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Exercise as a Modulator of Biological Age: The Role of Epigenetic Clocks in Assessing Exercise-Induced Rejuvenation – A Narrative Review

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Abstract
Background: Biological age is increasingly recognized as a valuable indicator of the aging process. Compared with chronological age, it may provide a more accurate representation of an individual's health status and disease risk. DNA methylation–based epigenetic clocks are among the most widely used biomarkers of biological aging.
Aim: This narrative review aimed to summarize the current evidence on the association between physical activity and epigenetic aging and to evaluate the potential role of exercise as a modulator of biological age.
Materials and methods: PubMed and Embase databases were searched from their inception through July 2026 using a combination of relevant keywords. A total of 79 studies were included in the review.
Results: Current evidence indicates that higher levels of physical activity and physical fitness are generally associated with a lower rate of epigenetic aging and more favorable biological aging profiles. Aerobic exercise is the most extensively studied modality and demonstrates the most consistent associations with slower biological aging. Resistance training, high-intensity interval training, and multicomponent exercise programs may also exert beneficial effects through mechanisms involving mitochondrial function, regulation of inflammation, metabolic adaptation, and epigenetic remodeling. However, the findings remain heterogeneous due to differences in study populations, exercise protocols, follow-up durations, and the epigenetic clocks employed.
Conclusions: Physical activity appears to be a promising, modifiable factor influencing biological aging. Accumulating evidence suggests that regular exercise may contribute to slower epigenetic aging and enhanced physiological resilience. Nevertheless, the magnitude and clinical significance of exercise-induced changes in epigenetic age remain incompletely understood. Further research is warranted.
Keywords: biological age; epigenetic clocks; DNA methylation; physical activity; exercise; healthy aging

1. Introduction

Population aging has emerged as one of the most pressing public health challenges of the 21st century. Although life expectancy has increased substantially over recent decades, this extension of lifespan has not always been accompanied by a proportional increase in healthy life expectancy. Consequently, an increasing number of individuals spend a substantial proportion of later life affected by chronic diseases, functional decline, and disability. This phenomenon has intensified scientific interest in the biological mechanisms underlying aging and in strategies that may slow or modify the age-related deterioration of health [1–4].

Traditionally, aging has been assessed using chronological age, defined as the number of years lived since birth. However, chronological age does not adequately capture the substantial interindividual variability in health status, physical functioning, and susceptibility to disease observed among individuals of the same age. Consequently, the

concept of biological age has emerged as a more informative indicator of the aging process [5–7]. Biological age aims to quantify the cumulative effects of genetic, environmental, and lifestyle-related factors on physiological integrity and may predict morbidity, mortality, and functional capacity more accurately than chronological age alone [5,6,8]. Recent advances in molecular biology have enabled the development of increasingly sophisticated biomarkers capable of estimating biological aging trajectories [5,6].

Among the most promising biomarkers of biological aging are DNA methylation-based epigenetic clocks. These tools use age-associated DNA methylation patterns at specific cytosine-phosphate-guanine (CpG) sites across the genome to estimate biological age and assess the rate of aging [9–11]. Since the introduction of first-generation clocks by Horvath and Hannum in 2013, the field has evolved rapidly, leading to the development of second- and third-generation clocks, including PhenoAge, GrimAge, and DunedinPACE [9–14].

Lifestyle-related factors are increasingly recognized as major determinants of biological aging. Among these, regular physical activity is considered one of the most effective non-pharmacological interventions for promoting healthy aging. Exercise exerts beneficial effects on multiple physiological systems, including the cardiovascular, musculoskeletal, and nervous systems, as well as on metabolic processes [15,16]. Furthermore, physical activity influences several molecular pathways involved in aging, including mitochondrial biogenesis, regulation of oxidative stress, chronic low-grade inflammation, autophagy, and cellular senescence [16,17]. Emerging evidence suggests that exercise may also modulate epigenetic regulation, including DNA methylation patterns, providing a potential molecular link between physical activity and biological aging [18,19].

Over the past decade, an increasing number of observational and interventional studies have investigated the association between physical activity and epigenetic aging.

The aim of this narrative review is to summarize the current knowledge regarding the association between physical activity and epigenetic aging, discuss the biological mechanisms through which exercise may influence DNA methylation–based aging biomarkers, evaluate evidence from observational and interventional studies, and identify future research directions in the emerging field of exercise-based longevity medicine.

2. Biological Age and Epigenetic Clocks

2.1. Biological age as a measure of the aging process

Chronological age provides a simple and universal measure of the time elapsed since birth. However, it does not fully reflect the substantial differences in physiological functioning and susceptibility to disease observed among individuals of the same chronological age. The concept of biological age was introduced to address this limitation by describing an individual's functional and molecular state relative to that of a population of the same chronological age [5–7,20].

The rationale for estimating biological age is based on the observation that aging is a multidimensional and heterogeneous process. Individuals may experience accelerated deterioration in the functioning of certain physiological systems, while other systems may retain relatively preserved function. Factors such as genetic background, physical activity, nutritional status, smoking, psychosocial stress, socioeconomic conditions, and exposure to environmental factors may

contribute to interindividual differences in the rate of biological aging. Biological age therefore represents an attempt to quantify interindividual variability in the aging process [5–7,21].

Several approaches have been developed to estimate biological age. Early methods relied primarily on physiological measurements and clinical biomarkers, such as blood pressure, lipid levels, glucose metabolism, pulmonary function, and indicators of physical fitness. More complex algorithms subsequently integrated multiple biomarkers to generate estimates of biological age. More recently, advances in molecular biology have enabled the assessment of biological aging using genomic, transcriptomic, proteomic, metabolomic, and epigenetic data [5,7,21]. Among these approaches, DNA methylation–based measures have attracted particular interest because they provide scalable molecular biomarkers of aging and have been associated with a range of age-related health outcomes [5,21].

2.2. DNA methylation as a biomarker of aging

DNA methylation is an epigenetic modification involving the addition of a methyl group to cytosine residues, primarily within cytosine-phosphate-guanine (CpG) dinucleotides. This process contributes to the regulation of gene expression and cellular identity without altering the underlying DNA sequence. DNA methylation patterns are influenced by both developmental processes and environmental exposures and undergo characteristic changes throughout the lifespan [10,22].

Age-related changes in DNA methylation occur at numerous genomic loci. Some CpG sites exhibit a gradual increase in methylation with age, whereas others undergo progressive hypomethylation. These changes are not uniformly distributed throughout the genome and may vary according to tissue and cell type. The reproducibility of age-associated methylation patterns has provided the basis for the development of mathematical models that enable the estimation of an individual's chronological or biological age from DNA methylation data [10,22,23].

Importantly, DNA methylation should not be interpreted as a single, direct marker of aging. Rather, it represents one component of the complex molecular processes underlying biological aging. Changes in DNA methylation may reflect exposure to environmental and lifestyle-related factors, age-related cellular alterations, or changes in cellular composition. Therefore, the interpretation of DNA methylation–based measures requires consideration of the tissue analyzed, the specific CpG sites incorporated into the model, and the biological construct that a given epigenetic clock is designed to capture [23–26].

2.3. Development of epigenetic clocks

The term "epigenetic clock" refers to a statistical model that uses DNA methylation levels at selected CpG sites to estimate age-related biological characteristics. First-generation epigenetic clocks were developed primarily to predict chronological age. Two landmark studies published in 2013 independently demonstrated that DNA methylation patterns could be used to estimate chronological age with high accuracy [10,11].

Horvath developed a multi-tissue clock based on 353 CpG sites and demonstrated that the model could estimate chronological age across multiple human tissues and cell types. In the same year, Hannum et al. developed a blood-

based clock using 71 CpG sites. Although both models were highly accurate in predicting chronological age, their primary purpose was age estimation rather than the direct prediction of health outcomes or the rate of biological deterioration [10,11].

Subsequent studies shifted from the estimation of chronological age toward the identification of biomarkers that better reflect biological aging and the risk of age-related diseases. This led to the development of second-generation clocks, including PhenoAge and GrimAge. PhenoAge was developed by integrating chronological age with clinical biomarkers associated with morbidity and mortality, thereby creating an epigenetic measure more closely related to phenotypic aging and healthspan [12]. GrimAge was subsequently developed using DNA methylation surrogates of plasma proteins and smoking exposure and demonstrated stronger associations with mortality and age-related disease outcomes than earlier chronological age clocks [13].

A further conceptual advancement was the distinction between biological age and the rate of biological aging. Whereas many epigenetic clocks estimate an age-related state at a given point in time, DunedinPACE was developed to estimate the rate at which biological aging occurs. This distinction is particularly relevant in studies of physical exercise, as an intervention may potentially alter the trajectory or rate of aging without causing a large, immediate change in estimated biological age [14].

2.4. Measures of epigenetic age acceleration

To facilitate interpretation, researchers often compare estimated epigenetic age with chronological age. The difference between these values is commonly referred to as epigenetic age acceleration (EAA). A positive value indicates that an individual's epigenetic age is higher than expected for their chronological age, whereas a negative value indicates a younger-than-expected epigenetic age [10,27].

Several statistical methods can be used to calculate age acceleration. Simple age acceleration can be expressed as the residual difference between epigenetic age and chronological age, whereas intrinsic and extrinsic measures have been developed to account for differences in blood cell composition and other biological factors [12,27–29]. These distinctions are important because apparent differences in DNA methylation may partly reflect variability in cellular composition rather than changes occurring within individual cell populations [23,29].

The interpretation of EAA also depends largely on the specific clock used. An individual may exhibit accelerated aging according to one epigenetic clock, while showing little or no acceleration according to another clock. This is not necessarily contradictory, as different clocks have been developed using different CpG sites and biological outcomes. Therefore, epigenetic age acceleration should not be regarded as a single, standardized clinical endpoint [12,23].

3. Mechanisms Through Which Exercise May Influence Epigenetic Aging

The biological effects of exercise extend far beyond improvements in physical fitness and cardiovascular capacity. Increasing evidence suggests that regular physical activity influences multiple molecular pathways involved in the aging process and may therefore affect biological age as measured by DNA methylation–based epigenetic clocks. The

exact mechanisms linking exercise to epigenetic aging remain incompletely understood. Currently available evidence indicates that exercise may lead to adaptations in inflammation, oxidative stress regulation, mitochondrial function, cellular metabolism, autophagy, and cellular senescence [17,30].

3.1. Regulation of Chronic Low-Grade Inflammation

One of the most characteristic features of aging is the development of chronic, systemic low-grade inflammation. Aging is associated with persistent activation of pro-inflammatory signaling pathways and increased concentrations of inflammatory mediators in the blood, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP). Chronic inflammation contributes to tissue dysfunction, dysregulation of the immune system, and the development of age-related diseases, and is also associated with accelerated epigenetic aging.

Regular exercise exerts strong anti-inflammatory effects through multiple mechanisms. Repeated periods of physical activity reduce visceral adiposity, improve immune system regulation, and promote the release of anti-inflammatory cytokines from skeletal muscle. Exercise is also associated with reduced activation of nuclear factor kappa B (NF-κB), a central regulator of inflammatory gene expression. Since inflammatory signaling may influence DNA methyltransferase activity and epigenetic regulation, the reduction of chronic inflammation may contribute to more favorable DNA methylation profiles and lower epigenetic age acceleration. Exercise-induced changes in DNA methylation have been observed in genes involved in immune and inflammatory pathways, supporting the hypothesis that inflammation represents an important mediator between physical activity and biological aging [31–34].

3.2. Mitochondrial Function and Energy Metabolism

Mitochondrial dysfunction is widely recognized as a hallmark of aging. Aging cells exhibit reduced mitochondrial efficiency, impaired oxidative phosphorylation, decreased ATP production, and increased accumulation of mitochondrial DNA damage [35].

Exercise is one of the most effective physiological stimuli for improving mitochondrial function. During physical activity, increased energy demand activates signaling pathways involving AMP-activated protein kinase (AMPK), sirtuin 1 (SIRT1), and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which collectively promote mitochondrial biogenesis and metabolic adaptation. Importantly, exercise-induced changes in DNA methylation have been documented in genes regulating mitochondrial metabolism and oxidative capacity, including PGC-1α. These epigenetic modifications may increase transcriptional responsiveness and contribute to long-term improvements in cellular energy homeostasis. By preserving mitochondrial function and metabolic flexibility, exercise may indirectly attenuate mechanisms associated with accelerated biological aging [35–39].

3.3. Oxidative Stress and Redox Signaling

Oxidative stress has long been associated with the aging process. Excessive production of reactive oxygen species (ROS) may damage DNA, proteins, and lipids, contributing to cellular dysfunction and age-related cognitive decline.

However, contemporary research suggests that ROS are not exclusively harmful by-products of metabolism but also function as important signaling molecules. Exercise provides a significant example of this dual role. Intense physical exercise transiently increases ROS production. However, repeated exposure induces adaptive responses that strengthen endogenous antioxidant mechanisms. This phenomenon, often referred to as hormesis, leads to improved cellular resistance to oxidative stress. Redox-sensitive signaling pathways activated during exercise may influence the activity of DNA methyltransferases (DNMTs) and ten-eleven translocation (TET) enzymes, which regulate DNA methylation patterns. Consequently, exercise-induced redox signaling may directly contribute to epigenetic remodeling and the maintenance of a more favorable biological aging profile [40–43].

3.4. Autophagy and Cellular Quality Control

Autophagy is a highly conserved cellular process responsible for the degradation and recycling of damaged proteins, dysfunctional organelles, and other cellular components. Aging is characterized by a progressive decline in autophagic capacity, leading to the accumulation of cellular damage and impaired tissue function. Reduced autophagy is associated with numerous age-related diseases, including neurodegenerative, cardiovascular, and metabolic diseases [44,45].

Exercise stimulates autophagic pathways in multiple tissues, particularly skeletal muscle, the liver, and cardiovascular tissues. Activation of AMPK and inhibition of the mechanistic target of rapamycin (mTOR) signaling pathway during exercise promote cellular recycling processes and support the maintenance of proteostasis. Although direct evidence linking exercise-induced autophagy to epigenetic clocks remains limited, enhanced cellular quality control may reduce biological stressors that contribute to age-related epigenetic drift. Therefore, autophagy represents a plausible mechanism through which regular physical activity may influence biological aging [44,46–48].

3.5. Cellular Senescence and Intercellular Communication

Cellular senescence refers to a state of irreversible cell-cycle arrest accompanied by profound changes in cellular function. Senescent cells accumulate with age and secrete numerous pro-inflammatory cytokines, growth factors, and proteases, collectively referred to as the senescence-associated secretory phenotype (SASP). This secretory profile contributes to chronic inflammation, tissue dysfunction, and the propagation of age-related changes to neighboring cells.

Emerging evidence suggests that regular exercise may reduce the burden of senescent cells or mitigate their harmful effects. Improved immune surveillance, reduced systemic inflammation, and enhanced metabolic function may collectively limit senescence-related signaling [49–52].

3.6. Tissue-Specific Epigenetic Adaptations

An important consideration in exercise epigenetics is that methylation responses are highly tissue-specific. Most human studies of epigenetic age rely on peripheral blood samples because of their accessibility. However, exercise induces substantial molecular adaptations in skeletal muscle, adipose tissue, cardiovascular tissues, and the central nervous system. Consequently, changes

observed in blood methylation profiles may not fully reflect epigenetic adaptations occurring in other organs.

Skeletal muscle appears to be particularly responsive to exercise-induced epigenetic remodeling. A study by Voisin et al. demonstrated that both acute and chronic exercise were associated with gene-specific changes in DNA methylation [53]. In turn, studies by Garcia et al. demonstrated that even 8 weeks of training was able to induce changes in skeletal muscle DNA methylation in specific genes and pathways [54]. These findings suggest that tissue-specific epigenetic adaptations may represent an important component of the anti-aging effects of exercise [53–56]. Future studies integrating multiple tissues and advanced epigenetic clocks may provide a more comprehensive understanding of the effects of physical activity on biological aging at the organismal level.

4. Evidence Linking Physical Activity and Epigenetic Age

4.1. Evidence from Observational Studies

Most of the initial evidence linking physical activity with epigenetic aging came from observational studies. These studies focused on examining associations between self-reported or objectively measured physical activity and epigenetic age acceleration (EAA) in community-dwelling adults.

In a meta-analysis by Shana et al. including seven cross-sectional studies, higher physical activity was found to be significantly associated with lower epigenetic age acceleration assessed using the Horvath and GrimAge clocks. No significant associations were found for the Hannum and PhenoAge clocks. The authors concluded that physical activity was associated with a younger biological age. However, due to the predominance of cross-sectional studies, a causal relationship could not be confirmed. Nevertheless, not all observational studies demonstrated significant associations [57].

The study by Quach et al. was one of the first large-scale studies to assess the relationship between lifestyle factors and the rate of biological aging measured using DNA methylation–based epigenetic clocks. The analysis included a total of 4,575 participants, including 4,173 postmenopausal women from the Women's Health Initiative (WHI) cohort and 402 individuals from the Italian InCHIANTI study. The authors demonstrated that higher physical activity was associated with lower epigenetic age acceleration, particularly with regard to extrinsic epigenetic age acceleration, which reflects both cellular aging processes and changes occurring in the immune system. In contrast, a higher body mass index (BMI) and features of metabolic syndrome were significantly associated with accelerated biological aging. Longitudinal analyses additionally demonstrated that an increase in BMI over time was correlated with an increase in both intrinsic (IEAA) and extrinsic (EEAA) epigenetic age acceleration. The authors emphasized that although the effects of individual components of diet and physical activity on the rate of aging were relatively small, the findings support the beneficial effect of a healthy lifestyle on the biological aging process and indicate that obesity and metabolic disturbances may substantially accelerate this process [29].

Another important limitation of observational data is the possibility of residual confounding. Individuals who engage in regular physical activity often differ from less active individuals in terms of several health-related behaviors, including dietary habits, smoking, alcohol consumption, sleep quality,

educational attainment, and socioeconomic status. Although statistical adjustments may partially account for these factors, observational studies cannot ultimately establish a cause-and-effect relationship, as demonstrated in the study by Wu and Lin, which assessed the relationship between lifestyle factors, physiological parameters, and epigenetic age acceleration [58].

4.2. Cardiorespiratory Fitness and Biological Age

Cardiorespiratory fitness (CRF) has emerged as one of the strongest physiological correlates of healthy aging. In contrast to self-reported physical activity, CRF reflects the integrated capacity of the cardiovascular, respiratory, and musculoskeletal systems to deliver and utilize oxygen during exercise. Because CRF is less susceptible to reporting bias, it may represent a more objective indicator of long-term exposure to physical exercise.

Evidence of a significant association between cardiorespiratory fitness and biological age was provided by Leong et al. (2024), who assessed 78 individuals aged ≥40 years using direct measurement of cardiorespiratory fitness during cardiopulmonary exercise testing (CPET) and epigenetic clocks. A higher VO_2peak was associated with lower epigenetic age acceleration assessed using DNAmAgeSkinBlood, DNAmGrimAge, and DNAmGrimAge2. The associations were particularly significant for DNAmGrimAge ($p = 0.012$) and DNAmGrimAge2 ($p = 0.011$). Furthermore, lower cardiorespiratory fitness was associated with greater epigenetic age acceleration, and baseline epigenetic age measures were also associated with VO_2peak levels after three years. DNA methylation analysis additionally indicated changes in genes and biological pathways related, among other processes, to cellular aging. These findings suggest that higher cardiorespiratory fitness may be associated with slower biological aging and may represent a potentially modifiable factor supporting healthy aging [59].

In a study by Kawamura et al. involving 144 men aged 65–72 years, both VO_2 at the ventilatory threshold and VO_2peak showed significant negative correlations with epigenetic age acceleration. This indicates that higher cardiorespiratory fitness was associated with slower biological aging. However, after accounting for other lifestyle factors, the effect of CRF was smaller than that of, among other factors, smoking, triglyceride levels, carbohydrate intake, and body composition [60].

4.3. Evidence from Exercise Intervention Studies

Although observational studies provide valuable insights, intervention studies provide stronger evidence regarding causal relationships. In recent years, several exercise intervention studies have investigated whether structured physical activity programs can modify epigenetic measures of age.

Etayo-Urtasun et al. conducted a systematic review of 12 randomized controlled trials involving a total of 827 previously inactive adults to assess the effects of exercise interventions on DNA methylation. The duration of the interventions ranged from 6 weeks to 12 months, and the programs primarily included aerobic training, resistance training, or a combination of both. Most of the studies analyzed demonstrated significant changes in DNA methylation in response to exercise, both at the level of specific genes and at the global and epigenome-wide levels. Importantly, studies in which beneficial changes in DNA

methylation were observed also frequently reported improvements in physical fitness, including VO_2max or VO_2peak [19].

Meanwhile, Yang et al. conducted a systematic review of 29 intervention studies evaluating the effects of exercise on DNA methylation in peripheral blood. The studies analyzed included both short-term and long-term interventions, including aerobic training, resistance training, and high-intensity interval training (HIIT), conducted in healthy individuals and patients with various chronic diseases. It was demonstrated that single exercise sessions resulted in only small and mostly transient changes in DNA methylation, which in most cases did not remain significant after statistical correction. A different pattern was observed with long-term training, which resulted in more pronounced changes in DNA methylation, particularly in genes related to metabolism, inflammatory processes, and immune system function. More favorable and pronounced changes were observed primarily with interventions lasting at least 12 weeks, performed ≥3 times per week, and lasting ≥45 minutes per session. The authors therefore indicate that regular, sufficiently prolonged physical exercise may induce persistent remodeling of the epigenetic profile, whereas single training sessions have a considerably weaker and shorter-lasting effect [61].

4.4. Current State of Evidence

Overall, current evidence suggests that physical activity is associated with more favorable epigenetic aging profiles and may contribute to slower biological aging. The consistency of findings across multiple populations, study designs, and aging biomarkers supports the biological plausibility of this association. However, important uncertainties remain.

First, the causal nature of the association has not yet been definitively established. Second, the magnitude of exercise-induced changes in epigenetic age remains relatively small and varies depending on the clock used. Third, it remains unclear which form of exercise, intensity, frequency, or duration is most effective in influencing biological aging. Finally, evidence linking exercise-induced changes in epigenetic age to clinically meaningful long-term health outcomes remains limited.

Therefore, although existing data support the hypothesis that physical activity may act as a modulator of biological aging, further large-scale longitudinal studies and randomized controlled trials are needed to determine the extent to which exercise can meaningfully alter epigenetic aging trajectories and extend healthy life expectancy [23,57,62,63].

5. Which Type of Exercise Appears Most Effective?

5.1. Aerobic Exercise

Aerobic exercise is the most extensively studied form of physical activity in the context of biological aging. Activities such as walking, running, cycling, swimming, and other endurance exercises induce broad physiological adaptations affecting cardiovascular, metabolic, and immune function. These adaptations are highly relevant to aging because they influence several hallmarks of aging, including mitochondrial dysfunction, chronic inflammation, impaired nutrient sensing, and oxidative stress [36,37,64].

Observational studies consistently report that individuals engaging in moderate- to vigorous-intensity aerobic activities tend to exhibit lower epigenetic age acceleration and more favorable biological aging profiles [29,57,65,66]. Similarly, higher cardiorespiratory fitness, often considered a long-term indicator of habitual aerobic activity, is associated with slower biological aging according to several epigenetic clocks [29,66]. These findings are biologically plausible because aerobic exercise promotes mitochondrial biogenesis, improves insulin sensitivity, enhances endothelial function, and reduces systemic inflammation [36,37,64].

Intervention studies have also demonstrated that structured aerobic exercise programs can induce changes in DNA methylation patterns and, in some cases, reduce accelerated epigenetic aging. However, the observed effects are generally small, and not all studies have demonstrated significant improvements. Differences in study populations, intervention duration, and the epigenetic clocks used likely contribute to these inconsistencies [19,57,61].

Overall, aerobic exercise currently represents one of the most extensively studied exercise modalities in relation to biological aging, and the available evidence generally supports a beneficial association with epigenetic aging [29,57,65,66].

5.2. Resistance Training

Resistance training has traditionally been studied primarily in the context of muscle strength, functional independence, and the prevention of sarcopenia. However, increasing evidence suggests that resistance exercise may also influence molecular pathways involved in biological aging [37,67–69]. Mechanical loading stimulates skeletal muscle remodeling and activates signaling pathways associated with protein synthesis, mitochondrial adaptation, and metabolic regulation [35,37,69]. Resistance training is associated with favorable changes in inflammatory markers, glucose metabolism, and body composition, which may indirectly contribute to slower biological aging [35,67,68,70]. Moreover, skeletal muscle appears to be particularly responsive to exercise-induced epigenetic remodeling, and studies have demonstrated changes in DNA methylation patterns following both acute and chronic resistance training [39,54,71].

Despite these promising observations, relatively few studies have directly examined the effects of resistance training on epigenetic age acceleration [19,57]. Existing evidence suggests that resistance exercise may produce beneficial effects comparable to those observed with aerobic exercise, particularly in older individuals. Improvements in muscle strength and physical fitness have also been associated with lower estimates of biological age in several cohorts [19,57,66].

Given the importance of maintaining muscle mass and functional capacity throughout aging, resistance training may represent a particularly valuable strategy for promoting healthy aging, even though its direct effects on epigenetic clocks remain less thoroughly characterized [19,57,66].

5.3. High-Intensity Interval Training

High-intensity interval training (HIIT) has gained considerable popularity as an exercise strategy that allows efficient use of time while eliciting substantial

physiological adaptations. HIIT typically consists of repeated short periods of high-intensity exercise interspersed with recovery periods [72–74].

Compared with traditional continuous moderate-intensity exercise, HIIT may produce similar or greater improvements in cardiorespiratory fitness while requiring less training time. Mechanistically, HIIT strongly stimulates mitochondrial biogenesis, glucose regulation, vascular adaptation, and cellular stress-response pathways. These processes are closely linked to mechanisms involved in biological aging [36,38,74].

Although studies investigating the effects of HIIT on epigenetic age remain limited, available evidence suggests that high-intensity exercise may induce pronounced changes in DNA methylation patterns and gene expression. Some researchers have suggested that the intermittent metabolic stress generated during high-intensity interval training may trigger adaptive responses consistent with the concept of hormesis, according to which exposure to controlled physiological stress enhances long-term resilience [36,38,74].

Nevertheless, current evidence remains insufficient to conclude that HIIT is more effective than other forms of exercise in slowing epigenetic aging. Moreover, the applicability of HIIT may vary depending on age, baseline physical fitness, and health status [53,74].

5.4. Combined and Multicomponent Exercise Programs

Because aging affects multiple physiological systems simultaneously, combined exercise programs incorporating aerobic, endurance, flexibility, and balance training have attracted increasing interest. Such interventions may provide broader physiological benefits than any single exercise modality [75–77].

Multicomponent exercise programs are frequently recommended for older adults because they simultaneously target cardiovascular health, muscle strength, mobility, balance, and functional independence. Emerging evidence suggests that these interventions may also exert beneficial effects on biological markers of aging. By simultaneously influencing multiple pathways associated with aging, combined exercise programs may theoretically generate greater cumulative benefits than isolated exercise modalities [75–79].

Several intervention studies involving older adults have reported improvements in health biomarkers following multicomponent training programs. Although evidence regarding epigenetic clocks remains limited, the multidimensional nature of these interventions is closely aligned with contemporary models of healthy aging and biological resilience [19].

6. Conclusions

The concept of biological age has revolutionized contemporary aging research by providing a framework that extends beyond chronological age and better reflects individual variability in health status, functional capacity, and disease risk. Among the available biomarkers of biological aging, DNA methylation–based epigenetic clocks have emerged as powerful tools for assessing aging trajectories and the effects of lifestyle-related factors on the aging process [10,12–14].

Physical activity is associated with more favorable biological aging profiles. Individuals who regularly engage in physical activity and maintain higher levels of physical fitness generally exhibit lower epigenetic age acceleration and slower rates of biological aging. These associations are biologically plausible given the broad effects of exercise on key mechanisms involved in aging, including mitochondrial function, regulation of

oxidative stress, chronic inflammation, metabolic homeostasis, autophagy, and cellular senescence [29,36,66].

Among different exercise modalities, aerobic exercise currently has the strongest evidence linking it to beneficial effects on epigenetic aging. Resistance training, high-intensity interval training, and multicomponent exercise programs also show considerable potential and may influence biological aging through complementary physiological pathways. However, direct comparisons between exercise modalities remain limited, and current evidence does not support definitive conclusions regarding the superiority of any single exercise strategy [19,36,57,66].

Despite the promising findings, several important limitations remain. Studies demonstrate substantial heterogeneity in participant characteristics, exercise interventions, follow-up periods, and the epigenetic clocks used for assessment. Furthermore, although exercise-induced changes in epigenetic aging markers have been observed, the extent to which these molecular changes translate into clinically meaningful improvements in health, disease prevention, and longevity remains uncertain [19,57,63].

Overall, the available literature supports the hypothesis that exercise acts as a modifiable regulator of biological aging and may contribute to healthier aging trajectories. Nevertheless, epigenetic clocks should currently be regarded primarily as research tools rather than established clinical endpoints. Future studies should focus on large prospective studies and well-designed randomized controlled trials that directly compare exercise modalities, investigate dose–response relationships, and determine whether improvements in epigenetic biomarkers of aging result in measurable long-term health benefits [14,19,57,63].

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