stem from its ability to combat age-related diseases.

Despite its effectiveness, it is unlikely that a 30%–40% reduction in calories over much of the lifespan will be widely practiced. CR mimetics are compounds or strategies that mimic the health-promoting and anti-aging effects of CR without actually restricting caloric intake. These compounds target metabolic and stress response pathways affected by CR. The development of CR mimetics provides an alternative strategy for slowing human aging. Studies have found that 2-deoxy-D-glucose (2-DG) [258], resveratrol [259], metformin [260], and many other compounds [261] mimic certain effects of CR. However, the balance between anti-aging efficacy and toxicity must be fully assessed in animals. The next phase of CR studies includes basic investigations and potential clinical trials of various candidate CR mimetics.

Plant-based diet

Generally, it has been reported that centenarians often consume a diet rich in vegetables [262]. They frequently eat plant foods such as cereals, vegetables, fruits, and legumes, and consume less meat, particularly in regions like Abruzzo [251] and the Sicani Mountains [262] in Italy. Plant-based diets are associated with a significantly lower risk of developing type 2 diabetes [263,264], cardiovascular disease [265], Parkinson's disease [266], dementia [267], frailty [268], and overall mortality [269]. Healthy plant-based diets can also slow cognitive decline with aging [270]. However, unhealthy plant-based diets

are linked to higher total and disease-specific mortality rates [269,271], highlighting the importance of plant food quality in reducing mortality. Healthy plant foods include nuts, fruits, legumes, vegetables, and whole grains, whereas less healthy options include sweets, potatoes, refined grains, fruit juices, and sugar-sweetened beverages [272].

Physical activity

Studies on centenarians show that a physically active lifestyle enhances mental and physical health, promoting longevity [251,273]. Physical activity, which involves skeletal muscles and increases energy expenditure compared to the resting state, can partially reverse aging effects on physiologic functions and maintain functional reserve in the elderly. Numerous studies demonstrate that maintaining adequate exercise decreases mortality risk [274], prevents certain cancers [275], lowers osteoporosis risk, and increases longevity [276,277]. This risk reduction translates to an additional 1–2 years of life for those who exercise compared to those who do not [278]. Meta-analyses reveal that regular physical activity reduces the risk of all-cause and cardiovascular mortality by 30% in both men and women [279]. These analyses also show a clear dose–response relationship between physical activity and longevity [275,280,281]. Greater exercise volume (duration × intensity) correlates with more significant mortality benefits, and higher intensity for a given volume offers additional benefits [281]. For example, competitive athletes, who engage in high exercise volumes and/or intensity, often live longer than age-matched sedentary individuals [282,283]. For longevity and slowing aging, endurance exercise, including high-intensity training to improve cardiorespiratory fitness, is recommended; strength training should also be included to slow muscle mass loss associated with aging and disease [284].

Other environmental or lifestyle factors

A longitudinal study spanning up to 34 years has identified five key healthy lifestyle practices that significantly reduce premature mortality and extend life expectancy in the US [285]. These include non-smoking, maintaining a body mass index between 18.5 to 24.9 kg/m^2, regular physical activity, moderate alcohol consumption, and a healthy diet low in processed foods. Similar associations with increased life expectancy have been observed in other countries such as Japan [286], Canada [287], Germany [288], the UK [289,290], and China [291]. Together, these longevity-promoting practices encompass adequate sleep, non-smoking, a diet rich in green leafy vegetables and low in processed foods, regular physical activity, and moderate or no alcohol intake. Thus, adopting a healthy lifestyle can significantly enhance life expectancy without substantial costs.

Cigarette smoking accelerates the aging process and increases mortality rates [292]. Instances of smoking are predominantly linked to poor health conditions and dependence, suggesting detrimental effects on health status and life expectancy in long-lived individuals [53]. Conversely, non-smokers generally enjoy a longer life expectancy compared to smokers [293], and quitting smoking, even in older adults, can increase survival by mitigating smoking-induced biological damage [294]. Thus, it is observed that smoking is exceptionally rare among centenarians [295–297].

Psychosocial factors, including personality traits associated with mortality in old age [298], play a crucial role in longevity [299]. Centenarians often exhibit personality profiles characterized by low neuroticism, high competence, extraversion, conscientiousness, and openness, which contribute to longevity through health-conscious behaviors and stress management [300–302]. Leading a stress-free lifestyle is integral to the daily routines of centenarians.

Beyond nutrition and lifestyle, numerous factors environmental have contributed to the rise in life expectancy since the late 19th century. Socioeconomic development, marked by increased job opportunities, higher incomes, improved working conditions, and education, has played a pivotal role [303,304]. Advances in medical technology [305], improvements in water and sanitation [306], widespread vaccination [307], and the availability of antibiotics [308] have collectively reduced deaths from infectious diseases, further extending life expectancy.

Discussions

Although LLIs delay the onset of high mortality risk-associated diseases toward the end of their lives, many of them have a history of enduring chronic age-related diseases for many years, with women experiencing these more than men. However, the majority of centenarians seem to manage these chronic diseases effectively, often avoiding disability until well into their nineties. This variability in health among long-lived individuals suggests multiple pathways to longevity in humans. One approach is complete avoidance of chronic diseases until late in life, known as the “compression of morbidity” hypothesis [27], observed in approximately one-third of centenarians categorized as “escapers” [31] or Group A [56]. Conversely, others survive with one or more chronic age-related diseases, sharing similar genetic risk mutations [309,310]. Future research should stratify centenarians based on health status to explore distinct protective mechanisms and factors associated with longevity.

Despite delaying or avoiding most age-related diseases, LLIs carry genetic risk factors for such diseases, as highlighted by recent GWAS data [309,310]. These studies indicate that LLIs share the same number of risk alleles for AD, CVD, cancer, and type 2 diabetes (T2D) as younger controls from the same population. This suggests that human longevity is not compromised by the cumulative effect of these risk alleles [309]. Protective mechanisms likely play a role in determining human longevity, possibly through favorable genetic or nongenetic factors that counteract the deleterious effects of age-related disease genotypes. CVD, which results from increased cholesterol levels and activation of the inflammatory cascade [311], is mitigated in LLIs due to their less atherogenic plasma lipid profile and enhanced anti-inflammatory responses. Insulin resistance, a risk factor for T2D [312] and CVD [313], typically increases with age, peaking around 80 years, but LLIs aged 90 to 100 years exhibit significantly lower insulin resistance [314]. This preserved low insulin resistance in LLIs may help mitigate T2D and CVD risks. Additionally, LLIs may protect against AD through lower frequencies of APOE-ε4 alleles and the IL-10 promoter −1082A allele, both of which are risk factors for AD [73,315].

Longevity is influenced by a complex interplay of genetic, epigenetic, and environmental factors, exhibiting considerable variability within families and populations. This complexity makes it challenging to replicate findings across different populations due to the interaction of genetic and environmental factors. For instance, while genetic polymorphisms around or within APOE and FOXO have been consistently associated with longevity, other GWAS have struggled to replicate these findings [69]. Given the intricate nature of genetic and environmental interactions, confirming common functional genetic variants contributing to longevity across diverse ethnicities and regions worldwide remains difficult. Therefore, omics approaches such as transcriptomics, proteomics, and metabolomics are crucial for elucidating the underlying mechanisms associated with longevity in LLIs. For example, transcriptomic analysis of peripheral white blood cells in Chinese centenarians revealed enhanced autophagy-lysosomal function as a promoter of human longevity [316]. Additionally, transcriptomes of LLIs from separate Chinese longevity cohorts identified significant downregulation of the ribosome pathway, attributed to reduced ETS proto-oncogene 1, transcription factor (ETS1) levels [317]. Furthermore, studies of the serum metabolome in LLIs highlighted elevated fatty acid oxidation (FAO) as a prominent metabolic feature [318]. Reports on the serum proteome of LLIs compared to controls indicated slower aging in LLIs [319] and identified several longevity-related pathways [320]. However, these studies often lack animal experiments to explore anti-aging mechanisms and specific functional factors *in vivo*. Recent findings suggest that administering single serum proteins or supplementing specific metabolites can potentially ameliorate age-related functional declines in mice [321–324]. Future research should focus on identifying and validating potential longevity-promoting factors through serum proteomics or metabolomics of LLIs, corroborating their anti-aging effects through functional experiments in live animals.

Conclusions

Longevity is a multifaceted characteristic shaped by genetic factors, environmental influences, and their interplay. LLIs, as exemplars of human longevity, often evade or delay the onset of age-related diseases, making them an outstanding subject for studying healthy aging and discovering potential anti-aging factors.

The identified factors associated with longevity can be categorized as follows:

(1) Genetic polymorphisms at numerous loci, encompassing nuclear genomic variants, mitochondrial variants, and telomere-related variants.

(2) Epigenetic features, including the role of non-coding RNA in longevity and anti-aging processes.

(3) Metabolic profiles characterized by less atherogenic lipid profiles, lower insulin resistance, and reduced oxidative stress, along with specific endocrine factors and sex hormones.

(4) Immune factors, such as preserved immune cell functionality and an enhanced anti-inflammatory response.

(5) Environmental and lifestyle factors, which may include a gut microbiota that promotes longevity, caloric restriction, plant-based diets, regular physical activity, and other lifestyle choices.

Looking ahead, further research should employ transcriptomics, proteomics, and metabolomics to uncover additional factors that may promote longevity. These studies should leverage large, diverse longevity cohorts and incorporate longitudinal study designs to enhance understanding. Most importantly, future studies must establish the causal relationships of potential longevity factors through functional experiments using model organisms, particularly mice and nonhuman primates. Further, clinical trials should be conducted to evaluate the benefits and potential side effects of these longevity-promoting factors, as well as their possible role in ameliorating age-related diseases.

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Compliance with ethics guidelines

Conflicts of interest Fan-Qian Yin, Fu-Hui Xiao, and Qing-Peng Kong declare no conflicts of interest.

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