How Chronic Stress Accelerates Biological Aging Through Physiological and Cellular Mechanisms

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Abstract

Chronic stress is more than a persistent anxiety or exhaustion; its effects extend deep within the body, disrupting physiological and cellular processes over time. While individuals initially experience acute stress as a temporary, short-term response to challenging situations, persistent hardship and adversity can prolong and contribute to the development of chronic stress. Beyond its psychological effects, chronic stress is increasingly recognized as a key agonist in accelerating biological aging in humans. This literature review seeks to examine the underlying physiological and cellular mechanisms contributing to this process, including telomere shortening, oxidative stress, mitochondrial dysfunction, cellular senescence, impaired neural stem cell function, chronic inflammation, and epigenetic aging associated with prolonged stress. Current research suggests that chronic stress can significantly disrupt multiple physiological systems, leading to a rapid decline in biological function and increased susceptibility to aging-related diseases. Collectively, these mechanisms interact and contribute to accelerated biological aging. Understanding these mechanisms may contribute to increasing public awareness of the long-term consequences of chronic stress and provide a strong foundation for future research aimed at preventing biological aging due to chronic stress.

1. Introduction

Stress is a natural physiological response experienced by all humans. It assists the body's ability to respond to danger or challenging situations by releasing hormones such as adrenaline and cortisol. While acute stress is a short-term response that can be beneficial in helping the body adapt to immediate threats, repeated exposure to stress can develop into chronic stress, which may cause significant damage to the body over time. Chronic stress is the persistent exposure to stress that lasts for weeks, months, or even longer (Hansen et al., 2024). For example, some families may experience financial hardship, such as long-term debt or poverty, creating ongoing worry about providing for their children. As these stressors persist, parents may experience daily anxiety, physical fatigue, and emotional exhaustion. Over time, this continuous burden can negatively affect multiple physiological systems and accelerate biological aging. Globally, the prevalence of chronic stress has increased due to ongoing psychological, social, and environmental stressors, as well as the lasting effects of trauma and adversity experienced throughout life.

While chronological age represents the number of years a person has lived, biological age measures the functional condition of cells, tissues, and organ systems. Depending on genetics, lifestyle, and the amount of stress an individual experiences, a person's biological age may differ

from their chronological age. Growing evidence suggests that chronic stress influences biological aging by disrupting multiple physiological and cellular mechanisms. Physiological mechanisms describe processes involving the function and interaction of organs and organ systems that help maintain the body's overall health and balance. In contrast, cellular mechanisms describe processes occurring at the cellular level, including changes in function, growth, and communication. Although physiological and cellular mechanisms are often used together in situations, they contribute to biological aging in distinct ways. Over the past few decades, researchers have increasingly investigated the relationship between chronic stress and biological aging, identifying several factors that contribute to this process. Rather than being driven by a single biological factor, studies suggest that accelerated biological aging results from the complex interplay of multiple mechanisms. As these mechanisms influence one another, they amplify the long-term biological effects of chronic stress.

Understanding the relationship between chronic stress and biological aging has become increasingly important as chronic stress continues to affect millions of people worldwide. By synthesizing current research across multiple physiological and cellular pathways, this literature review provides a more comprehensive understanding of how chronic stress contributes to accelerated biological aging.

2. Telomere Shortening

Telomeres are protective DNA-protein structures located at the end of chromosomes that consist of repeating DNA sequences. During cell division, DNA must be replicated so that each new cell receives a complete copy of DNA. However, the enzymes responsible for DNA replication cannot fully copy the very ends of chromosomes, leaving a small portion of the telomere unreplicated and gradually shortening the telomere with each cell division (Lin & Epel, 2021). Although telomere shortening occurs naturally, chronic stress may accelerate this process through increased oxidative stress, chronic inflammation, and impaired telomerase activity (an enzyme that helps maintain telomere length by adding repeated DNA sequences to chromosome ends). As shown in Figure 1, higher perceived stress has been associated with shorter telomere length, supporting the connection between chronic stress and biological aging.

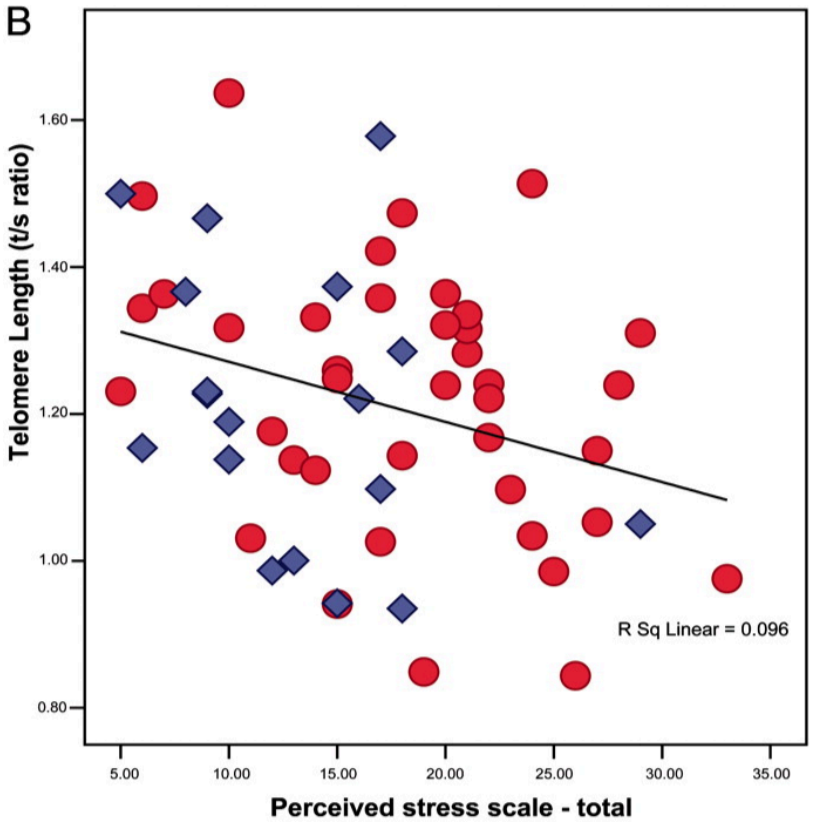

Figure 1. *Relationship Between Perceived Stress and Telomere Length*. *Note.* Adapted from "Accelerated Telomere Shortening in Response to Life Stress," by E. S. Epel et al., 2004, *Proceedings of the National Academy of Sciences, 101(49)*, 17312–17315.

3. Oxidative Stress & Mitochondrial Dysfunction

One mechanism through which chronic stress may contribute to biological aging is the disruption of the body's normal stress response. Chronic reactivation of the stress response and repeated surges of cortisol can lead to cortisol dysfunction, which may impair cortisol's normal anti-inflammatory effects (Hannibal & Bishop, 2014). As a result, increased inflammation can contribute to oxidative stress and subsequent cellular damage. Oxidative stress occurs when the production of reactive oxygen species (ROS) exceeds the body's ability to neutralize them (Yegorov et al., 2020). Mitochondria are major producers of ROS within cells, and although ROS serve important roles in normal cellular processes, excessive production can contribute to oxidative stress. Chronic stress can alter mitochondrial function, including processes involved in cellular energy production, and some experimental studies have observed increased mitochondrial ROS production following chronic stress (Picard & McEwen, 2018). Over time, these alterations may contribute to mitochondrial dysfunction, further increasing oxidative stress, inflammation, and cellular damage.

As mitochondrial function progressively deteriorates, these effects can contribute to the aging process (López-Otín et al., 2023). In addition to causing cellular damage, elevated oxidative stress can increase the loss of telomeric DNA, contributing to accelerated telomere shortening. According to Yegorov et al. (2020), an earlier study of premenopausal women found an association between psychological stress, oxidative stress, and accelerated telomere shortening, providing evidence of this relationship within a specific human population. As telomeres become critically short, they can signal DNA damage and cause cells to stop dividing, potentially leading to cellular senescence. Therefore, accelerated telomere shortening from chronic stress may contribute to biological aging by causing cells to stop dividing, leading to the accumulation of senescent cells that can contribute to tissue dysfunction and degeneration (Lin et al., 2021).

4. Cellular Senescence

Cellular senescence is a fundamental aging process in which damaged cells stop dividing while remaining metabolically active. Although this process initially serves an important function by preventing damaged cells from replicating, senescent cells can resist apoptosis (programmed cell death) and accumulate over time, contributing to tissue dysfunction and biological aging (Lyons et al., 2023). Cellular senescence can be triggered by several forms of cellular damage, including severe DNA damage, telomere shortening, and mitochondrial dysfunction, demonstrating how multiple effects of chronic stress may contribute to biological aging (Polsky et al., 2022). Chronic stress can cause the body to repeatedly release stress hormones, including norepinephrine and epinephrine (hormones involved in the fight-or-flight response). Prolonged exposure to these stress hormones can increase DNA damage, causing damaged cells to stop dividing to prevent the damaged DNA from being passed on to new cells (Hansen et al., 2025). Although senescent cells can no longer divide, they remain metabolically active and can release pro-inflammatory cytokines, chemokines, and growth factors, collectively known as the senescence associated secretory phenotype (SASP). These factors can promote chronic inflammation and contribute to age-related tissue dysfunction (Miller et al., 2011). Supporting this relationship in humans, Hansel et al. (2025) studied 531 adults and found that higher norepinephrine levels were associated with a higher DNA damage response (DDR) and SASP (Hansen et al., 2025). Childhood chronic stress exposure was also associated with higher norepinephrine levels in adulthood, suggesting that stress-related hormonal activity may contribute to cellular senescence and biological aging. Overall, these cellular changes may accumulate over time, promoting dysfunction and chronic inflammation that can impair organ function and increase susceptibility to age-related diseases.

5. Loss of Stem Cell Function

Stem cells are responsible for maintaining and regenerating tissues through their ability to self-renew and differentiate into specialized cells. However, chronic stress can disrupt these

processes, preventing the stem cell from properly performing its role in maintaining and regenerating tissues. For example, psychological stress can alter the function of intestinal stem cells (ISCs), which continuously renew the intestinal lining and differentiate into specialized cells necessary for maintaining intestinal homeostasis (Zhang et al., 2023). Stress-related changes in hormones, inflammation, and other signaling pathways may therefore interfere with normal stem cell activity and reduce the body's regenerative abilities.

Evidence from animal research further supports this relationship. Jung et al. (2020) found that chronic stress caused the death of neural stem cells in the hippocampus and reduced the formation of new neurons, demonstrating one way prolonged stress can interfere with stem cell maintenance. Over time, impaired stem cell function may limit the body's ability to regenerate and repair tissues, contributing to the progressive decline in tissue function associated with biological aging.

6. Chronic Inflammation

Inflammation is the body's natural immune response to protect itself from injuries and infections. Under normal conditions, cortisol released through the hypothalamic-pituitary-adrenal (HPA) axis helps regulate this response by suppressing pro-inflammatory signaling and reducing the production of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α (Nunez et al., 2025). However, chronic stress can cause repeated activation of the HPA axis, leading to increased cumulative cortisol exposure over time (Herman et al., 2016). Prolonged cortisol exposure can contribute to glucocorticoid resistance, a condition in which immune cells become less sensitive to the effects of cortisol. As a result, cortisol becomes less effective at suppressing inflammation, allowing pro-inflammatory cytokines to remain elevated and contributing to chronic inflammation (Zefferino et al., 2021).

7. Epigenetic Aging

Unlike mechanisms related to cellular damage, epigenetic aging involves alterations in DNA methylation patterns that can affect gene regulation without altering the DNA sequence itself. DNA methylation occurs when chemical groups called methyl groups are added to DNA, helping regulate gene expression by influencing whether certain genes are turned on or off. This helps cells control which genes are read and which should remain inactive, allowing them to maintain their normal functions. Chronic stress may contribute to changes in these epigenetic patterns, potentially accelerating biological aging. Harvanek et al. (2021) investigated this relationship in 444 healthy adults between the ages of 18 and 50 using GrimAge, an epigenetic clock based on DNA methylation. The researchers found that the relationship between cumulative stress and GrimAge acceleration was statistically significant, even after taking factors such as smoking, alcohol use, race, sex, and income into consideration. Furthermore, the relationship between cumulative stress and epigenetic aging varied depending on emotion regulation. Among

individuals with poor emotion regulation, higher cumulative stress was associated with approximately 0.48 additional years of GrimAge acceleration, while this relationship was not significant among those with good emotion regulation (Harvanek et al., 2021).

8. Conclusion

Biological age is significantly impacted by chronic stress, including several mechanisms such as telomere shortening, oxidative stress, mitochondrial dysfunction, cellular senescence, loss of stem cell function, chronic inflammation, and epigenetic aging. Rather than acting independently, these mechanisms can interact and reinforce one another, collectively contributing to accelerated biological aging. For example, oxidative stress can accelerate telomere shortening and cellular damage, while the accumulation of senescent cells can promote chronic inflammation and tissue dysfunction. Overall, these findings emphasize the importance of understanding the potential long-term consequences of chronic stress on the body. Managing stress and supporting overall well-being may help reduce prolonged stress and its associated effects on biological aging and the risk of age-related diseases.

References

[1]. E.S. Epel, E.H. Blackburn, J. Lin, F.S. Dhabhar, N.E. Adler, J.D. Morrow, & R.M. Cawthon (2004). Accelerated telomere shortening in response to life stress, Proc. Natl. Acad. Sci. U.S.A. 101 (49) 17312-17315, https://doi.org/10.1073/pnas.0407162101

[2]. Hannibal, K. E., & Bishop, M. D. (2014). Chronic Stress, cortisol dysfunction, and pain: A Psychoneuroendocrine Rationale for Stress management in Pain Rehabilitation. *Physical Therapy*, *94*(12), 1816–1825. https://doi.org/10.2522/ptj.20130597

[3]. Hansen, J. L., Carroll, J. E., Seeman, T. E., Cole, S. W., & Rentscher, K. E. (2024). Lifetime chronic stress exposures, stress hormones, and biological aging: Results from the Midlife in the United States (MIDUS) study. *Brain Behavior and Immunity*, *123*, 1159–1168. https://doi.org/10.1016/j.bbi.2024.10.022

[4]. Harvanek, Z. M., Fogelman, N., Xu, K., & Sinha, R. (2021). Psychological and biological resilience modulates the effects of stress on epigenetic aging. *Translational Psychiatry*, *11*(1), 601. https://doi.org/10.1038/s41398-021-01735-7

[5]. Herman, J. P., McKlveen, J. M., Ghosal, S., Kopp, B., Wulsin, A., Makinson, R., Scheimann, J., & Myers, B. (2016). Regulation of the Hypothalamic-Pituitary-Adrenocortical stress response. *Comprehensive Physiology*, *6*(2), 603–621. https://doi.org/10.1002/cphy.c150015

[6]. Jung, S., Choe, S., Woo, H., Jeong, H., An, H., Moon, H., Ryu, H. Y., Yeo, B. K., Lee, Y. W., Choi, H., Mun, J. Y., Sun, W., Choe, H. K., Kim, E., & Yu, S. (2019). Autophagic death of neural stem cells mediates chronic stress-induced decline of adult hippocampal neurogenesis and cognitive deficits. *Autophagy*, *16*(3), 512–530. https://doi.org/10.1080/15548627.2019.1630222

[7]. Lin, J., & Epel, E. (2021). Stress and telomere shortening: Insights from cellular mechanisms. *Ageing Research Reviews*, *73*, 101507. https://doi.org/10.1016/j.arr.2021.101507

[8]. Lin YF, Wang LY, Chen CS, Li CC, Hsiao YH. Cellular senescence as a driver of cognitive decline triggered by chronic unpredictable stress. Neurobiol Stress. 2021 May 18;15:100341. doi: 10.1016/j.ynstr.2021.100341. PMID: 34095365; PMCID: PMC8163993.

[9]. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2023). Hallmarks of aging: An expanding universe. *Cell*, *186*(2), 243–278. https://doi.org/10.1016/j.cell.2022.11.001

[10]. Lyons, C. E., Razzoli, M., & Bartolomucci, A. (2023). The impact of life stress on hallmarks of aging and accelerated senescence: Connections in sickness and in health. *Neuroscience & Biobehavioral Reviews*, *153*, 105359. https://doi.org/10.1016/j.neubiorev.2023.105359

[11]. Miller, G. E., Chen, E., & Parker, K. J. (2011). Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. *Psychological Bulletin*, *137*(6), 959–997. https://doi.org/10.1037/a0024768

[12]. Nunez, S. G., Rabelo, S. P., Subotic, N., Caruso, J. W., & Knezevic, N. N. (2025). Chronic stress and autoimmunity: the role of HPA axis and cortisol dysregulation. *International Journal of Molecular Sciences*, *26*(20), 9994. https://doi.org/10.3390/ijms26209994

[13]. Picard, M., & McEwen, B. S. (2018). Psychological Stress and Mitochondria: A Systematic review. *Psychosomatic Medicine*, *80*(2), 141–153. https://doi.org/10.1097/psy.0000000000000545

[14]. Polsky, L. R., Rentscher, K. E., & Carroll, J. E. (2022). Stress-induced biological aging: A review and guide for research priorities. *Brain Behavior and Immunity*, *104*, 97–109. https://doi.org/10.1016/j.bbi.2022.05.016

[15]. Yegorov, Y. E., Poznyak, A. V., Nikiforov, N. G., Sobenin, I. A., & Orekhov, A. N. (2020). The Link between Chronic Stress and Accelerated Aging. *Biomedicines*, *8*(7), 198. https://doi.org/10.3390/biomedicines8070198

[16]. Zhang, H., Wang, Z., Wang, G., Song, X., Qian, Y., Liao, Z., Sui, L., Ai, L., & Xia, Y. (2023). Understanding the Connection between Gut Homeostasis and Psychological Stress. *Journal of Nutrition*, *153*(4), 924–939. https://doi.org/10.1016/j.tjnut.2023.01.026

[17]. Zefferino, R., Di Gioia, S., & Conese, M. (2020). Molecular links between endocrine, nervous and immune system during chronic stress. *Brain and Behavior*, *11*(2), e01960. https://doi.org/10.1002/brb3.1960