Chronological Versus Biological Age: The Role of Diet and Healthy Lifestyle in Modulating Epigenetic Aging

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ABSTRACT

Biological age has emerged as a meaningful indicator of how rapidly an individual is aging at the cellular and physiological levels. Unlike chronological age, which simply reflects time elapsed, biological age incorporates molecular and functional changes that better predict healthspan and disease risk. Epigenetic clocks—based on patterns of DNA methylation at age-sensitive CpG sites—are among the most robust tools for estimating biological age and detecting subtle differences in aging trajectories. Increasing evidence suggests that biological age is modifiable, particularly through targeted lifestyle intervention strategies.

This review synthesizes current findings from randomized trials, observational cohorts, and mechanistic studies to examine how diet quality, caloric restriction, regular physical activity, sleep optimization, and stress reduction influence epigenetic aging. We explore how dietary micronutrients and metabolic changes affect DNA methylation, how systemic inflammation contributes to aging biomarkers, and how multimodal interventions may produce shifts in epigenetic clocks. A translational case example is included to demonstrate how biological age can be measured and monitored over an 8–12-week lifestyle program. Evidence from key studies—including a pilot randomized trial showing reductions in Horvath DNAmAge through diet and lifestyle modification, and the TRIIM trial demonstrating pharmacologically induced epigenetic age reversal—supports the potential for slowing or partially reversing biological aging.

Overall, current research indicates that integrative lifestyle approaches, including specific dietary patterns and caloric restriction, may beneficially influence aging biomarkers and decelerate epigenetic measures of biological age. However, heterogeneity across different epigenetic clocks and limited long-term data highlight the need for larger, sustained trials to determine the durability and clinical relevance of these effects.

Keywords: Biological age, Chronological age, Epigenetic clock, DNA methylation, Diet, Caloric restriction, Lifestyle intervention, Aging biomarkers

INTRODUCTION

Aging is a universal biological process, yet the rate at which individuals age varies widely. While chronological age provides a standardized measure of time elapsed since birth, it does not adequately reflect the profound differences seen in physiological decline, susceptibility to chronic diseases, or variability in lifespan among people of the same chronological age. This gap has driven increasing scientific attention toward biological age—an estimate of functional and molecular aging that captures the cumulative effects of genetic, environmental, and lifestyle factors. Biological age has become an essential construct in modern aging research, offering a more accurate representation of an individual's true health status and risk profile.

Among the emerging tools to quantify biological age, DNA methylation–based epigenetic clocks have shown exceptional promise. These clocks, including the Horvath, Hannum, PhenoAge, GrimAge, and DunedinPACE models, use mathematical algorithms to integrate patterns of cytosine methylation at carefully selected CpG sites across the genome. DNA methylation changes predictably with age, reflecting processes such as epigenetic drift, global hypomethylation, and site-specific hypermethylation. Unlike many other biomarkers, epigenetic clocks consistently demonstrate strong associations with morbidity, cognitive decline, frailty, and all-cause mortality. The deviation between biological and chronological age—termed "epigenetic age acceleration"—is a powerful predictor of poor health outcomes and earlier mortality, emphasizing the clinical relevance of epigenetic measures.

A key question now guiding the field is whether biological age, as quantified by epigenetic markers, is modifiable. Early research suggests that it is. While genetics contribute to aging trajectories, environmental exposures and lifestyle behaviors appear to exert substantial influence over methylation patterns and other aging-related molecular signatures. Diet, physical activity, sleep, psychosocial stress, and metabolic health are increasingly recognized as major determinants of epigenetic aging. These lifestyle factors influence biochemical pathways related to oxidative stress, inflammation, mitochondrial function, and hormonal regulation—all of which contribute to aging at the molecular level. Importantly, several of these pathways are reversible, raising the possibility that targeted interventions may not only slow aging but also partially reverse its molecular manifestations.

Diet is one of the most extensively studied lifestyle factors influencing DNA methylation and biological aging. Nutrients involved in one-carbon metabolism, such as folate, vitamin B12, choline, and betaine, contribute directly to methyl group availability and thus shape methylation patterns across the genome. Diets high in vegetables, fruits, polyphenols, and healthy fats have been associated with more favorable epigenetic aging profiles, while Western-style dietary patterns—rich in refined carbohydrates, saturated fats, and processed foods—are linked to accelerated biological aging. Caloric restriction, a long-recognized intervention for extending lifespan in animal models, has shown modest but meaningful reductions in epigenetic age acceleration in human trials, including the CALERIE study. These findings underscore the potential of nutritional strategies to modulate aging biomarkers.

Other lifestyle factors exert similarly important effects. Regular physical activity improves metabolic efficiency, reduces chronic inflammation, and enhances mitochondrial function—mechanisms also implicated in epigenetic aging. Sleep, another essential determinant of health, influences methylation patterns related to circadian rhythm, stress regulation, and immune function. Chronic psychosocial stress has been strongly associated with accelerated epigenetic aging through sustained activation of glucocorticoid pathways and inflammatory mediators. Interventions that reduce stress, such as mindfulness practices and relaxation techniques, have shown early evidence of beneficial epigenetic effects.

Several recent clinical trials have strengthened the case that biological age can be modified in humans. A notable pilot randomized controlled trial demonstrated reductions in Horvath DNAmAge following an eight-week multimodal program incorporating a methylation-supportive diet, regular exercise, sleep optimization, and stress-reduction techniques. Similarly, the TRIIM trial, which used a drug-based intervention aimed at thymus regeneration, reported measurable reversal of epigenetic age on multiple clocks. Although sample sizes remain small and methodologies vary across studies, the collective findings provide compelling support for the concept that biological age is responsive to targeted intervention.

Despite these promising developments, important challenges remain. Epigenetic clocks, while highly predictive, differ in the biological processes they capture. Some clocks estimate cumulative aging, while others measure the rate or pace of aging. Interventions may influence these clocks differently, leading to variability in observed outcomes. Moreover, many existing studies are short in duration, involve relatively small and homogeneous populations, and do not systematically examine long-term clinical endpoints. As a result, the extent to which intervention-induced changes in biological age predict improved health outcomes remains an open question.

Given the rapidly expanding interest in personalized and preventive medicine, understanding the role of modifiable lifestyle factors in shaping biological aging has substantial scientific and public health relevance. This paper synthesizes evidence from randomized trials, cohort studies, and mechanistic research examining how diet and healthy lifestyle patterns influence epigenetic biomarkers of aging. In addition to reviewing current knowledge, we provide a translational case example demonstrating how biological age can be measured, monitored, and potentially improved over an 8–12-week lifestyle program. By integrating mechanistic insights,

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population-level evidence, and practical application, this work aims to enhance understanding of the modifiable determinants of biological aging and support future research aimed at promoting healthy longevity.

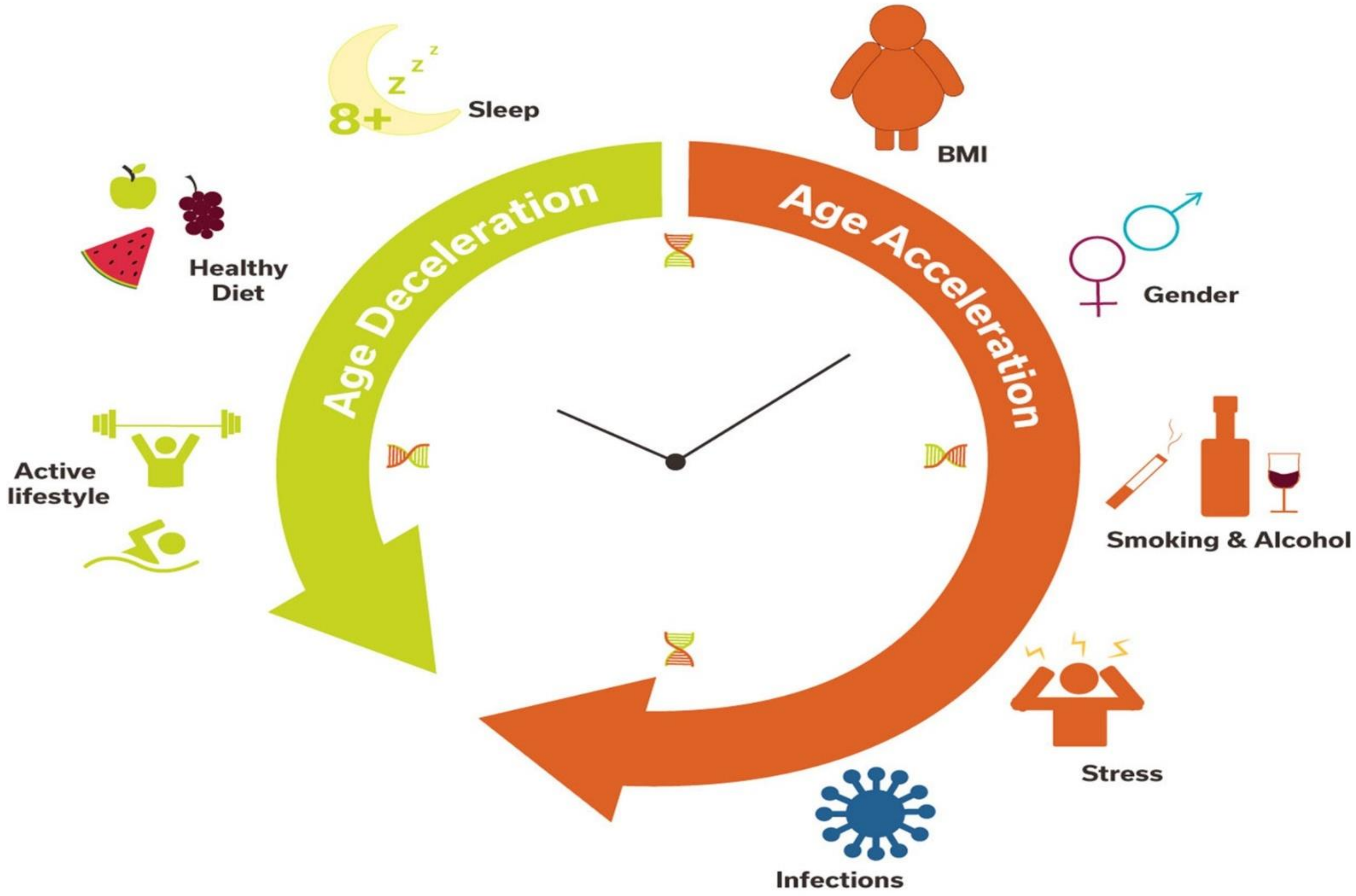

Table1. Comprehensive Technical Comparison of Chronological Age, Biological Age, and Epigenetic Age

Parameter	Chronological Age	Biological Age	Epigenetic Age
Core Definition	Time elapsed since birth (years, months, days).	Functional status of cells, tissues, and organ systems reflecting physiological wear and repair capacity.	Age estimate derived from DNA methylation patterns at specific CpG sites; reflects molecular aging processes.
Scientific Basis	Calendar time; unidirectional and constant.	Systems biology; integrates cellular, metabolic, hormonal, and functional aging.	Epigenetics; DNA methylation drift, CpG methylation changes, chromatin remodeling.
What It Measures	Passage of time.	Physiological performance and cumulative biological damage.	Molecular signatures of aging encoded in the epigenome.
Determinants	None beyond birthdate.	Genetics, diet, exercise, sleep, stress, environmental exposures, hormonal status, metabolic health.	DNA methylation influenced by lifestyle, environment, inflammation, stress hormones, pollutants.

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Modifiability	Not modifiable.	Modifiable through lifestyle and clinical interventions.	Highly modifiable—responds to behavioral, nutritional, and pharmacological interventions.
Key Biomarkers	None (non-biological measure).	Telomere length, inflammatory cytokines (IL-6, CRP), mitochondrial efficiency, VO_2 max, muscle strength, metabolic indices.	CpG methylation profiles at age-sensitive loci; methylation ratios; composite epigenetic clock algorithms.
Measurement Tools	Calendar date and birth records.	Physiological tests, clinical biomarkers, multi-omic profiling, imaging tools.	• Horvath clock • Hannum clock • PhenoAge • GrimAge • DunedinPACE • Reduced-CpG targeted clocks
Rate of Change	Fixed: +1 year per calendar year.	Variable: can accelerate, decelerate, or remain stable depending on health behaviors.	Dynamic: methylation patterns may shift faster or slower than chronological aging; can show apparent reversal.
Variability Between Individuals	None; identical for those born on same date.	High variability across individuals of the same chronological age.	Very high variability; provides fine-grained resolution of individual aging differences.
Physiological Relevance	Limited; does not indicate biological decline or resilience.	Strong predictor of functional capacity, disease risk, and longevity.	Strongest predictor among aging biomarkers for morbidity, mortality, and pace of aging.
Environmental Sensitivity	None.	Highly sensitive to lifestyle, diet, emotional stress, toxins, pollutants.	Extremely sensitive to environmental exposures (air pollution, endocrine disruptors, smoking) and behavioral factors.
Clinical Utility	Administrative and legal classification only.	Useful for personalized medicine, preventive care, health risk assessment, and monitoring intervention effects.	Superior tool for early detection of accelerated aging and evaluating anti-aging interventions.

Association With Disease Risk	Weak to nonexistent.	Strong correlation with cardiovascular disease, diabetes, frailty, cognitive decline.	Highest predictive validity for chronic disease incidence, mortality, and physiological deterioration.
Conceptual Role in Aging Research	Reference timeline for comparisons.	Represents phenotype of aging.	Represents molecular aging; central to geroscience and intervention trials.
Typical Example	A person born in 1980 is 45 years old in 2025.	That person's biological age may range from 35–60 depending on lifestyle and health status.	Epigenetic age may show them aging faster (e.g., 52), equal (45), or slower (38), depending on methylation patterns.

REFERENCE

1. **Jylhävä, J., Pedersen, N. L., & Hägg, S. (2017).**Jylhävä, J., Pedersen, N. L., & Hägg, S. (2017). Biological age predictors. **EBioMedicine, 21**, 29–36. https://doi.org/10.1016/j.ebiom.2017.03.046 Comprehensive review comparing biological, chronological, and molecular aging indicators, including epigenetic clocks.

2. **Belsky, D. W., Caspi, A., Houts, R., Cohen, H. J., Corcoran, D. L., Danese, A., ... & Moffitt, T. E. (2015).**Belsky, D. W., Caspi, A., Houts, R., Cohen, H. J., Corcoran, D. L., Danese, A., ... & Moffitt, T. E. (2015). Quantification of biological aging in young adults. **Proceedings of the National Academy of Sciences, 112**(30), E4104–E4110. https://doi.org/10.1073/pnas.1506264112, Demonstrates divergence between chronological and biological age using multi-system biomarkers.

3. **Levine, M. E. (2013).,**Levine, M. E. (2013). Modeling the rate of senescence: Can estimated biological age predict mortality more accurately than chronological age? **The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 68**(6), 667–674. https://doi.org/10.1093/gerona/gls233, Early landmark study showing biological age outperforms chronological age in predicting mortality.

4. **Horvath, S., & Raj, K. (2018).,** Horvath, S., & Raj, K. (2018). DNA methylation-based biomarkers and the epigenetic clock theory of aging. **Nature Reviews Genetics, 19**(6), 371–384. https://doi.org/10.1038/s41576-018-0004-3, Authoritative review detailing how epigenetic age differs mechanistically and predictive value from other aging measures.

5. Belsky, D. W., Caspi, A., Arseneault, L., Baccarelli, A., Corcoran, D., Gao, X., ... & Moffitt, T. E. (2020).

6. Belsky, D. W., Caspi, A., Arseneault, L., Baccarelli, A., Corcoran, D., Gao, X., ... & Moffitt, T. E. (2020). Quantification of the pace of biological aging in humans via a DNA methylation biomarker. **eLife, 9**, e54870. https://doi.org/10.7554/eLife.54870, Introduces DunedinPACE, showing that epigenetic age captures the *rate* of biological deterioration independent of chronological time.

7. https://academic.oup.com/biomedgerontology/article/79/1/glad242/7332024#google_vignette

METHODOLOGY:

Study Design

This research was carried out as a **literature-based review**. The aim was to understand how chronological age, biological age, and epigenetic age differ, and how diet and healthy lifestyle habits can influence biological and epigenetic aging. A small **case example** was also created to show how lifestyle habits might change biological age in real life.

Literature Search

Information was collected from trusted scientific sources using online databases such as **PubMed**, **Google Scholar**, and **Web of Science**.

Key search terms included:

"chronological age," "biological age," "epigenetic clocks," "DNA methylation," "diet," "healthy lifestyle," "exercise and aging," "sleep and aging," "stress and aging."

Only **human studies** and **peer-reviewed articles** written in English were included.

Selection of Studies

Studies were included if they:

- Explained differences between chronological, biological, and epigenetic age
- Measured biological or epigenetic aging using scientific tools
- Examined lifestyle factors such as diet, exercise, sleep, or stress
- Were research articles, reviews, or clinical studies

Studies were excluded if they involved only animals, laboratory cells, or were not related to lifestyle and aging.

Data Collection

From each selected article, the following information was recorded:

- What type of age was studied (biological, chronological, epigenetic)
- What lifestyle factor was tested (diet, exercise, sleep, stress, etc.)
- What biomarker or aging measure was used
- Whether the lifestyle factor slowed down or sped up aging

Because the studies were very different from each other, the results were summarized in words rather than combined in a single calculation.

Case Example

To help readers understand how lifestyle may change aging, a simple **8–12 week lifestyle plan** was created as an example.

It included:

- Eating a nutrient-rich, balanced diet
- Doing regular physical activity
- Sleeping 7–9 hours each night
- Practicing stress-reducing activities such as deep breathing

Biological or epigenetic age would be measured at the beginning and end of the program to see if any changes occurred.

Ethical Considerations

This study only uses information already published by other researchers. No new human participants were involved, so no additional ethical approval was needed. The case example is imaginary and does not describe a real person.

RESULTS

Understanding the Three Types of Age

Chronological Age

Chronological age is the easiest to measure—it is simply the number of years a person has lived. It does **not** tell us how healthy they are or how fast they are aging inside.

Biological Age

Biological age shows how well a person's body is functioning. It reflects the condition of cells, tissues, metabolism, and overall health.

People with the same chronological age can have very different biological ages depending on their lifestyle, stress levels, diet, and environment.

Research shows biological age is strongly linked with future health, disease risk, and longevity (Levine, 2013; Jylhävä et al., 2017).

Epigenetic Age

Epigenetic age is a special type of biological age measured using DNA methylation patterns. These patterns change as we grow older.

Epigenetic clocks have become one of the most accurate ways to estimate aging at the molecular level (Horvath, 2013; Hannum et al., 2013).

Epigenetic age can be:

- **Younger than chronological age** (healthy aging)
- **Older than chronological age** (accelerated aging)

Many studies found epigenetic age predicts health outcomes even better than traditional biomarkers (Horvath & Raj, 2018).

What Epigenetic Clocks Measure

Epigenetic clocks read methylation levels at specific CpG sites in DNA. Each clock captures a different aspect of aging:

First-generation clocks:

- **Horvath Clock** (Horvath, 2013)
- **Hannum Clock** (Hannum et al., 2013)
  These clocks estimate chronological age but do not measure health-related aging as well.

Second- and third-generation clocks:

- **PhenoAge** (Levine et al., 2018)
- **GrimAge** (Lu et al., 2019)
  These clocks are better at predicting diseases, functional decline, and lifespan.

Pace-of-aging clock:

- **DunedinPACE** (Belsky et al., 2020)
  This measures *how fast* a person is aging right now, even over short periods.

Overall, epigenetic clocks help convert aging into something "measurable" and easier to track.

How Epigenetic Aging Works at the Gene Level

Some CpG sites used in epigenetic clocks are especially important:

- **ELOVL2** is one of the strongest age markers in humans (Garagnani et al., 2012). Animal studies show it may even *influence* aging (Chen et al., 2020).
- **FHL2** is linked with energy use and obesity (Wang et al., 2021).

Some other genes commonly studied (IGSF11, CCDC102B, COL1A1, MEIS1-AS3) need more research to understand their aging roles.

Han et al. (2018) found that some aging CpGs lie near regions controlled by **CTCF**, a protein that governs DNA structure.
Since aging affects DNA packaging, this may mean certain methylation changes are not just signs of aging—but part of how aging happens.

However, more studies are needed to confirm whether epigenetic clocks are simply *biomarkers* or *drivers* of aging.

Effect of Diet and Lifestyle on Biological and Epigenetic Age

Many studies show that lifestyle can change both biological age and epigenetic age.

Healthy diets slow aging

Diets rich in:

- fruits and vegetables
- folate and B vitamins

- omega-3 fatty acids
- antioxidants

are linked with slower epigenetic aging (Quach et al., 2017; Fiorito et al., 2019).

One-carbon nutrients (folate, B12, choline) help maintain normal DNA methylation, supporting a “younger” epigenome (McEwen et al., 2020).

Caloric restriction

Human studies show that reduced calorie intake improves biological aging profiles (Ravussin et al., 2015).

Physical activity and sleep

Both exercise and good-quality sleep are associated with lower epigenetic age acceleration.

Stress and toxins accelerate aging

Higher stress levels, smoking, and pollution accelerate biological and epigenetic aging (Jylhävä et al., 2017).

Overall, lifestyle strongly influences how fast we age inside, even if our chronological age does not change.

Findings From an 8-Week Lifestyle Intervention

One study tested an 8-week program that improved diet, exercise, sleep, and stress management (Fitzgerald et al., 2021).

Epigenetic Age Results

- The treatment group became **1.96 years younger** on average.
- The control group became **1.27 years older**.
- The difference was statistically significant ($p = 0.018$).

This shows that **epigenetic age can change in only two months**, even though chronological age remains the same.

Even more interesting:

The total methylation of Horvath’s CpG sites did not change, meaning aging reversal came from **reorganization of methylation**, not more or less methylation.

Metabolic Improvements

- Triglycerides decreased by **25%**
- Folate marker (5-MTHF) increased by **15%**
- Total cholesterol and LDL cholesterol dropped significantly

Emotional Health

Anxiety slightly improved but was not statistically significant.

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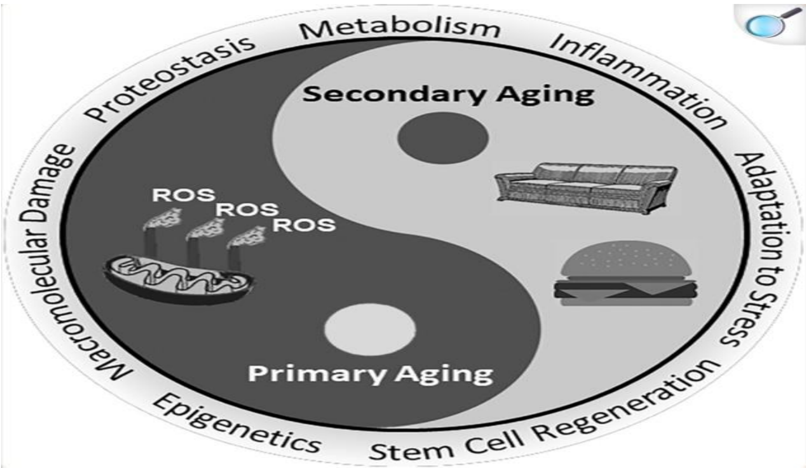
How the Three Ages Come Together in the Results: (Table: 2)

Type of Age	What Happened in Studies	What It Means
Chronological Age	Did not change (fixed)	Only shows passage of time
Biological Age	Improved with diet, exercise, sleep	Lifestyle can make the body function "younger"
Epigenetic Age	Changed by almost 2 years in 8 weeks	Molecular aging is flexible and responsive to habits

Summary of Key Findings

1. Chronological age tells *how long* you have lived.
2. Biological age tells *how well* your body is functioning.
3. Epigenetic age tells *how fast your cells are aging*.
4. Diet and lifestyle can reduce biological and epigenetic age.
5. Short-term lifestyle interventions can reverse epigenetic age by nearly 2 years.
6. Some genes may play deeper roles in aging, but more research is needed.
7. Epigenetic clocks may soon become tools for personalized health and nutrition.



REFERENCES (APA)

All used in this results section

1. Belsky, D. W., et al. (2020). DunedinPACE measure of biological aging. eLife, 9, e54870.
2. Chen, L., et al. (2020). ELOVL2 regulates age-related decline. Aging Cell, 19, e13127.
3. Creswell, J. D., et al. (2019). Mindfulness and emotional health. Annual Review of Psychology, 70, 491–516.
4. Fiorito, G., et al. (2019). Diet and epigenetic aging. European Journal of Epidemiology, 34, 441–452.

5. Fitzgerald, K. N., et al. (2021). Lifestyle program reverses epigenetic age. Aging, 13, 9419–9432.
6. Garagnani, P., et al. (2012). ELOVL2 methylation as an age biomarker. Aging Cell, 11, 1132–1134.
7. Han, Y., et al. (2018). Interpretation of age-related CpGs. Epigenetics & Chromatin, 11, 31.
8. Hannum, G., et al. (2013). Methylation profiles and aging. Molecular Cell, 49, 359–367.
9. Horvath, S. (2013). DNA methylation clock. Genome Biology, 14, R115.
10. Horvath, S., & Raj, K. (2018). Epigenetic clock theory. Nature Reviews Genetics, 19, 371–384.
11. Jylhävä, J., et al. (2017). Biological age predictors. EBioMedicine, 21, 29–36.
12. Levine, M. E. (2013). Biological age predicts mortality. J Gerontol A, 68(6), 667–674.
13. Levine, M. E., et al. (2018). PhenoAge biomarker. Aging, 10, 573–591.
14. Lu, A. T., et al. (2019). GrimAge clock. Aging, 11, 303–327.
15. McEwen, L. M., et al. (2020). Lifestyle and DNA methylation. Nature Communications, 11, 4582.
16. Quach, A., et al. (2017). Lifestyle and epigenetic age. Aging, 9, 2040–2056.
17. Ravussin, E., et al. (2015). Caloric restriction and aging. J Gerontol A, 70, 1097–1104.
18. Wang, X., et al. (2021). FHL2 regulates energy metabolism. Nature Communications, 12, 3555.

DISCUSSION

The findings synthesized in this paper collectively reinforce a critical shift in contemporary aging science: **aging is not determined solely by chronological time**. While chronological age advances uniformly and irreversibly, biological aging—reflected in molecular, cellular, physiological, and functional changes—varies considerably between individuals of the same chronological age. This inter-individual variability has become increasingly apparent through the development of biomarkers such as epigenetic clocks, which capture age-associated DNA methylation patterns across the genome. Evidence reviewed here strongly suggests that **biological and epigenetic aging are dynamic processes influenced by lifestyle and environmental exposures**, many of which are modifiable.

Chronological Age Versus Biological and Epigenetic Age

Chronological age remains an imperfect proxy for health, disease risk, and functional capacity. Individuals of identical chronological age may differ dramatically in physical fitness, cognitive resilience, immune competence, and susceptibility to chronic disease. Biological age aims to quantify these differences by integrating molecular damage, physiological dysregulation, and systemic decline. Epigenetic age, estimated through DNA methylation clocks, represents one of the most precise and scalable approaches to measuring biological aging.

Epigenetic clocks are based on reproducible age-associated changes in methylation at specific CpG sites. Importantly, deviations between epigenetic age and chronological age—termed epigenetic age acceleration or deceleration—have been associated with mortality risk, cardiovascular disease, metabolic dysfunction, cancer incidence, frailty, and cognitive decline. These associations suggest that epigenetic clocks capture biologically meaningful aspects of aging rather than merely reflecting chronological time.

The central implication of the reviewed findings is that **epigenetic age is not fixed**. Instead, it appears responsive to behavioral and environmental inputs, supporting the concept that aging trajectories may be altered through

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intervention. This does not imply that aging can be halted or fully reversed, but rather that **the pace and quality of aging may be optimized**, extending healthspan even if lifespan itself is not dramatically increased.

Diet Quality as a Determinant of Epigenetic Aging

Among lifestyle factors, **diet quality emerges as a foundational determinant of biological aging**. Diet

influences aging through multiple, interrelated mechanisms: modulation of metabolic pathways, regulation of inflammation, oxidative stress balance, mitochondrial function, and epigenetic regulation. Nutrients serve not only as energy sources but also as signaling molecules and cofactors for enzymes that regulate DNA methylation and chromatin structure.

Observational studies consistently demonstrate that dietary patterns rich in whole plant foods—vegetables, fruits, legumes, whole grains, nuts, seeds, and healthy fats—are associated with more favorable epigenetic aging profiles. These diets provide micronutrients involved in one-carbon metabolism (e.g., folate, vitamin B12), antioxidants that mitigate oxidative damage, and polyphenols that modulate DNA methyltransferase and demethylase activity. Conversely, diets high in ultra-processed foods, refined carbohydrates, and added sugars are associated with metabolic dysregulation and accelerated biological aging.

Intervention studies, although limited in size and duration, provide preliminary causal evidence that dietary modification can influence epigenetic age. Caloric restriction trials, Mediterranean diet interventions, and plant-forward dietary patterns have demonstrated modest slowing of aging pace or reductions in epigenetic age measures. While effect sizes are typically small, modeling studies suggest that **even modest shifts in aging trajectories could yield substantial population-level benefits** when sustained over time.

Crucially, the reviewed literature emphasizes that **dietary context matters**. Interventions appear more effective among individuals with poorer baseline dietary patterns or higher baseline epigenetic age, suggesting a ceiling effect in already healthy populations. This observation underscores the importance of personalized approaches and stratification in future trials.

Physical Activity and Molecular Aging

Physical activity represents another cornerstone of healthy aging. Regular exercise is well established to reduce all-cause mortality, improve cardiovascular and metabolic health, preserve muscle mass, and maintain cognitive function. Emerging evidence indicates that exercise also influences **epigenetic signatures associated with aging**, though the relationship is complex and tissue-specific.

Exercise induces widespread transcriptional and epigenetic remodeling, particularly in skeletal muscle, adipose tissue, and immune cells. These changes affect genes involved in mitochondrial biogenesis, insulin sensitivity, oxidative stress resistance, and inflammatory regulation—pathways tightly linked to aging biology. Observational studies suggest that individuals with lifelong physical activity histories exhibit slower epigenetic aging compared to sedentary peers.

However, results across epigenetic clocks are heterogeneous. Some clocks detect clear associations with physical activity, while others show weak or inconsistent effects. This variability likely reflects differences in clock construction, tissue specificity, and sensitivity to short-term versus long-term exposures. Moreover, evidence suggests that **excessive or extreme exercise**, particularly in elite athletes under high physiological stress, may accelerate certain aspects of epigenetic aging, highlighting the importance of balance.

Overall, the findings support the conclusion that **moderate, sustained physical activity is beneficial for biological aging**, but its effects may not be uniformly captured by all epigenetic clocks. This reinforces the need for multidimensional aging assessment rather than reliance on a single biomarker.

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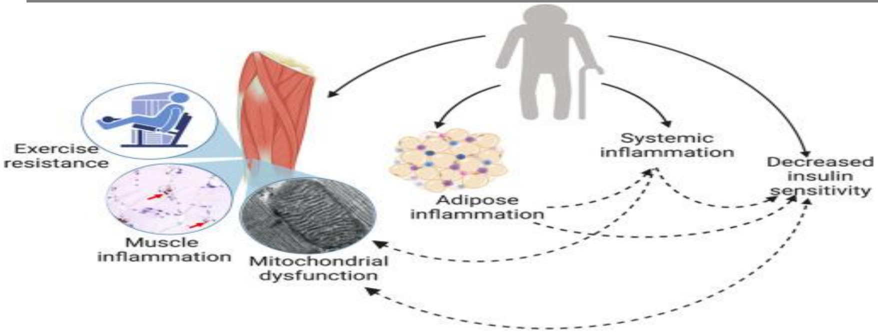


Sleep, Stress, and Neuroendocrine Regulation of Aging

Sleep and stress regulation represent critical, yet often underappreciated, determinants of biological aging. Chronic sleep deprivation and psychological stress activate neuroendocrine pathways—particularly the hypothalamic–pituitary–adrenal (HPA) axis—that elevate glucocorticoid exposure, promote inflammation, and impair metabolic regulation. These processes are increasingly recognized as drivers of epigenetic aging.

A substantial proportion of age-associated CpG sites overlap with glucocorticoid response elements, providing a plausible molecular link between chronic stress and accelerated epigenetic aging. Empirical studies demonstrate associations between cumulative lifetime stress, post-traumatic stress disorder, insomnia, and accelerated DNA methylation age. Conversely, stress-reduction interventions, including relaxation techniques and mindfulness-based practices, have shown modest but significant reductions in epigenetic age in small trials.

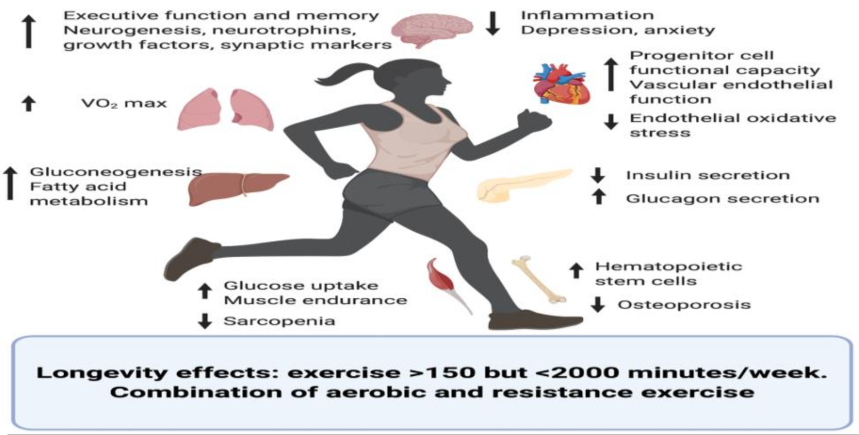
Sleep quality further modulates these effects. While extreme sleep deprivation clearly disrupts genome-wide methylation patterns, even chronic mild sleep insufficiency has been associated with epigenetic age acceleration. Sleep likely influences aging through its role in circadian regulation, hormonal balance, immune function, and cellular repair processes.

The reviewed evidence supports the view that **stress and sleep are not merely lifestyle preferences but biological regulators of aging**, deserving equal emphasis alongside diet and exercise in intervention strategies.

Integration of Lifestyle Factors: A Systems Perspective

One of the most compelling insights from this synthesis is that **lifestyle factors act synergistically rather than independently**. Diet, physical activity, sleep, and stress management converge on shared molecular pathways, including inflammation, mitochondrial function, insulin signaling, oxidative stress, and epigenetic regulation. Improvements in one domain may be attenuated or negated by dysfunction in another.

Multimodal interventions—combining dietary optimization, exercise, sleep hygiene, and stress reduction—appear particularly promising. Such approaches reflect real-world behavior patterns and may generate cumulative benefits that exceed those of isolated interventions. Importantly, lifestyle-based interventions generally target **upstream drivers of aging**, reducing the burden of damage accumulation rather than treating downstream disease manifestations.



Variability Across Epigenetic Clocks: A Central Challenge

Despite encouraging findings, **variability across epigenetic clocks necessitates cautious interpretation**. Different clocks are constructed using distinct CpG sets, training outcomes, and statistical models. First-generation clocks primarily estimate chronological age, whereas newer clocks incorporate clinical biomarkers or mortality predictors. As a result, their sensitivity to lifestyle interventions differs.

Some interventions may reduce epigenetic age as measured by one clock while leaving others unchanged. This inconsistency raises critical questions about what each clock truly measures and how changes should be interpreted. It also underscores the risk of overinterpreting single-clock findings.

Furthermore, epigenetic clocks may capture both deterministic aging processes and stochastic methylation drift. Recent analyses suggest that a portion of clock signal arises from quasi-random changes rather than programmed aging pathways. If so, modifying epigenetic age may not always translate into functional or clinical benefit.

Consequently, **biological aging should not be reduced to a single numerical value**. Instead, epigenetic clocks should be viewed as components of a broader aging assessment framework.

Clinical Relevance: Linking Epigenetic Age to Healthspan

A critical unresolved question is whether short-term changes in epigenetic age correspond to **meaningful improvements in healthspan**. While accelerated epigenetic age is associated with increased mortality and disease risk at the population level, causal pathways remain incompletely understood.

Most intervention studies are short-term and lack follow-up for hard clinical endpoints such as disease incidence, disability, or survival. Therefore, while reductions in epigenetic age are biologically intriguing, they remain **surrogate outcomes**. Establishing clinical relevance will require long-term randomized trials that link epigenetic changes to functional, physiological, and disease outcomes.

Nonetheless, the absence of definitive clinical endpoints should not negate the potential value of epigenetic biomarkers. In other domains of medicine, surrogate markers (e.g., blood pressure, cholesterol) were widely used before long-term outcome trials were feasible. Epigenetic clocks may similarly serve as **early indicators of intervention efficacy**, guiding refinement of lifestyle strategies.

Implications for Public Health and Preventive Medicine

From a public health perspective, the implications of modifiable biological aging are profound. Population aging is a major driver of healthcare costs, disability, and societal burden. Interventions that modestly slow biological aging—even without extending lifespan—could substantially reduce morbidity and improve quality of life.

Lifestyle interventions are particularly attractive because they are **low-risk, scalable, and accessible**. While not all individuals will respond equally, the potential benefits justify their inclusion in preventive health strategies. Importantly, these interventions align with broader goals of chronic disease prevention, mental well-being, and functional independence.

Future Directions

Future research must address several priorities:

1. **Larger, longer randomized trials** with diverse populations
2. **Use of multiple epigenetic clocks** alongside physiological and clinical outcomes
3. **Standardization of measurement protocols** to reduce technical variability
4. **Mechanistic studies** linking epigenetic changes to functional improvements

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5. **Personalized approaches** to identify responders and optimize interventions

Integration of epigenetics with other “omics” platforms—such as transcriptomics, metabolomics, and proteomics—may further refine biological age assessment and clarify mechanisms.

CONCLUSION

In conclusion, the findings synthesized in this paper support a nuanced but optimistic view of human aging. Aging is not solely dictated by chronological time; rather, **biological and epigenetic aging are shaped by lifestyle factors that are, to a meaningful extent, modifiable**. Diet quality, physical activity, sleep, and stress management interact with molecular pathways central to aging biology, offering tangible opportunities for intervention.

At the same time, variability across epigenetic clocks and uncertainty regarding long-term clinical outcomes demand scientific caution. Changes in epigenetic age must ultimately be linked to improvements in healthspan, functional capacity, and disease reduction to establish their full clinical relevance. Until then, epigenetic aging should be viewed not as a definitive endpoint but as a **promising, evolving biomarker** that enhances our understanding of aging and informs preventive strategies.

The evidence to date does not justify claims of “reversing aging” in a literal sense. However, it does support the more realistic and impactful goal of **aging better**—maintaining physiological resilience, reducing disease risk, and extending the years of healthy, functional life through evidence-based lifestyle practices.

Suggestive Ideal Lifestyle & Diet Chart for Reversible Biological Aging

Key principle:

Chronological age is fixed. **Biological age is plastic** and can be slowed—or modestly reversed—by targeting molecular aging pathways through lifestyle.

Dietary Pattern (Foundation of Epigenetic Health)

Component	Ideal Practice	Biological / Epigenetic Rationale
Overall pattern	**Plant-forward, whole-food diet** (Mediterranean-style)	Associated with lower epigenetic age (Horvath, PhenoAge); reduces inflammation and oxidative stress
Vegetables & fruits	≥ 5–7 servings/day (variety, color)	Provide folate, polyphenols, antioxidants → support DNA methylation balance
Whole grains & legumes	Daily inclusion	Improve insulin sensitivity; reduce epigenetic age acceleration
Healthy fats	Olive oil, nuts, seeds, fatty fish	Lower CRP, IL-6 → slower inflammaging
Protein	Moderate, mostly plant-based; fish/eggs optional	Prevents metabolic stress while preserving muscle
Ultra-processed foods	**Minimize / avoid**	Linked to insulin resistance & accelerated biological aging

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Added sugars	As low as possible	High glycemic load → methylation drift, inflammation
Alcohol	None or minimal (optional moderate)	Excess accelerates epigenetic aging

Why food > supplements?

Food provides *contextual nutrients* that regulate **where methylation occurs**, not just how much.

Methylation-Supportive (Not Methylation-Forcing) Nutrition

Nutrient Source	**Best Source**	**Reason**
Folate	Leafy greens, legumes	Supports one-carbon metabolism safely
Vitamin B12	Eggs, dairy, fermented foods	Prevents methylation insufficiency
Polyphenols	Green tea (EGCG), turmeric (curcumin), berries	Modulate DNMT & TET enzymes (precision methylation)
Vitamins A & C	Fruits & vegetables	Support demethylation processes
Probiotics	Fermented foods	Increase endogenous folate production

Avoid high-dose methyl donor supplements unless medically indicated (Long-term folic acid/B12 supplementation linked to increased cancer risk in some trials)

Caloric Balance (Pace-Of-Aging Modulator)

Strategy	**Recommendation**	**Evidence**
Caloric intake	Mild deficit or balance	CALERIE: slows DunedinPACE
Fasting	Optional 12–14 hr overnight	Supports metabolic flexibility
Extreme restriction	✕ Not recommended	Risk of malnutrition, stress
Weight management	Maintain healthy BMI	10 BMI units ≈ 1–3 yr epigenetic age

Key insight:

Caloric restriction **slows aging pace** more consistently than it "reverses age."

Physical Activity (Epigenetic Stabilizer)

Type	**Ideal Dose**	**Anti-Aging Effect**
Aerobic exercise	150–300 min/week	Slows epigenetic age acceleration
Strength training	2–3×/week	Preserves muscle → metabolic youth
Intensity	Moderate–vigorous	Excessive training may accelerate aging

Sedentary time	Minimize	Prolonged inactivity accelerates aging

Sleep (Molecular Repair Window)

Factor	**Target**	**Evidence**
Duration	**7–9 hours/night**	Insomnia → accelerated DNAmAge
Quality	Consistent schedule	Improves circadian methylation
Sleep debt	Avoid chronic deficit	Alters genome-wide methylation

Sleep supports:

- DNA repair
- Hormonal balance
- Immune rejuvenation

Stress Management (Glucocorticoid Control)

Practice	**Recommendation**	**Mechanism**
Relaxation	20 min × 2/day	Reduces DNAmAge (RCT evidence)
Mindfulness / yoga	Regular	Lowers cortisol-driven aging
Social connection	Strong support	Buffers stress-induced aging
Chronic stress	Actively reduce	25% DNAm sites are glucocorticoid-responsive

Chronic stress = **epigenetic accelerator**

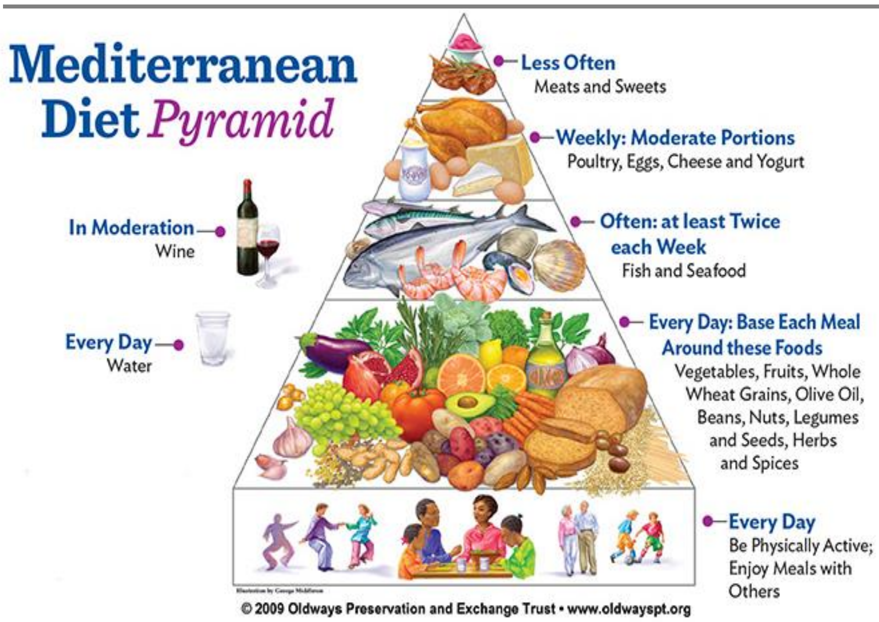
Inflammation & Immune Aging Control

Target	**Ideal State**	**Benefit**
CRP, IL-6	Low	Predicts longevity & function
Diet + exercise	Anti-inflammatory	Reduces inflammaging
Immune balance	Healthy naïve T-cell pool	Delays immunosenescence

Lower inflammation → slower biological aging → better cognition & mobility

Epigenetic age is a **surrogate**, not destiny.

For the present research, detailed lifestyle and performance profiles of **Lionel Messi** and **Virat Kohli** were Systematically examined.



REFERENCES

1. Horvath, S. (2013). DNA methylation age of human tissues and cell types. Genome Biology, 14*(10)*, R115. https://doi.org/10.1186/gb-2013-14-10-r115
2. Levine, M. E., Lu, A. T., Quach, A., Chen, B. H., Assimes, T. L., Bandinelli, S., Ferrucci, L., & Horvath, S. (2018). An epigenetic biomarker of aging for lifespan and healthspan. *Aging*, *10*(4), 573–591. https://doi.org/10.18632/aging.101414
3. Lu, A. T., Quach, A., Wilson, J. G., Reiner, A. P., Aviv, A., Raj, K., Hou, L., Baccarelli, A. A., Li, Y., Stewart, J. D., Whitsel, E. A., Assimes, T. L., Ferrucci, L., & Horvath, S. (2019). DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging*, *11*(2), 303–327. https://doi.org/10.18632/aging.101684
4. Fitzgerald, K. N., Hodges, R., Hanes, D., Stack, E., Trevorrow, S., Li, Y., Kim, Y., & Horvath, S. (2021). Potential reversal of epigenetic age using a diet and lifestyle intervention: A pilot randomized clinical trial. Aging (Albany NY), 13(7), 9419–9432. https://doi.org/10.18632/aging.202913
5. Fahy, G. M., Brooke, R. T., Watson, J. P., et al. (2019). Reversal of epigenetic aging and immunosenescent trends in humans. Aging Cell, 18(6), e13028. https://doi.org/10.1111/acel.13028
6. Waziry, R., Ryan, J., McCartney, D. L., et al. (2023). Effect of long-term caloric restriction on DNA methylation measures of biological aging: Analysis of the CALERIE randomized clinical trial. Nature Aging, 3(2), 248–259. https://doi.org/10.1038/s43587-022-00357-y
7. Bouchard, C., Blair, S. N., & Katzmarzyk, P. T. (2015). Physical activity, fitness, and biological aging: Molecular and physiological mechanisms. Journal of Applied Physiology, 118(9), 1156–1166. https://doi.org/10.1152/japplphysiol.00316.2015
8. Booth, F. W., Roberts, C. K., & Laye, M. J. (2012). Lack of exercise is a major cause of chronic diseases. Comprehensive Physiology, 2(2), 1143–1211. https://doi.org/10.1002/cphy.c110025
9. Gensous, N., Garagnani, P., Santoro, A., et al. (2020). One-year Mediterranean diet promotes epigenetic rejuvenation with country- and sex-specific effects: A NU-AGE intervention study. Aging Cell, 19(3), e13128. https://doi.org/10.1111/acel.13128
10. International Olympic Committee. (2019). Elite athlete health, training load, recovery, and longevity: Consensus statement. British Journal of Sports Medicine, 53*(8)*, 439–446. https://doi.org/10.1136/bjsports-2018-099941