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To what extent does telomere length influence aging and related diseases, and what are the relative contributions of genetic and environmental factors to telomere length?

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Abstract. In recent years, aging and anti-aging have become a very common problem among some middle-aged people. Biologists have discovered that telomeres play a crucial part in our aging process because they can prevent genes on chromosomes from being lost. Moreover, some diseases are also associated with telomere length. Around 85% of malignant cells reactivate telomerase, enabling infinite cell division and continuous growth. Additionally, a variety of environmental factors, such as smoking and genetic factors, can influence telomere length. These make it worthwhile to investigate the subject. The primary research question of this project is how telomere length is related to aging and some related diseases, and what factors influence it. To address this question, this research adopts literature review, data comparisons, theoretical research. Besides, this research collects and analyzes academic sources, official data, and authoritative studies. Key findings indicate that telomere length has a significant relationship with genetic and environmental factors. Some studies also show that telomere length can increase in those who have healthy lifestyles. Furthermore, the telomere length is also associated with diseases related to some organelles. As people's ages increase, the telomere length will decrease because telomere length will be shortened at each cell division. Overall, this project clarifies the connection between telomere length and the aging process as well as several ways to shorten telomeres. However, there are also several limitations, such as limited area coverage and tiny sample sizes. Therefore, more research should be conducted and thoroughly investigated.

Keywords: telomere, cellular senescence, age-related diseases, telomerase

1. Introduction

1.1. Introduction to telomeres

Aging is an inevitable, poly-factorial biological process characterized by progressive physiological decline, increased susceptibility to chronic diseases, and reduced functional capacity across all organ systems [1]. For decades, researchers have worked to understand the molecular mechanisms driving aging, and one of the most compelling candidates is the telomere: a repeated DNA sequence (TTAGGG) that caps the ends of linear chromosomes, preserving coding genes from loss during cell division [2]. During each DNA replication,

telomere length is shortened slightly, "end-replication problem" first described by Alexey Olovnikov. Once telomeres reach a critically short length, cells will no longer grow and will enter an irreversible state known as replicative senescence, or undergo apoptosis, limiting the reproductive capacity of somatic cells [3, 4]. The "telomere theory of aging" holds that telomere attrition is a major cause of aging and age-related diseases. These diseases include cancer, neurodegenerative disease, cardiovascular disease, and others [5, 6].

However, there is much more to the association between telomere length and aging than just a simple linear correlation. Shorter telomeres are consistently linked to older age and a higher risk of age-related morbidity and mortality, according to cross-sectional research [7]; the causal direction and magnitude of this association remain subjects of intense scientific debate [8].

Furthermore, telomere length is not solely determined by chronological age: it is a complex trait that can be controlled by genetic and environmental factors and also has a very close relationship with lifestyle [9]. Key loci linked to telomere preservation have been found through genome-wide association studies. These loci include variations in the TERT, TERC, and POT1 genes, which encode elements of the shelterin protein network and the telomerase complex [10, 11]. At the same time, the rate of telomere shortening can be accelerated by controllable factors. For example, oxidative stress, chronic stress, inflammation, nutrition, physical activity, and socioeconomic position can speed up telomere shortening [12-14].

1.2. Aims of the project

This raises two important, linked research concerns that are at the center of this Extended Project Qualification (EPQ) project: first, how much does telomere length act as a factor that can cause human aging and the emergence of age-related disorders, as opposed to just acting as a correlative biomarker? Second, how much do environmental and genetic factors contribute to inter-individual variance in telomere length over the course of a lifetime, and how might these factors interact to shorten telomere length?

This project aims to address these questions through a comprehensive, systematic analysis of existing epidemiological, genetic, and molecular research. The primary objectives are: 1) to critically evaluate the evidence supporting telomere length's impact on age-related diseases and aging, distinguishing between correlation and causation; 2) to quantify the heritability of telomere length and identify key genetic loci and pathways that regulate telomere maintenance; 3) to synthesize the impact of modifiable environmental and lifestyle factors on telomere attrition, and assess their relative contribution compared to genetics.

This research aims to provide a comprehensive, evidence-based understanding of telomere biology in the context of human aging by combining data from population health, human genetics, and molecular biology. This research addresses common misconceptions, such as the oversimplified view of telomeres as a "biological clock" that directly determines lifespan, and highlight the complex, bidirectional relationships between telomere length, disease, and lifestyle. Ultimately, this research contributes to the broader goal of understanding the mechanisms of aging, with the potential to inform strategies for delaying age-related decline and improving healthspan in the global population.

2. Literature review

2.1. Structure and function of telomeres

Telomeres are special structures at the ends of eukaryotic chromosomes and are non-coding parts of DNA. In vertebrates, telomeres are composed of TTAGGG repeats [15]. Blasco states that T-loops are formed as a result of a G-rich overhang (G-tail) which is single-stranded at the 3' end. The T-loop might be a rudimentary telomere protection mechanism (as shown in Figure 1). In conclusion, a T-loop effectively shields a

chromosome's natural terminus. Additionally, each cell division causes the telomeres at the ends of human chromosomes to naturally shrink [2].

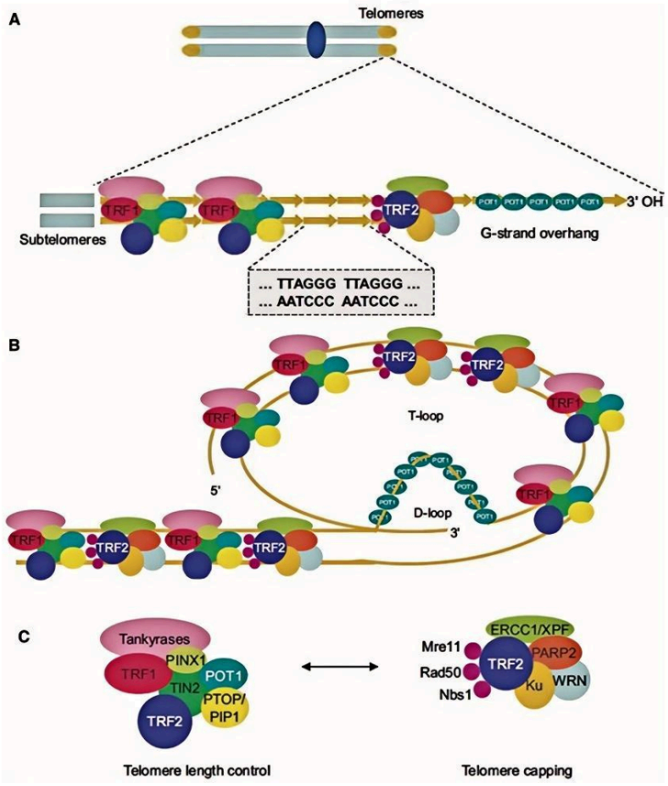

Figure 1. A telomere structure composed by a double strand region of –TTAGGG– repetitions and by a G-strand overhang [16]

Huang state that after every cell division, about 200 to 500 base pairs of telomeres are lost from DNA, despite the protection provided by the protein shelterin [17]. This is because DNA polymerase only synthesizes DNA in the direction from 5' to 3', which makes it impossible to fully replicate the ends of chromosomes. Telomeres protect the integrity of genetic information by acting as buffers. Telomeres are frequently regarded as the "mitotic clock" of human biological age because telomere length reflects cellular replicative history.

2.2. The link between telomeres and aging

Telomeres are a very important part of our chromosomes. Because of them, our coding regions can be protected. According to Herrmann: On the one hand, telomeres can protect chromosomal ends by preventing unwanted recombination and destruction [16]. On the other hand, because they prevent the loss of coding DNA, they are essential to DNA replication. At the end of each chromosome, the free 3′-OH end is protected from detection as a double strand break by the three-dimensional folding of telomeres [18].

Additionally, telomeres play a vital role in developmental pluripotency. Pluripotent stem cells are unspecialized and retain the ability to divide indefinitely and then specialize into body cells. There is some evidence to support this. At Nankai University, a group demonstrated that Embryonic Stem Cells (ESCs) with long telomeres showed bona fide developmental pluripotency, especially in generating complete ESC-derived pups and germline-competent chimeras. From these observations, it appears that functional telomeres are

crucial for maintaining embryonic stem cells or inducing pluripotent stem cells, and may be a marker for evaluating pluripotency. In order to produce germline-competent chimeras and complete ESC pups, this group demonstrated that ESCs with extended telomeres showed genuine developmental pluripotency. These findings demonstrate the need for functioning telomeres to preserve embryonic stem cells or to generate pluripotent stem cells, and they may serve as a marker for assessing pluripotency.

The idea that cells have a limited number of divisions, or the Hayflick limit, is strongly related to telomeres. Critically short telomeres cause cells to go into a senescent state and lose the capacity to divide normally, and eventually lead to malfunction and cell cycle arrest [17]. In the United States, the mortality risk in the adult population is additively increased by shorter telomeres and accelerated epigenetic aging (as illustrated in Figure 2). At birth, telomeres are at their longest, and as people age, they progressively become shorter. At the cellular level, telomere length and age are tightly related; however, this relationship is less clear at the organism level, such as in humans, whose telomere length varies greatly from 5,000 bp to 15,000 bp at birth [19, 20].

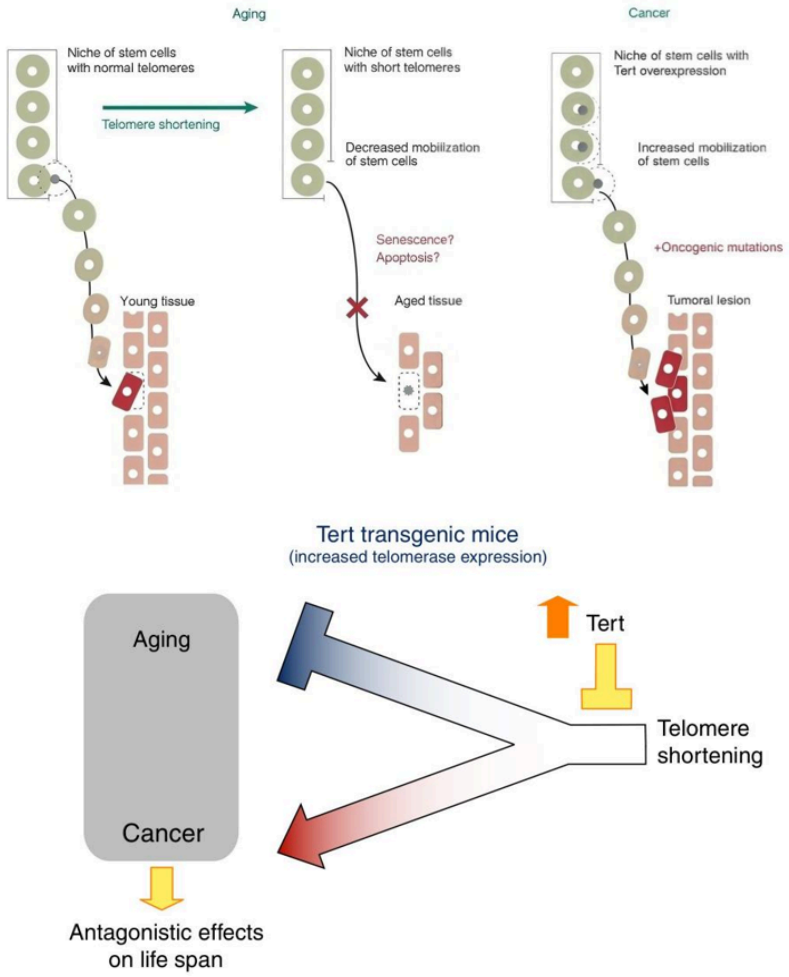

Figure 2. Changes in Chromosome structure

2.3. Diseases linked to telomeres

Xu state that telomere length shortening can result in a variety of illnesses [17].

Non-Alcoholic Fatty Liver Disease (NAFLD) progression is significantly correlated with telomere length, according to research ([21-23]. Telomere Length (TL) is probably a key player in this intricate relationship, leading to the senescence of liver cells, which impacts the liver's general health and advances NAFLD. According to the findings of a controlled experimental study, the telomeres of liver cells in patients with NAFLD are shorter than those in the control group [24]. TL and heart disease have been found to be strongly associated in numerous studies [25, 26].

Telomere shortening and dysfunction are caused by oxidative stress and persistent inflammation, which frequently accompany the pathogenic course of Cardiovascular Disease (CVD). A meta-analysis investigated 12 studies including 18,293 participants on Leukocyte Telomere Length (LTL) and atrial fibrillation and concluded that LTL can be a predictor [27]. Furthermore, in a study with a sample of 22,233 patients, telomere gene testing revealed genetic variations connected to shorter telomeres. The results show an association between shorter telomeres and risk of coronary artery disease [10]. The severity of atherosclerotic plaques is correlated with a decrease in TL in Vascular Smooth Muscle Cells (VSMCs).

Furthermore, it is found that in atherosclerotic plaques, oxidatively damaged DNA and a number of aging markers are expressed by VSMCs. Telomere shortening-related atherosclerosis is accelerated by accelerated telomere attrition, which also worsens endothelial damage, hinders vascular lesion repair, and increases oxidative stress and inflammatory processes [17] (see Figure 3).

According to a case-control study that included 206 Essential Hypertension (EH) patients and an equivalent number of sex-matched healthy controls, EH patients had significantly shorter TL [27]. In contrast to earlier research, a genome-wide association study found that there is a relationship between longer TL and an increased risk of hypertension [28].

Other conditions, such as bronchiectasis, kidney diseases, chronic obstructive pulmonary disease, kidney fibrosis, neurological diseases, and skeletal abnormalities, are also linked to telomere length reductions, as shown in Figure 4.

Additionally, the risk of death in US adults is additively increased by shorter telomeres and rapid epigenetic aging. Telomere length can be used as a significant biomarker of aging and mortality risk, as evidenced by the cumulative influence of these two factors on mortality rather than their separate effects. The combined effects of decreased telomere length and accelerated epigenetic aging are especially pronounced in older adults over 65 [29]. (* The Horvath Epigenetic Clock model served as the foundation for the computation of epigenetic age acceleration.)

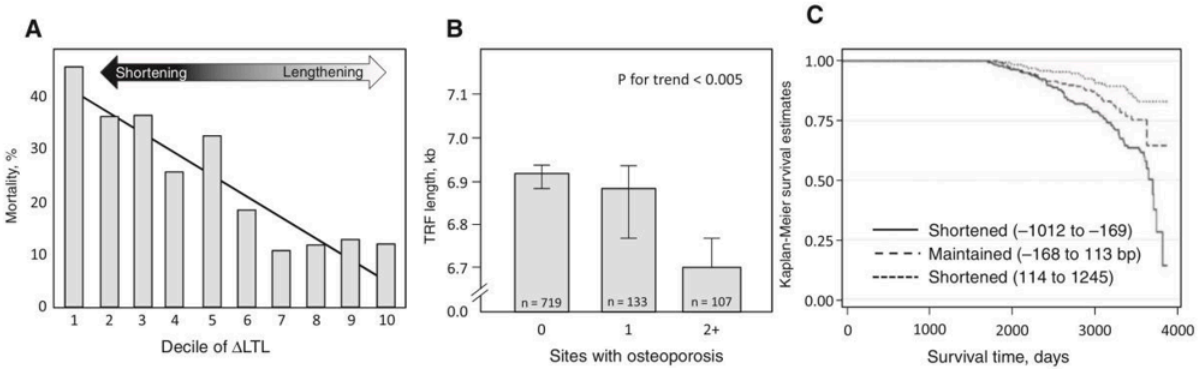

Figure 3. Telomere protction mechanisms [17]

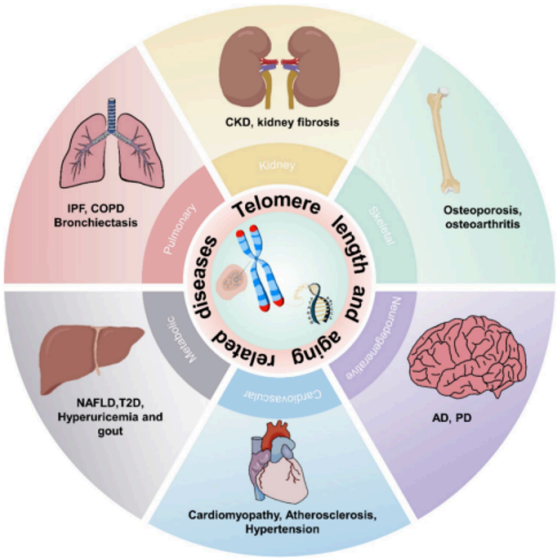

Figure 4. Telomere lengthassociated agingrelated multiorgan diseases

2.4. Genetic factors influencing telomere length

Telomeres can be impacted by genetic factors such as telomerase. They have the ability to stop telomeres from getting shorter. Human embryonic tissues have the highest telomerase activity, which is inversely correlated with age [30]. When telomerase is absent during normal somatic cell division, telomere length is reduced and telomeric repeats are eroded.

Additionally, telomerase catalyzes the activity of human telomerase reverse transcriptase. It also comprises a crucial auxiliary protein called dyskerin and a related template RNA called telomerase RNA component [18]. Telomere erosion can be prevented and cellular senescence can be avoided by using retroviral-mediated active gene transfer into primary human fibroblasts [31]. However, telomerase is expressed in cells that are rapidly proliferating and it maintains the immortal state by stabilizing telomere lengths. Telomerase activity is necessary for the stability of telomeres, which are crucial for many cellular functions.

Telomere length can therefore be used to predict the prognosis of diseases, including different types of cancer, and is a possible sign of telomerase activity [32]. DNA polymerase can only synthesize a new DNA strand in the direction from 5' to 3', so the replication of the lagging strand is incomplete. As a result, during each cell division, telomere length is shortened, according to Saldanha [33].

Senescent cells lose their ability to proliferate and have short telomere lengths. In contrast, around 90% of immortal tumorigenic cell lines express high quantities of telomerase and have only slightly decreased telomere lengths. Thus, telomerase can be used to preserve the stability of telomere length, as shown in Figure 5. Furthermore, telomere length can be influenced by gender. Additionally, as noted by Sergio Andreu-Sánchez, telomere length and gene sequence vary among cells.

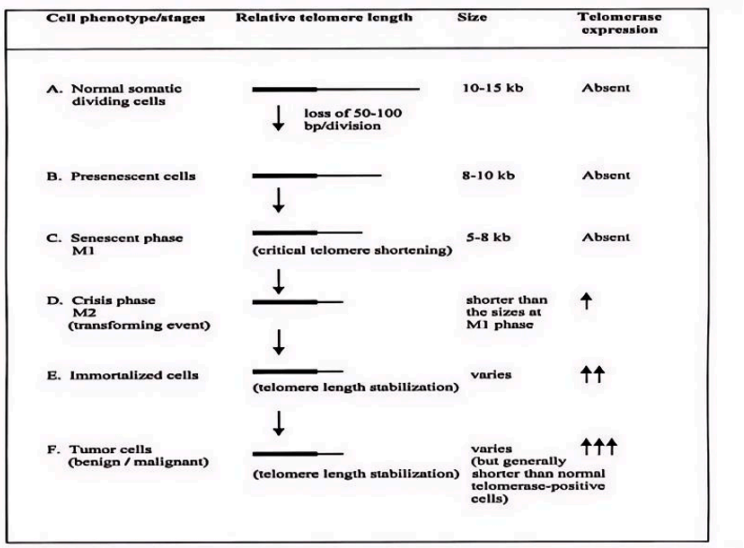

Figure 5. Telomere length and lelomerase expression in different cell states [33]

2.5. Environmental factors influencing telemere length

Environmental variables can also influence telomere length. The average leukocyte telomere length is 11 kbp at birth and decreases to less than 4 kbp in older people. Numerous factors are related to short telomere length, such as gender, physical activity level, smoking, alcohol consumption, hormones, dietary antioxidants, socioeconomic status, and perceived stress levels [34, 35]. For instance, women's telomeres are longer than men's due to higher levels of estrogen, which can boost telomerase activity and have antioxidant benefits. Additionally, people with higher levels of stress have shorter telomeres than people with lower levels [36].

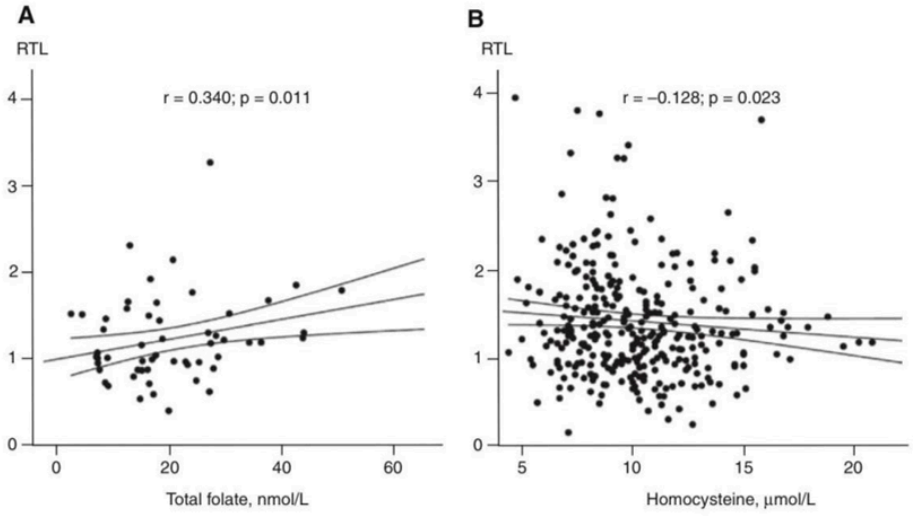

Figure 6. Associations of relative telomere length with total folate and homocysteine levels [37]

Additionally, vitamins (such as nicotinamide, vitamins A, B12, and C), minerals (such as iron, magnesium, and zinc), and other dietary components (such as omega-3 fatty acids and polyphenols) can influence LTL in a variety of ways. Herrmann found that LTL and the availability of B and D vitamins have been consistently linked in studies [37-39].

In an investigation, Herrmann discovered a correlation between LTL and serum folate and its metabolites, as shown in Figure 6 [16]. Additionally, Sergio Andreu-Sánchez claims that a mother's age and habits, such as whether or not she smokes, have an impact on the methylation levels of her offspring. This is supported by a study which included a sample of 674 fathers and 381 mothers.

3. Discussion

3.1. Telomere in aging causation or correlation

Telomere shortening is generally accepted as one of the key features of cellular aging, and a lot of the cross-sectional evidence seems to back this up. Studies tend to show that telomere length in blood cells declines by about 20–30 base pairs each year [40]. for example, Mather found that older adults with shorter telomeres had a 24% higher risk of dying from any cause, which on the surface makes telomere length look like a pretty good marker of biological aging [41]. But I think it's important to be careful here correlation isn't causation. Although shorter telomeres are linked to aging, we cannot say that they are the main factor that makes people age. This is a crucial limitation. Most epidemiological studies only show associations, not causal relationships, and over-reliance on correlation may lead to an overestimation of telomeres' direct role in aging. The animal evidence is more convincing on this point. Blasco's team did an experiment called "telomerase reactivation rescue" [15]. They used gene knockout technology to delete the mouse telomerase RNA component gene (mTR gene), which created mice without any telomerase activity. The results showed that the first and second generations had a normal appearance and could reproduce, but did not show any premature aging.

However, after the third generation, every generation showed a result that the telomeres became shorter sharply and continuously. Moreover, starting from generation 4, severe premature aging occurred, such as graying hair, spinal curvature, decline in immune function, anemia, markedly shortened lifespan, and significantly increased mortality rate. This experiment is well-designed with clear loss-of-function and gain-of-function controls, providing strong causal evidence linking telomerase, telomere maintenance, and aging in mice. Then the team also did a reverse experiment: they added telomerase to the telomeres of the mice that had premature aging, and this caused some symptoms of aging to be reversed, and the lifespan could be lengthened. From this experiment, we can infer that telomerase plays a vital role in maintaining telomere length, maintaining the stability of chromosomes, and delaying aging and mortality. That kind of experimental evidence suggests telomere length isn't just a passive clock ticking away—it might actually be playing an active role in how we age. In addition, there are some differences between human telomeres and mouse telomeres; now we know the function of telomerase in mice, but the real function in humans remains to be further explored because the conclusion so far is based on mice; the role of telomerase in humans is inferred from such animal studies. Directly extrapolating mouse data to humans is risky because telomere regulation and telomerase activity differ significantly between species. This is a major limitation when applying animal findings to human aging. That raises the question: why do some people seem to age faster than others? From what I've read, genetics seems to set the baseline. Twin studies give us a pretty clear picture here. Broer et al. looked at data from 28 twin studies and estimated that somewhere between a third and two-fifths of the variation in telomere length is due to genetics, and that figure stays fairly consistent throughout adulthood [42]. GWAS have also identified a number of genes involved in telomere maintenance—TERT, TERC, OBFC1, RTEL1, to name a few [43]. What struck me was the size of the effect: the TERT variant rs10936599, for instance, is linked to a difference in telomere length equivalent to about four to six years of aging. That suggests that for some people, their genetic makeup effectively "ages" them from birth. Twin and GWAS

studies complement each other effectively, strongly supporting that genetics establishes the baseline length of telomeres.

3.2. The relationship between aging and genetic factors like telomerase

There's also a really interesting intergenerational effect that I came across. Paternal age seems to matter—children born to older fathers actually have longer telomeres, and this carries over into the next generation. From the study we know that the leukocyte telomere length of offspring increases on average by 17 base pairs for each one-year increase in paternal age. This is because as a man's age increases, the activity of telomerase (which can be continuously activated) elongates the telomere length of sperm. This lets the telomeres of the sperm become longer; moreover, this can be inherited [44]. The experiment conducted by De Meyer et al. had a sample limited to a middle-aged white Belgian population.

This conclusion has not shown that such a phenomenon also exists in other races and age groups. The paternal age effect is an intriguing discovery, but the sample is narrow and ethnically restricted, so the generalizability of this conclusion is low. Apparently, this is because telomerase in sperm cells becomes more active with age, which means older fathers pass on longer telomeres to their children. It's a clear example of how genetic and epigenetic factors can shape aging trajectories right from the start, independently of lifestyle or environment. Also, I think that there are some limitations to the experiments that I referred to in this essay. For example, the experiment studying telomere length in different regions was limited to people in the USA, so it is not accurate to represent the pattern in the whole world. Over-concentration on western populations reduces the diversity and global validity of the overall conclusions.

3.3. The relationship between environmental factors and telomere length

Of course, that doesn't mean environment doesn't matter. Smoking, chronic stress, poor diet—these things clearly take a toll. Epel et al. found that women caring for a chronically ill child had telomeres that looked about a decade older than those of a control group, which is a pretty shocking finding [45]. Smoking is linked to a roughly 9% reduction in telomere length, equivalent to about three to four years of aging; also, as the amount and duration of smoking increase, telomere length decreases more significantly [46]. This study strongly connects psychological stress to accelerated telomere loss and provides key evidence for environmental effects on aging. But I think what's more interesting is that these effects don't hit everyone equally. Some evidence suggests that people with genetically longer telomeres are more resilient to environmental stress, while those with shorter telomeres are more vulnerable. In this study, the independent variables included environmental stress and some bad habits, as well as baseline telomere length. The dependent variable was the rate of telomere length shortening. This research found that in the longer telomere length group, although exposed to higher pressure, smoking, or other adverse environments, telomere length decreased less significantly than in the shorter telomere length group, which had a rate twice that of the longer telomere length group [46]. This finding is valuable because it explains why people age differently under the same environmental pressures. The limitation of Kim et al.'s research lies in the measurement of baseline telomere length. Most studies only measure telomere length at a single time point, which cannot fully distinguish between genetically determined baseline length and age-related wear and tear caused by external factors. To me, that suggests environment is more of a modulator than a primary driver—it can speed things up or slow them down, but it's working within boundaries that genetics has already set.

3.4. Ways to improve telomerase activity

What I found particularly interesting and a bit surprising is that even fairly intensive lifestyle interventions don't seem to fundamentally alter genetically determined trajectories. Ornish et al. ran a randomized controlled trial looking at comprehensive lifestyle changes—diet, exercise, stress management—and did find an increase in telomerase activity. For instance, through exercise and stress control, oxidative stress and chronic inflammation in the body can be reduced, thereby minimizing oxidative damage to telomeres and slowing down telomere attrition [47]. This experiment lasted for five years and investigated the impact of lifestyle changes on telomerase activity and telomere length in men with low-risk prostate cancer. The final conclusion was that the telomere length of volunteers who followed a healthy lifestyle increased significantly over time, while that of the control group decreased over time. The research is the first to provide human evidence that proves that lifestyle can affect aging processes by regulating telomere dynamics. This is a high-quality RCT with strong internal validity, making it one of the most reliable human studies in this field. In addition, the assay conducted by Ornish et al. has some deficiencies: the sample is too small and cannot represent all the cases; the intervention group contained only 10 people and the control group had only 25 people; to obtain more accurate conclusions, the same type of test should be conducted on a larger sample. Moreover, the sample contained only men and not women, and the study was also limited to the USA. However, whether that actually translates into reversing telomere shortening in a meaningful way over the long term remains uncertain. The evidence does not yet convincingly support this conclusion.

3.5. Argument

Some articles argue that environmental factors are the most significant factor that can affect telomere length. For example, Delfarre et al. obtained results showing that if people are exposed to air pollution such as PM2.5, NO_2, and SO_2, the telomere length of white blood cells decreases significantly. According to Cushing et al., traffic pollution, noise pollution, lack of green space, and psychological stress act together to cause the telomere length of newborns to decrease sharply. Valdes et al. found that smoking, heavy metals, and chronic stress are associated with shorter telomeres, whereas a healthy diet and regular exercise are associated with longer telomeres [48]. These experiments are based on large samples rather than individual cases.

Other studies suggest that genetic factors play a major role. For example, Broer et al. found that approximately 70% of telomere length is hereditary, and genetic factors account for the vast majority of individual differences in telomere length [42]. Moreover, Codd et al. found 197 independent genetic loci that control telomere length; genetically determined telomere differences can influence lifespan and the risk of diseases directly [49]. According to Nelson et al., mutations in telomere-related genes such as POT1 and RTEL1 cause telomere length to be short in an entire family, and this increases the risk of developing cancer [50]. Both sides present strong evidence, and their disagreement shows that telomere regulation is complex and cannot be reduced to one single factor. In my opinion, both environmental factors and genetic factors play very important roles in telomere length. Just as mentioned above, maintaining healthy living habits may effectively improve telomere length. However, telomere length is also controlled by genes and has a very close relationship with telomerase. Overall, genetics sets the baseline and limits, while environment modifies the rate of telomere loss. This integrated view best fits the current evidence.

4. Conclusion

By carefully analyzing the evidence for telomeres' role in aging, this project has addressed two major questions: the causal extent of telomere length's influence on aging and disease, as well as the contributions of

genetic versus environmental factors to interindividual variation in telomere length.

First, research shows that telomere length is a trustworthy indicator of aging. A higher all-cause mortality rate and an increased risk of numerous age-related diseases, including cardiovascular disease, type 2 diabetes, neurodegenerative diseases, and some types of cancer, are linked to shorter telomere length in white blood cells, according to consistent epidemiological evidence. However, the causal nature of these associations remains nuanced. While experimental and genetic studies (e.g., Mendelian randomization) support a causal role for short telomeres in driving specific pathologies, such as pulmonary fibrosis and bone marrow failure, the relationship with common age-related diseases is often bidirectional: chronic inflammation, oxidative stress, and disease states themselves accelerate telomere attrition, creating a vicious cycle. Telomere shortening is therefore not a primary, universal "cause" of aging, but rather a key mediator and biomarker of the aging process, reflecting cumulative biological damage and stress over time.

Second, regarding the determinants of telomere length, this research demonstrates that both genetic and environmental factors play significant, complementary roles. Genetic factors, including variants in telomere maintenance genes (e.g., TERT, TERC, POT1) and global polygenic scores, explain approximately 30-50% of interindividual variation in baseline telomere length, with particularly strong effects on early-life telomere setting. Environmental and lifestyle factors, by contrast, primarily influence the rate of telomere attrition across adulthood. Chronic psychological stress, exposure to adversity, poor diet, physical inactivity, smoking, and low socioeconomic status are consistently associated with accelerated telomere shortening, while healthy lifestyle behaviors (e.g., regular physical activities, balanced diet, stress management) may mitigate attrition. Critically, environmental factors can modify the expression of genetic predispositions, highlighting the importance of gene-environment interactions in shaping telomere dynamics.

These findings have profound implications for clinical practice and public health. Telomere length measurement has potential as a prognostic biomarker for age-associated risk for diseases from a clinical standpoint, but its routine clinical use is currently constrained by technical variability and the absence of standardized reference ranges. From a public health standpoint, the modifiability of telomere attrition through lifestyle and social interventions underscores the potential to promote healthy aging at a population level. Interventions targeting chronic stress, improving access to healthy food and healthcare, and reducing health disparities may slow telomere shortening, delay age-related disease, and extend healthspan.

Looking forward, future research should address key limitations in the current literature, including the need for large, longitudinal cohort studies with repeated telomere measurements, standardized assay methods, and integration of data to unravel the causal pathways linking telomeres to aging. Additionally, research into telomere-targeted therapies, such as telomerase activation, should proceed with caution, given the well-documented link between telomerase upregulation and cancer risk.

In conclusion, telomere biology offers a powerful lens through which to understand the aging process, bridging molecular genetics, population health, and clinical medicine. While telomere length is not a simple "clock" that dictates lifespan, it is a critical indicator of biological resilience and cumulative life stress. By understanding the factors that shape telomere length and attrition, we can move toward a future where aging is not just a process of decline, but a period of health, vitality, and well-being, supported by evidence-based strategies to protect and preserve telomere integrity across the lifespan.

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