Available online at www.sciencedirect.com

ScienceDirect

Journal of Sport and Health Science

Review

Exercise attenuates the hallmarks of aging: Novel perspectives

Yan Qiu [a,b,†], Benjamin Fernández-García [c,d,†], H. Immo Lehmann [e,f], Guoping Li [e,g], Guido Kroemer [h,i,j,k,*], Carlos López-Otín [h,i,l,*], Junjie Xiao [a,b,*]

[a] *Institute of Geriatrics (Shanghai University), Affiliated Nantong Hospital of Shanghai University (The Sixth People's Hospital of Nantong) and School of Life Science, Shanghai University, Nantong 226011, China*

[b] *Cardiac Regeneration and Ageing Lab, Institute of Cardiovascular Sciences, Shanghai Engineering Research Center of Organ Repair, School of Life Science, Shanghai University, Shanghai 200444, China*

[c] *Health Research Institute of the Principality of Asturias (ISPA), Oviedo 33011, Spain*

[d] *Department of Morphology and Cell Biology, Anatomy, University of Oviedo, Oviedo 33006, Spain*

[e] *Cardiovascular Division of the Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA*

[f] *Albert Einstein College of Medicine, Department of Internal Medicine, NCB, New York, NY 10461, USA*

[g] *Department of Anesthesia, Critical Care, and Pain Medicine, MA General Hospital and Harvard Medical School, Boston, MA 02114, USA*

[h] *Université Paris Cité, Sorbonne Université, Inserm, Centre de Recherche des Cordeliers, F-75006 Paris, France*

[i] *Centre de Recherche des Cordeliers, Equipe labellisée par la Ligue contre le cancer, Institut Universitaire de France, Paris 75006, France*

[j] *Université Paris-Saclay, INSERM US23/CNRS UAR 3655, Metabolomics and Cell Biology Platforms, Institut Gustave Roussy, Villejuif 94808 France*

[k] *Institut du Cancer Paris CARPEM, Department of Biology, Hôpital Européen Georges Pompidou, AP-HP, Paris 75015, France*

[l] *Facultad de Ciencias de la Vida y la Naturaleza, Universidad Nebrija, Madrid 28045, Spain*

Received 3 June 2025; revised 3 September 2025; accepted 22 September 2025
Available online 4 December 2025

Abstract

The number and proportion of individuals aged 60 years and older are steadily increasing. However, increased life expectancy is accompanied by a decline in functional capacity and a heightened risk of age-related diseases, ultimately leading to reduced quality of life. Interventions that support physiological function in later life and hence extend healthspan are therefore of considerable importance. Among these, regular physical exercise is strongly associated with numerous health benefits and is recognized as a key strategy for promoting healthy aging and extending healthspan. In this review, we highlight the impact of an active lifestyle, particularly regular physical activity, on the major hallmarks of aging. These include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, impaired macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, changes in the extracellular matrix, stem cell exhaustion, altered intercellular communication, chronic inflammation, dysbiosis, and psychosocial isolation. A deeper understanding of the mechanisms by which exercise confers these benefits will aid in enhancing both physical and mental health in the elderly and in mitigating the onset of aging-associated diseases.

Keywords: Exercise; Healthy aging; Healthspan; Hallmarks of aging

1. Introduction

Lifespan has significantly increased throughout the 20th century. According to the World Health Organization (WHO), the global population of individuals over 60 years old reached one billion in 2020 and is projected to double by 2050, approaching 2.1 billion, which is approximately 22% of the world's population.[1] However, this demographic shift is accompanied by a growing burden of late-life diseases, including cancer, diabetes, cardiovascular diseases (CVDs), and neurodegenerative disorders,[2] posing an irrefutable public health challenge. With advancing age, physiological functions progressively decline, affecting multiple organ systems and often coinciding with the onset of chronic diseases.[3] This gradual decline, referred to as aging, is characterized by visible physical and mental changes, including altered posture, decreased exercise capacity, reduced range of motion and

Peer review under responsibility of Shanghai University of Sport.

* Corresponding authors.
E-mail addresses: kroemer@orange.fr (G. Kroemer), clo@uniovi.es (C. López-Otín), Junjiexiao@shu.edu.cn (J. Xiao).
† These two authors contributed equally to this work.

https://doi.org/10.1016/j.jshs.2025.101108
Cite this article: Qiu Y, Fernández-García B, Lehmann HI, et al. Exercise attenuates the hallmarks of aging: Novel perspectives. *J Sport Health Sci* 2026;15:101108.

slower mental processing, which are based on a variety of molecular and physiological mechanisms. Along with environmental influences, changes in intrinsic capacity and its individual domains (e.g., locomotion, psychological health, cognition, vitality, sensory function) determine an individual's functional ability—the cornerstone of healthy aging.[4] At the same time, aging is a major risk factor for numerous chronic diseases and functional impairments, severely threatening health and longevity.[5,6] Therefore, interventions aimed at preventing age-related diseases, prolonging "healthy life years" (defined as years free of diseases), and enhancing intrinsic capacity to promote healthy aging are of significant interest.[4,7] Furthermore, primary prevention must be developed before health risk factors appear.[8] Emerging evidence suggests that aging and age-related diseases are modifiable and, to some extent, preventable by targeting the fundamental molecular mechanisms underlying aging.[9−11]

Among these interventions, regular exercise/physical activity (PA) is a highly cost-effective and accessible strategy to improve overall health. In this review, exercise refers to a planned and structured regimen of PA aimed at enhancing physical fitness, with PA defined as any bodily movement that expends energy, such as walking, manual labor, and housework.[12,13] The seminal study has demonstrated that the relative risk of death is related to physical fitness not only in the general population but also in various diseases.[14] Human studies consistently demonstrate that regular PA mitigates the adverse effects of aging on key health indicators and reduces the risk of morbidity and mortality.[15−18] Specifically, exercise can attenuate the age-related decline in maximal oxygen uptake (VO_{2max}), lower the production of reactive oxygen species (ROS), minimize oxidative damage to cellular components, and preserve the function of various organ systems.[19] For this reason, regular physical exercise can help to prevent various chronic diseases that become more prevalent with age.[20] Of note, even low volumes of PA confer longevity benefits. Individuals who perform an average of 90 min of PA per week, or just 15 min per day, experience a 14% reduction in all-cause mortality and gain approximately 3 additional years of life expectancy.[21] Although the underlying mechanisms linking exercise to longevity remain unclear, improvements in aerobic capacity appear to play a central role. Long-term exercise is known to significantly enhance aerobic fitness, which is not only positively associated with longevity but is also considered one of its most robust physiological predictors.[22−24] Moreover, regular exercise performed even in older adulthood can yield substantial health benefits. Evidence suggests that 1 year of endurance exercise can improve aerobic exercise capacity and cognitive performance as well as exert favorable effects on arterial compliance and vascular health in previously sedentary older adults.[25,26] Furthermore, higher levels of moderate-to-vigorous PA have been associated with enhanced intrinsic capacity in older adults, further highlighting the importance of promoting PA for healthy aging.[4] Growing evidence also indicates that adopting an active lifestyle early in life has long-lasting benefits. A 25-year longitudinal study conducted in Amsterdam and Purmerend found that individuals who maintained PA during youth exhibited better health outcomes in later life, including improved aerobic capacity, greater bone mineral density, and lower fat mass.[27] Similarly, a retrospective study reported that PA during childhood and adolescence was associated with a reduced risk of arterial hypertension and type 2 diabetes in adulthood.[28] Notably, another study showed that 3 months of swimming initiated at 1 month of age in mice produced long-lasting improvements in immune regulation, even after 11 months of detraining.[29]

Exercise is a modifiable behavioral factor that not only reduces the risk of chronic diseases but also improves outcomes in age-related conditions such as CVD, diabetes, and neurodegeneration. In contrast, sedentary behavior is strongly associated with increased risk of age-associated diseases.[30] Notably, the link between physical inactivity and an elevated CVD risk is more pronounced in older adults, underscoring the need for preventative strategies in this population.[31,32] There is now broad consensus on PA guidelines for older adults.[33−37] Current recommendations advise adults to engage in 150−300 min of moderate-intensity, or 75−150 min of vigorous-intensity PA weekly, or an equivalent combination, including aerobic and resistance exercise as well as balance, flexibility and coordination exercises. For adults aged 65 or older, it is recommended to engage in multicomponent PA (including balance training and muscle-strengthening activities) 2 or more days per week to improve functional ability and reduce fall risk.[34,36,37] Importantly, exercise should be personalized for older individuals based on their specific conditions and desired outcomes. It should be regarded as a form of treatment, with PA or structured exercise prescriptions tailored to health-related goals and integrated into daily care.[37] Notably, adults who meet the recommended guidelines by engaging in either a minimum of 75 min of vigorous-intensity or 150 min of moderate-intensity activity per week experience a 31% reduction in mortality risk compared to those who do not engage in leisure-time PA.[15]

Aging is a multifactorial process that involves alterations at the molecular, cellular, tissue, and organ-system levels.[38] The major hallmarks of aging include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, impaired macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, alterations in the extracellular matrix, stem cell exhaustion, disrupted intercellular communication, chronic inflammation, dysbiosis, and psychosocial isolation.[39,40] Accumulating data suggest that exercise can partially counteract several hallmarks of aging. Even before the most recent expansion of the hallmarks framework, prior studies had already outlined the anti-aging properties of exercise in relation to the previously proposed hallmarks.[41,42] Given our expanding knowledge on the biology of aging and the benefits of PA, this review aims to provide an updated overview of how exercise mitigates aging at the molecular and cellular levels. We specifically summarize the impact of exercise on the major hallmarks of aging (Fig. 1). The final objective is to provide a comprehensive summary of the critical biological pathways through which exercise confers protective

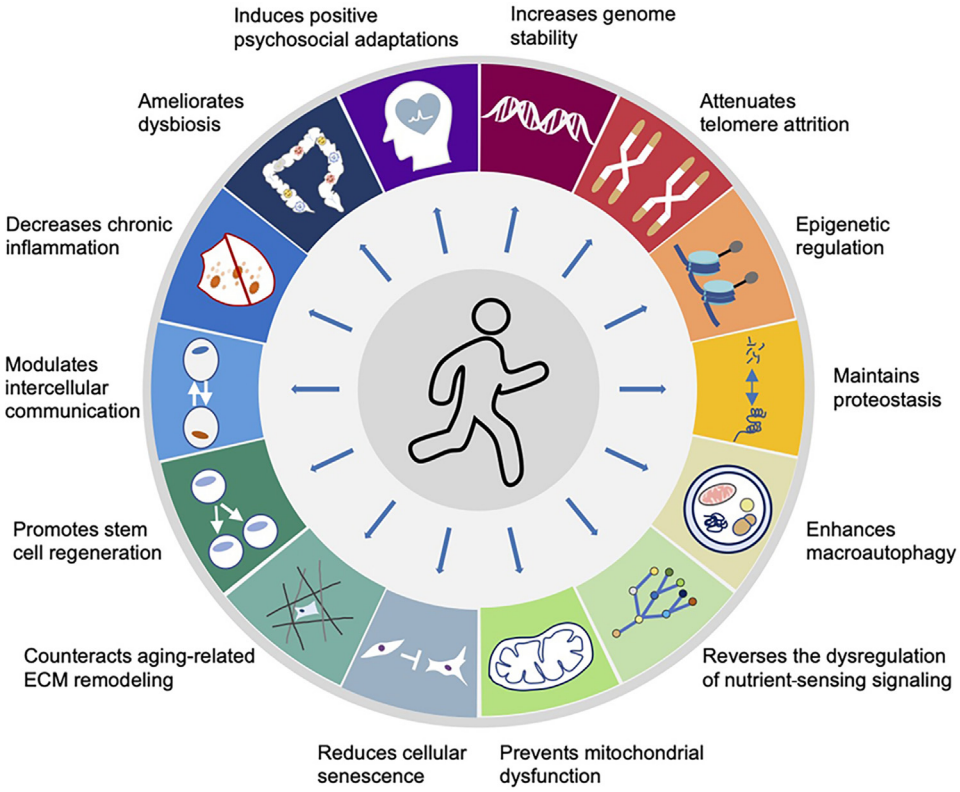

Fig. 1. Exercise attenuates the hallmarks of aging. The main regulatory mechanisms by which exercise delays aging include increased genome stability, attenuated telomere attrition, epigenetic regulation, maintenance of proteostasis, enhanced macroautophagy, reversal of the dysregulation of nutrient-sensing signaling, prevention of mitochondrial dysfunction, reduced cellular senescence, counteraction to aging-related ECM remodeling, promotion of stem cell regeneration, modulated intercellular communication, decreased chronic inflammation, ameliorated dysbiosis, and induction of positive psychosocial adaptations. ECM = extracellular matrix.

effects against aging and age-related diseases. For clarity and reference, Supplementary Table 1 outlines exercise protocols and models of aging in animal studies, Supplementary Table 2 summarizes exercise protocols used in human studies, and Supplementary Table 3 compiles evidence from randomized controlled trials (RCTs) cited in this review.

2. Study selection

This review broadly encompasses research articles that investigated the effects of PA and exercise on the hallmarks of aging. Specifically, it includes: (a) human studies that assess the effects of PA or exercise on aging hallmarks in older adults or individuals with age-related diseases; (b) animal studies that evaluate the effects of exercise on the hallmarks of aging in aged animals or in established models of age-related diseases; (c) RCTs that examine the effects of exercise on the hallmarks of aging in elderly adults or individuals with various health conditions. All studies were written in English, and the majority were published within the past decade (more than half within the past 5 years).

3. Exercise protects genome stability

Maintaining genomic stability is crucial for preserving cellular function, and its decline can accelerate the aging process. Genomic instability is characterized by several features, including the accumulation of DNA damage, activation of retrotransposons, telomere shortening, and impaired DNA repair capacity.[43] Regular PA appears capable of promoting genome stability by reducing DNA damage and enhancing DNA damage repair (Fig. 2).

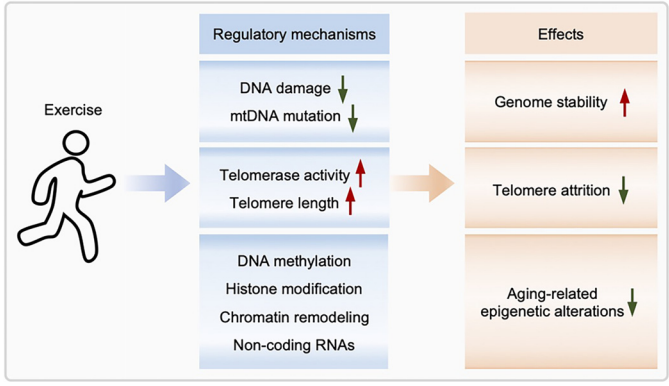

Fig. 2. Effects of exercise on genome stability, telomere attrition, and epigenome in the context of aging. Exercise can decrease DNA damage and mtDNA mutation rate and thus increase genome stability. Exercise can also activate telomerase and increase telomere length and thus decrease telomere attrition. Moreover, exercise can decrease aging-related epigenetic alterations through mechanisms that include DNA methylation, histone modification, chromatin remodeling, and non-coding RNAs. mtDNA = mitochondrial DNA.

3.1. Nuclear DNA

Aging is associated with increased nuclear DNA alterations such as DNA lesions, genomic mutations, and transcriptional disruptions across multiple organs and tissues, leading to increased DNA damage.[44] This genomic damage poses a serious threat to cellular viability and is implicated in the pathogenesis of several diseases, including neurodegenerative disorders and cancer.[45] Thus, interventions that decrease DNA damage or promote DNA damage repair represent promising strategies for preventing or treating these diseases. Exercise emerges as one such intervention. Studies in both humans and animal models demonstrate that regular PA can protect against aging-related DNA damage. For example, 14−16 weeks of moderate resistance exercise significantly reduced urinary levels of 8-hydroxy-2'-deoxyguanosine—a marker of oxidative DNA damage—in elderly individuals over 60 years old.[46,47] Similarly, a 16-week combined strength and aerobic exercise program was found to decrease DNA strand breaks and formamidopyrimidine DNA glycosylase-sensitive sites in peripheral blood lymphocytes of healthy adults aged 40−74, indicating reduced overall and oxidative DNA damage.[48] These benefits were accompanied by increased antioxidant enzyme activity and reduced lipid peroxidation, indicating that enhanced antioxidant defense may partly mediate the protective effects of exercise on DNA.[48] Moreover, elderly adults practicing long-term Tai Chi (duration 6.9 ± 0.6 years, mean ± SD) exhibited reduced levels of damaged DNA in peripheral blood mononuclear cells compared to sedentary individuals. This may reflect improved DNA repair mechanisms, as evidenced by a lower frequency of sister chromatid exchange in Tai Chi practitioners.[49] Similarly, an 8-week treadmill exercise program prevented age-associated increases in 8-oxo-2'-deoxyguanosine levels in nuclear DNA and enhanced the activity of 8-oxoguanine DNA glycosylase in the livers of aged rats, thereby promoting DNA repair.[50] Although regular exercise confers beneficial effects on genomic stability, acute unaccustomed exercise might induce transient DNA damage.[51] The molecular mechanisms by which regular exercise mitigates aging-induced DNA damage are not well understood. Emerging evidence suggests that exercise may enhance DNA repair capacity, potentially through upregulation of circulating or tissue-specific derived neurotrophic factor (e.g., brain-derived neurotrophic factor (BDNF)).[52]

3.2. Mitochondrial DNA (mtDNA)

mtDNA is a double-stranded circular molecule consisting of 16,569 base pairs and encoding 13 essential proteins, 2 ribosomal RNAs (rRNAs), and 22 transfer RNAs.[53] With advancing age, mtDNA copy number and function progressively decline across various tissues. Accumulation of mtDNA mutations, including deletions, tandem duplications, and single-base modifications, has been strongly associated with aging and the pathogenesis of age-related diseases.[54] Insights into the role of mtDNA mutations in aging have been gained from studies on mtDNA mutator mice, which harbor a mutation in the mtDNA polymerase-γ. These mice exhibit multiple premature aging phenotypes, such as weight loss, alopecia, hair graying, reduced subcutaneous fat, cardiac hypertrophy, diminished body weight and size, and a shortened lifespan.[55] Interestingly, long-term exercise has been shown to markedly counteract many of the aging-associated features in mtDNA mutator mice, such as alopecia and hair graying, body size reduction, and kyphosis, while increasing endurance capacity and decreasing mtDNA mutation burden.[56,57] It is important to recognize that different types and intensities of exercise can have distinct effects on mitochondrial health and aging. For instance, 5 months of treadmill exercise promoted mitochondrial biogenesis, prevented mtDNA depletion and mutations, enhanced mitochondrial function, reduced systemic apoptosis, and lowered premature mortality in mtDNA mutator mice.[56] Conversely, another study reported that more than 20 weeks of voluntary exercise reduced mtDNA mutations without significantly impacting mtDNA content or overall mortality.[57] Proteomics analyses have further revealed that long-term voluntary exercise mitigates mtDNA mutation-induced aging, at least partially, by counteracting protein dysfunction in both skeletal muscle and brain tissues.[57] However, the effects of exercise on aging-related mtDNA mutations in humans remain unclear. Existing evidence suggests that exercise appears to have no effect on mtDNA mutation load in patients with mtDNA mutations, but may help counteract mitochondrial dysfunction in these individuals.[58]

3.3. Nuclear architecture

Alterations in nuclear morphology and architecture, such as changes in nuclear size and shape, irregular nuclear margins, blebbing, and aberrant expression of laminar proteins, are common features of aging.[59] Disruption of nuclear structure can contribute to muscle pathologies and accelerate premature aging phenotypes. Despite the importance of the topic, relatively few studies have specifically investigated the effects of exercise on aging-associated changes in nuclear architecture. Available evidence suggests that exercise may positively influence nuclear structure and mechanical properties, thereby potentially mitigating the detrimental effects of aging. For example, one study reported notable differences in the nuclear shape of myonuclei in trained and untrained individuals.[60] Myonuclei from trained subjects displayed increased nuclear lamina deposition and reduced nuclear deformability compared to their untrained counterparts.[60] Furthermore, skeletal muscle from exercised mice exhibited elevated expression of lamin A and enhanced nuclear stiffness, suggesting that exercise may help preserve nuclear integrity during aging.[60]

4. Exercise attenuates aging-related telomere attrition

Telomeres are DNA–protein complexes composed of telomerase reverse transcriptase and the telomerase RNA component, located at the ends of chromosomes. They play a vital role in maintaining genomic stability.[61,62] Telomere length progressively shortens with each cell division due to incomplete replication of the lagging strand.[63,64] As a result, telomere length is widely regarded as a biomarker of biological aging. Critically shortened telomeres trigger cellular senescence and contribute

to organismal aging. Current evidence suggests that long-term, moderate-intensity exercise may be effective in slowing or preventing telomere attrition (Fig. 2).[65] For example, 8 weeks of combined strength and aerobic training promoted telomere elongation in obese women.[66] In another study, 6 months of exercise improved both telomere length and cognitive performance in healthy women over the age of 65.[67] Furthermore, exercise preserved telomere length in individuals with cardiometabolic conditions, including obesity, type 2 diabetes, and CVDs.[68] For example, a 3-month home-based aerobic training program in elderly patients with heart failure increased leukocyte telomere length.[69]

Interestingly, the impact of exercise on telomere length appears to be tissue specific. In wild-derived short telomere mice (CAST/Ei), 44 weeks of voluntary wheel running attenuated age-associated telomere shortening in the liver and heart. However, telomeres in exercised skeletal muscle were significantly shorter than those in sedentary controls.[70] Moreover, the effect of exercise interventions on telomere length seems to differ across exercise modalities. A recent meta-analysis of nine intervention studies (RCTs or controlled trials) found that among 4 types of exercise modalities—resistance training, aerobic exercise, high-intensity interval training (HIIT), and aerobic plus resistance training—only HIIT remarkably increased telomere length in healthy adults.[71] Although controversy exists regarding the effect of exercise interventions, PA levels have been more consistently related to longer telomere length.[72] Notably, 1 systemic review has suggested a significant correlation between telomere length and physical fitness levels.[72] Therefore, participants' fitness levels should be included in future investigations into how exercise modulates telomere biology and the aging process. Taken together, these findings highlight the need for further studies to investigate the tissue-specific responses to exercise, the differential effects of exercise modalities on telomere length, and the underlying mechanisms by which exercise influences telomere biology across different tissue systems.

Telomerase is a ribonucleoprotein complex that extends telomere repeats at the 3'-end of chromosomes; it is critical for telomere maintenance.[73] Several studies have demonstrated that regular PA is associated with enhanced telomerase activity and telomere length in humans.[74,75] A systematic review and meta-analysis further confirmed that long-term exercise training promotes telomerase activation and attenuates telomere shortening, supporting its role in healthy biological aging.[76] Importantly, the benefits of exercise on telomerase activity appear to vary depending on the type of exercise. An RCT reported that 6 months of aerobic endurance training or HIIT significantly increased telomerase activity and telomere length in peripheral blood mononuclear cells of previously sedentary adults.[77] In contrast, 6 months of resistance training did not produce significant changes in these parameters.[77] These findings suggest that different training modalities exert distinct cellular effects. Future mechanistic studies are warranted to clarify how specific exercise regimens influence telomere biology and to guide exercise prescription aimed at cellular senescence.

5. Exercise and epigenetic regulation

Aging is accompanied by widespread changes in the epigenome, including altered DNA methylation patterns, aberrant histone modifications, and deregulation of non-coding RNAs (ncRNAs).[78,79] Remarkably, recent evidence suggests that changes in epigenetic information are not merely consequences but also potential drivers of mammalian aging. Resetting the epigenome has been shown to restore youthful gene expression profiles in aged cells, underscoring the role of epigenetic reprogramming in aging and age-related disease prevention.[80] Exercise is emerging as a powerful modulator of the epigenome.[81] Accumulating evidence indicates that exercise-induced epigenetic modifications contribute to improved health outcomes in older adults (Fig. 2). This section focuses on the effects of exercise on aging-related epigenetic changes.

5.1. DNA methylation

DNA methylation was initially employed as a biomarker to estimate chronological age, a concept termed the "epigenetic clock".[82,83] Subsequently, DNA methylation-based age predictors were found to correlate with age-related diseases and outcomes, including frailty, mortality, and cancer risk.[84] Therefore, the epigenetic age is now considered a surrogate marker of both lifespan and healthspan.[82] Increasing evidence suggests that regular PA and exercise can partially reverse age-associated DNA methylation changes and slow epigenetic age.[85,86] An RCT reported that a 2-year PA intervention significantly reduced age-related DNA methylation alterations in healthy postmenopausal women.[87] Similarly, a meta-analysis encompassing 16 studies and 1580 participants demonstrated that nuclear DNA methylation generally declined with exercise, with greater changes observed in individuals aged over 40 years compared to younger individuals.[88] Several studies in this meta-analysis showed that many hypomethylated genes belong to a cancer-suppressive microRNA (miRNA) network, supporting the protective role of exercise in preventing age-related diseases.[88] In animal studies, aged mice (22−24 months) subjected to 8 weeks of progressive weighted wheel running exhibited an epigenetic age nearly 8 weeks younger than sedentary controls. These mice also showed lower levels of DNA methylation in skeletal muscle and a more youthful methylation profile overall.[89] Moreover, in mice, both endurance and resistance exercise lead to modifications in DNA methylation in the hippocampus, primarily decreasing it.[81] Exercise also appears to regulate mtDNA methylome in aged human skeletal muscle. In the skeletal muscle of elderly untrained individuals, 6 weeks of resistance training (twice weekly) led to significant alteration in mtDNA methylation. Most cytosine-phosphate-guanine (CpG) sites became hypomethylated, resulting in a methylation profile that closely resembled that of younger, trained individuals.[90] In addition to these findings, long-term exercise may prevent age-related diseases (e.g., CVDs) via epigenetic mechanisms. For instance, a 3-month aerobic exercise program significantly increased the methylation of long interspersed nuclear element 1 (LINE1), endothelin 1, and inducible nitric oxide synthase in

healthy and hypertensive individuals, and these increases were inversely associated with systolic and diastolic blood pressure.[91] Moreover, a 6-month aerobic training program in elderly African Americans with mild cognitive impairment was associated with higher VO_{2max} and global DNA methylation changes.[92] Notably, vacuolar protein sorting homolog 52 (*VPS52*), a gene involved in intracellular protein trafficking and amyloid biology, was among the most significantly hypomethylated genes following exercise.[92] This supports the hypothesis that exercise may protect against age-related cognitive decline through epigenetic mechanisms.

5.2. Histone modifications

An increasing body of evidence indicates that the health-promoting effects of exercise are closely linked to changes in histone structure and function. These post-translational modifications influence chromatin accessibility and gene transcription, thereby modulating key physiological processes relevant to aging. For example, an 8-week multimodal exercise intervention significantly improved balance, mobility, functional capacity, quality of life, and cognitive performance in elderly individuals, changes that were partially attributed to increased levels of histone H3 acetylation.[93] Similarly, in aged rats, 2 weeks of moderate treadmill exercise improved aversive memory performance and increased hippocampal levels of histone 4 lysine 12 acetylation (H4K12ac) and histone 3 lysine 9 acetylation (H3K9ac).[94] Notably, an increase in H4K12ac was also observed in young rats subjected to the same exercise protocol, suggesting a potential role of hippocampal histone acetylation in exercise-induced memory enhancement.[94] Further supporting these findings, a 4-week aerobic exercise regimen improved cognitive function in senescence-accelerated mice, alongside increased BDNF expression and decreased levels of p75 in the hippocampus. This was accompanied by the activation of histone acetyltransferases and histone deacetylases, indicating exercise-induced regulation of histone acetylation machinery.[95] Additionally, multiple types of exercise (i.e., aerobic, acrobatic, resistance, or combined exercise modalities) have been shown to enhance survival and aversive memory performance in aged rats, with these improvements linked to histone modifications at the promoters of memory-associated genes such as *Bdnf* and *fos proto-oncogene (cFos)*.[96] Importantly, different exercise modalities appear to exert distinct effects on histone marks: aerobic and resistance exercise decreased H3K4me3 at the *Bdnf* promoter in the hippocampus, while aerobic and acrobatic exercise significantly increased H3K9ac at the *cFos* promoter. Similarly, resistance and combined exercise increased H3K4me3 at the *cFos* promoter.[96] Taken together, these studies highlight histone modifications as a key epigenetic mechanism by which exercise confers neuroprotective and anti-aging benefits. The specificity of histone responses to different exercise modalities further underscores the potential for tailoring exercise prescriptions to optimize cognitive and functional outcomes in aging populations.

5.3. Chromatin remodeling

Aging is associated with significant chromatin structural remodeling, largely mediated by histone-modifying enzymes and adenosine triphosphate (ATP)-dependent chromatin-remodeling complexes.[79,97] These structural changes contribute to transcriptional instability, genomic dysregulation, and cellular aging. Although limited, emerging evidence suggests that exercise may counteract these chromatin alterations, thereby mitigating age-associated functional decline. One study demonstrated that 4 months of voluntary running in aged mice partially prevented age-related increases in nuclear permeability, mislocalization of nuclear signaling proteins such as transactivation response DNA-binding protein 43 and small ubiquitin-like modifier 1, and disorganization of chromatin within motoneurons of the spinal cord.[98] These findings suggest that PA may protect against aging-related motor neuron loss by preserving nuclear and chromatin integrity in the central nervous system. However, dedicated studies on the role of exercise in reversing chromatin remodeling during aging remain sparse, and further mechanistic investigations are needed.

5.4. Non-coding RNAs (ncRNAs)

ncRNAs, including miRNAs, long ncRNAs (lncRNAs), and circular RNAs (circRNAs), are key regulators of multiple cellular processes. Dysregulation of ncRNAs has been implicated in various age-related diseases, and they are increasingly being recognized as disease biomarkers and therapeutic targets.[99,100] Exercise significantly alters the expression of ncRNAs, contributing to their wide-ranging anti-aging effects across tissues. In skeletal muscle, exercise-mediated maintenance of muscle mass and strength during aging is closely linked to the preservation of type II muscle fibers, a process regulated in part by lncRNAs.[101,102] A key lncRNA in this context is Cytor, whose expression is decreased with aging and elevated following exercise in both humans and mice.[103] Downregulation of Cytor in skeletal muscle mimics functional and morphological features of sarcopenia, while its overexpression in aged muscle reverses the decline in type II muscle fibers and restores muscle mass and function, possibly by sequestering transcription factor Tead 1.[103] Additional studies have shown that both miRNAs and circRNAs are implicated in exercise-mediated protection against aging-related muscle atrophy. For instance, aged rats subjected to exercise show differential expression of miRNAs targeting key genes such as androgen receptor (*Ar*), insulin-like growth factor 1 (*Igf1*), hypoxia-inducible factor-1 subunit alpha (*Hif1a*), *Bdnf*, focal adhesion kinase (*Fak*), and neuroblastoma rat sarcoma (*Nras*).[104] Likewise, circBBS9, which is downregulated in aged sedentary muscles, is restored by exercise.[105] Overexpression of circBBS9 in aging mice increases the expression of genes related to mitochondrial function, such as peroxisome proliferator-activated receptor gamma coactivator-1 alpha (*Pgc-1α*), mitofusin 1 (*Mfn1*), and adenosine triphosphatase (*Atpase*), and decreases atrophy-related gene expression, including forkhead box O3 (*Foxo3*) and muscle atrophy F-box

(*Atrogin*), suggesting a direct role in modulating muscle aging.[105]

Beyond skeletal muscle, ncRNAs are also implicated in mediating the neuroprotective effects of exercise. Long-term exercise-induced exosomal miR-532-5p has been shown to enhance blood–brain barrier integrity, thereby facilitating the clearance of brain amyloid-β and improving memory performance in five familial Alzheimer's disease (5XFAD) mice, which carry mutations.[106] Mechanistically, miR-532-5p exerts its effects by downregulating the expression of Eph receptor A4, a key modulator of blood-brain barrier function.[106] In another model of brain aging, 6 weeks of swimming exercise effectively reversed D-galactose (D-gal)-induced neural aging by restoring impaired autophagy and correcting mitochondrial dysfunction through the downregulation of miR-34a.[107] Similarly, 8 weeks of voluntary wheel running in aging rats was found to attenuate brain aging via upregulation of miR-130a, which in turn enhances autophagic activity.[108] In the context of systemic aging, lifelong low-intensity exercise reduced chronic inflammation and prevented the onset of osteosarcopenic obesity in aged rats. This was accompanied by altered expression of a subset of miRNAs closely linked to immune regulation.[109] The differential expression of these miRNAs indicated that they might mediate aging-associated inflammatory response, thereby contributing to improved muscle function and mitigation of musculoskeletal decline.[109] In *Drosophila*, dmiR-283, which shares functional homology with mammalian miR-216a, has been identified as an age-dependent miRNA implicated in circadian rhythm disruption. Notably, dmiR-283 appears to be essential in mediating the beneficial effects of exercise on age-related sleep-wake disturbances.[110] Exercise training initiated in early adulthood and continued through middle age significantly reduced dmiR-283 level in the aging brain, ameliorating behavioral deficits associated with circadian dysfunction.[110]

5.5. Retrotransposons

Retrotransposons are genomic elements capable of duplicating and inserting themselves into new loci via RNA intermediates. Among these, LINE1 is an autonomous retrotransposon that remains active in the human genome and has been implicated in aging and various age-related diseases.[111] Despite their potential relevance, studies specifically examining the role of retrotransposons in exercise-mediated healthy aging are limited. One human study reported significantly elevated levels of LINE1 open reading frame 1 (ORF1) mRNA in the skeletal muscle of older individuals compared to younger subjects. Interestingly, exercise was shown to downregulate LINE1 ORF1 mRNA expression in both age groups.[112] Although these findings suggest a potential suppressive effect of exercise on retrotransposon activity, the functional implications of LINE1 activation in skeletal muscle remain unknown. Further investigation is warranted to clarify whether LINE1 contributes to age-related muscular decline and how exercise modulates its expression.

5.6. Gene expression changes

The aforementioned epigenetic regulatory mechanisms converge on transcriptional control, positioning gene expression changes as fundamental mediators of exercise-induced adaptations during aging. Exercise induces tissue-specific adaptive responses across multiple organ systems, and these adaptations are often associated with improved physiological function.[113] In skeletal muscle, for instance, 8 weeks of treadmill exercise in aged mice led to significant enrichment of genes associated with neurotransmission and neuroexcitation, particularly those involved in glutamate receptor signaling and transport, implicating neural regulation as a mechanism for enhanced muscle function.[114] Exercise also reverses aging-associated gene expression profiles in stem cells and immune compartments. A single-cell transcriptomic study evaluating stem cells from skeletal muscle, the subventricular zone of the brain, bone marrow hematopoietic stem and progenitor cells, and peripheral blood immune cells revealed that 5 weeks of voluntary running exercise partially reversed aging-associated changes in the cell composition and transcriptional programs in old mice. Notably, exercise suppressed the activation of inflammation-associated pathways, including interferon and tumor necrosis factor-alpha (TNF-α) targets, and increased the presence of tissue-remodeling monocytes absent in aged sedentary animals.[115] It also restored impaired cell-cell communication between monocytes/macrophage populations and resident stem cells within these tissues.[115] Additionally, findings from a meta-analysis of human skeletal muscle transcriptomes following exercise training showed that exercise shifts gene expression profile toward a younger signature, particularly in pathways involved in mitochondrial function, metabolism, and muscle structural integrity.[116] These changes highlight the systemic rejuvenating potential of PA through transcriptional reprogramming, reinforcing its role as a central modulator of healthy aging.

6. Exercise improves proteostasis

Proteostasis, or protein homeostasis, refers to the delicate balance between protein synthesis, folding, trafficking, and degradation, which is essential for cellular function and organismal health. With age, the ability of cells to sustain proteostasis decreases, resulting in the accumulation of misfolded or aggregated proteins and increased vulnerability to a range of age-related diseases, particularly neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease.[117,118] Here, we summarize the current evidence demonstrating that PA plays a significant role in preserving proteostasis in aging individuals, thereby contributing to disease prevention (Fig. 3).

6.1. Exercise restores aging-induced loss in proteostasis

Increasing evidence indicates that exercise can restore proteostatic mechanisms disrupted by aging. For example, elderly individuals with hypertension who engaged in regular PA exhibited lower plasma levels of ubiquitinated proteins

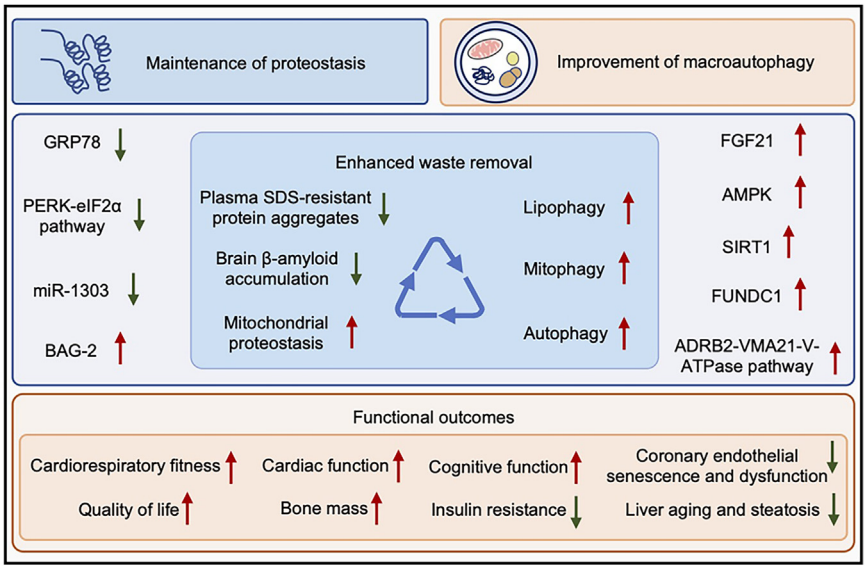

Fig. 3. Effects of exercise on the maintenance of proteostasis and macroautophagy. Exercise can enhance the removal of aging-induced accumulation of waste products through a variety of mechanisms, which are listed on the left and the right. The functional outcomes and healthy benefits of exercise are also included. ADRB2 = β2-adrenergic receptor; AMPK = adenosine 5-monophosphate-activated protein kinase; BAG-2 = BCL2-associated athanogene 2; eIF2α = eukaryotic initiation factor-2α; FGF21 = fibroblast growth factor 21; FUNDC1 = FUN14 domain containing 1; GRP78 = glucose-regulated protein of 78 kDa; miR = micro RNA; PERK = double-stranded RNA-activated protein kinase-like endoplasmic reticulum kinase; SDS = sodium dodecyl sulfate; SIRT1 = sirtuin-1; VMA21 = vacuolar ATPase assembly factor VMA21; V-ATPase = vacuolar-type H^+-translocating ATPase.

and higher levels of heat shock protein (HSP)70 compared to the age-matched control group, suggesting an improved protein quality control system.[119] Similarly, a 12-week combined aerobic and resistance training program in elderly patients with heart failure with reduced ejection fraction led to a significant decrease in plasma sodium dodecyl sulfate (SDS)-resistant protein aggregates (SRA), which includes proteins linked to amyloidosis and molecular chaperones. Additionally, the intervention decreased haptoglobin levels within SRAs, suggesting improved extracellular proteostasis.[120] These molecular changes were accompanied by improved cardiorespiratory fitness and quality of life among participants.[120] In preclinical models of neurodegeneration, similar benefits have been observed. For instance, 3 months of treadmill exercise in APPswe/PSEN1dE9 (APP/PS1) transgenic mice, a widely used model for AD, notably reduced β-amyloid protein accumulation in the brain, a hallmark pathological feature of AD. This reduction was accompanied by a significant downregulation of glucose-regulated protein of 78 kDa and the suppression of the double-stranded RNA-activated protein kinase-like endoplasmic reticulum (ER) kinase−eukaryotic initiation factor-2α pathways, suggesting that exercise dampens excessive ER stress and supports protein folding homeostasis.[121] Additionally, 12 weeks of treadmill training in APP/PS1 mice has been shown to enhance mitochondrial proteostasis by upregulating the mitochondrial unfolded protein response and promoting mitophagy, while concurrently reducing the accumulation of proteins destined for mitochondrial import.[122] These findings indicate that exercise not only improves cognitive function and attenuates AD-like symptoms but also restores proteostasis through both cytoplasmic and mitochondrial pathways.

6.2. *Exercise, proteostasis, and longevity*

Engaging in regular PA has been consistently associated with increased life expectancy, and autophagy is identified as an important mechanism through which exercise promotes longevity.[123−125] For instance, long-term football training has been shown to activate key markers of autophagy and protein quality control in the skeletal muscle of elderly individuals, including B-cell lymphoma 2 (Bcl2), HSP70, HSP90, autophagy related 5 homolog (ATG5)-ATG12 complex, and proteasome 26S subunit non-ATPase 13.[126] Subsequent work revealed that miR-1303 is a key regulatory molecule mediating these effects. Levels of miR-1303 were significantly lower in the skeletal muscle of elderly football players compared to age-matched sedentary individuals, suggesting that its downregulation may be linked to enhanced autophagic capacity and proteostasis.[127] One of the primary targets of miR-1303 is Bcl2-associated athanogene 2 (BAG-2), a chaperone protein involved in preventing protein aggregation. Notably, BAG-2 expression was significantly increased in the skeletal muscle of trained elderly individuals compared to untrained controls, further supporting the notion that long-term PA enhances the protein quality control system.[127] This molecular adaptation may contribute to extended healthspan and lifespan by mitigating the proteotoxic stress associated with aging.[128] It is noteworthy that enhanced proteostasis has also been implicated in the longevity of the longest-lived rodent, the naked mole-rat, which exhibits delayed aging and resistance to age-related diseases.[129−131] Further research into the mechanisms underlying the protective effects of exercise and the biology of long-lived animals may facilitate the development of preventive and therapeutic strategies for aging and age-related diseases in humans.

7. Exercise enhances macroautophagy

Macroautophagy (hereafter referred to as autophagy) is a fundamental catabolic process that facilitates the degradation and recycling of various intracellular components, including misfolded proteins, lipids (lipophagy), damaged organelles (e.g., mitophagy), and intracellular pathogens (xenophagy).[132] Autophagy plays a vital role in maintaining cellular homeostasis and protecting against metabolic and degenerative diseases. With aging, autophagic efficiency declines, contributing to the accumulation of damaged cellular components and the pathogenesis of numerous age-related diseases, such as neurodegenerative diseases, CVDs, and cancer.[133] Conversely, interventions that enhance autophagy have demonstrated promise in extending healthspan and lifespan in preclinical models.[132] Among non-pharmacological strategies, exercise has emerged as a potent inducer of autophagy, with accumulating evidence, particularly from animal models, demonstrating that PA can counteract age-related impairments in autophagic flux and restore tissue homeostasis.[134−136] In fact, exercise-induced Bcl2-regulated autophagy has been identified as essential for mediating the metabolic effects of exercise.[137] This section focuses on the effects of exercise on autophagy in the context of aging (Fig. 3).

Several studies have shown that exercise can reverse aging- and diet-induced impairments in autophagy across various tissues.[138−142] For example, 8 weeks of treadmill training significantly attenuated high-fat diet-induced hepatic aging and steatosis in rats via enhancing fibroblast growth factor 21 (FGF21) in skeletal muscle, which subsequently activated hepatic lipophagy via the adenosine 5-monophosphate-activated protein kinase (AMPK) pathway.[138] Likewise, 16 weeks of swimming exercise improved hepatic steatosis and insulin resistance in high-fat diet-fed mice, along with enhanced lipophagy and activation of AMPK/sirtuin-1 (SIRT1) axis.[139] In bone, 8 weeks of treadmill running improved bone formation capacity and restored bone mass in aging mice, likely through stimulation of osteogenic differentiation in bone marrow mesenchymal stem cells mediated by SIRT1-driven autophagy.[140] Exercise also modulates mitophagy, particularly in cardiovascular tissues. Four weeks of swimming exercise attenuated age-related coronary endothelial senescence and improved endothelial function in aged mice, effects that were associated with activation of FUN14 domain-containing 1-mediated mitophagy via peroxisome proliferator-activated receptor gamma signaling. This pathway also contributed to reduced susceptibility to ischemia-reperfusion injury in the aging heart.[141] Although human data remain limited, there is evidence that endurance training increases expression of mitophagy-related protein Parkin RBR E3 ubiquitin-protein ligase (PARKIN) and mRNAs involved in autophagosome formation in the skeletal muscle of elderly men, suggesting that exercise preserves mitochondrial quality control in aging humans.[142]

Considering the strong connection between impaired autophagy and age-related diseases, such as AD and cardiac pathologies, restoring autophagic flux has emerged as a promising therapeutic strategy.[143,144] Exercise is a potent autophagy stimulator, as demonstrated in relevant models of disease. In APP/PS1 mice, 12 weeks of treadmill running ameliorated cognitive function and attenuated disease progression by restoring autophagy-lysosomal flux. This effect was mediated by activation of the β2-adrenergic receptor-vacuolar ATPase assembly factor (VMA21)-vacuolar-type H^+-translocating ATPase (V-ATPase) axis and AMPK-mechanistic target of rapamycin kinase (mTOR) signaling.[145] In the context of diabetic cardiomyopathy, 4 weeks of HIIT significantly increased autophagy-related genes, including *Beclin-1*, *Atg-5*, and *Lamp2*, in myocardial tissue, resulting in improved cardiac function.[146] Collectively, these findings underscore the potential of exercise to stimulate autophagy and mitigate age- and disease-related tissue dysfunction.

8. Exercise reverses aging-associated dysregulation of nutrient-sensing signaling

Aging is associated with a progressive decline in metabolic organ function and subsequent metabolic impairment. Nutritional factors, including the composition, quantity, and sources of nutrients, can profoundly modulate this process.[147,148] An unhealthy diet (e.g., high-fat diet) promotes aging and increases the risk of various diseases, including obesity, type 2 diabetes, CVD, and cognitive impairment.[149,150] On the contrast, a healthy diet prevents or delays many age-related disorders and enhances overall well-being in later life.[148,151] Dietary nutrient availability and metabolic sensing are closely linked to the aging process and longevity. Data from the 2015−2018 National Health and Nutrition Examination Surveys, which include 4692 adults, revealed that inadequate intake of certain nutrients, such as protein, vitamins A and E, and iron, was negatively associated with biological age acceleration.[152] At the molecular level, a dysregulated nutrient-sensing network has emerged as a key mechanism that contributes to aging and age-related diseases.[153,154] Lifestyle factors such as poor diet and lack of exercise induce conditions like metabolic dysfunction and CVD, which share many molecular effects with aging.[153,155,156] For example, the common nutrient-sensing network between aging and CVD mainly involves the mTOR, AMPK, SIRT1, insulin and insulin-like growth factor-1 (IGF-1) signaling.[153]

Importantly, exercise is capable of modulating multiple nutrient-sensing pathways, and thus exerting anti-aging effects and promoting healthy aging (Fig. 4). For example, exercise is well known to have cardioprotective effects and to reduce the risk of CVD and cardiac events. The main mechanisms underlying these benefits involve the regulation of IGF-1/PI3K/AKT, AMPK, mTOR, and SIRT1 signaling pathways.[157−160] Moreover, accumulating evidence shows that exercise can enhance whole-body insulin sensitivity and skeletal muscle metabolism in older adults, effects that are believed to be mediated by the improvements in insulin signaling cascade and glucose utilization.[161] Preclinical studies[162−164] also provide strong evidence supporting the role of exercise in counteracting aging-related dysfunction of the

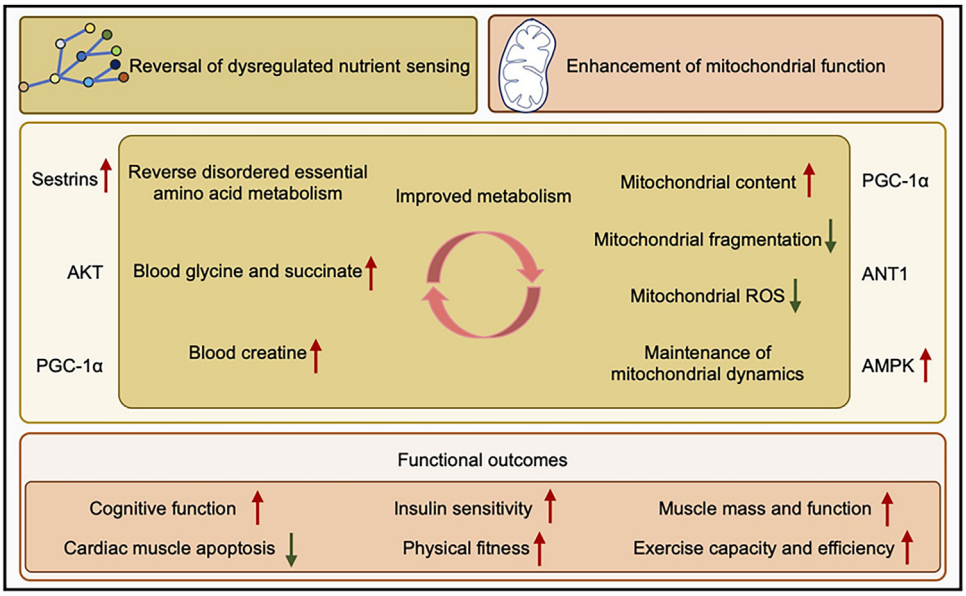

Fig. 4. Effects of exercise on aging-related dysregulated nutrient-sensing and mitochondrial dysfunction. Exercise can partly reverse aging-associated dysregulated nutrient sensing and enhance mitochondrial function, leading to improved metabolism. The involved mechanisms are listed on the left and the right. And the functional outcomes of exercise are included in the lower part of the graph. AKT = serine/threonine kinase; AMPK = adenosine 5-monophosphate-activated protein kinase; ANT1 = adenine nucleotide translocase 1; PGC-1α = peroxisome proliferator-activated receptor γ coactivator 1α; ROS = reactive oxygen species.

nutrient-sensing network. In a D-gal-induced aging model, an 8-week aerobic interval training program preserved metabolic homeostasis and mitigated age-associated decline in metabolic balance.[162] Specifically, this training regimen reversed D-gal-induced cognitive impairments and corrected abnormalities in essential amino acid metabolism, including glycine, serine, and threonine metabolism, as well as cysteine, methionine, and tryptophan metabolism.[162] Additional metabolomics-based studies using proton nuclear magnetic resonance (^{1}H NMR) approaches showed that long-term moderate-intensity exercise influenced circulating levels of key metabolites associated with carbohydrate, lipid, and protein metabolism. Lifelong exercise (from 3 to 21 months) or exercise performed during the first half of life (3−12 months) improved blood levels of glycine and succinate—2 metabolites positively associated with insulin sensitivity—in rats.[163] Moreover, the same study showed that exercise introduced during the latter half of life, was associated with potentially adverse effects on body weight and appetite, whereas earlier-life exercise elevated blood creatine levels, which may help counteract sarcopenia and age-related muscle mass loss.[163] Furthermore, sestrins, a family of evolutionarily conserved proteins, were found to be critical mediators of exercise-induced metabolic benefits. In mouse models, genetic deletion of sestrins blunted the improvements in insulin sensitivity and respiratory capacity typically conferred by exercise, whereas overexpression of sestrins mimicked the physiological and molecular outcomes of PA.[164] Mechanistically, sestrins mediate these effects via key signaling pathways, including AKT and PGC-1α, thereby promoting enhanced muscle metabolism, physical endurance, and mitochondrial function.[164] Altogether, these studies highlighted the positive role of exercise in modulating aging-related nutrient-sensing pathways, as well as the promise of dietary intervention combined with exercise training as a strategy for combating aging and age-related diseases.

9. Exercise prevents aging-related mitochondrial dysfunction

Mitochondrial health is crucial for cellular function because mitochondria serve as key bioenergetic organelles and regulators of diverse physiological processes, including calcium homeostasis, apoptosis, and inflammation, as well as AMPK- and mTOR-mediated energy and nutrient sensing.[165] Mitochondrial dysfunction is a hallmark of aging and has been implicated in the development and progression of multiple age-related diseases, such as Parkinson's disease,[166] AD,[167] type 2 diabetes,[168] and CVDs.[169] Therefore, interventions aimed at restoring mitochondrial homeostasis, including mitochondrial transplantation and modulation of mitochondrial regulatory pathways, are promising approaches to promote healthy aging and treat metabolic and degenerative conditions.[165,170]

9.1. Mitochondrial function and longevity

Age-related decline in mitochondrial function can result from increased ROS production, accumulation of mtDNA mutations, oxidative damage to proteins, impaired oxidative phosphorylation, and reduced mitochondrial biogenesis.[171] However, accumulating evidence highlights the protective role of regular PA in counteracting these mitochondrial deficits (Fig. 4). In elderly individuals, regular exercise is associated with improved mitochondrial health and enhanced physiological outcomes, including greater insulin sensitivity, superior muscle function, and elevated exercise capacity and efficiency,

even when compared to older adults who engage in recommended daily PA levels but lack structured training.[172] Lifelong high-volume exercise training has been shown to prevent age-related mitochondrial decline in human abdominal subcutaneous white adipose tissue by enhancing mitochondrial content and oxidative capacity, thereby contributing to metabolic resilience and healthy aging.[173] However, it is worth noting that excessive exercise training can impair mitochondrial respiratory function in healthy young volunteers, which is associated with reduced glucose tolerance.[174]

In preclinical studies, 8 weeks of treadmill exercise reversed age-associated impairments in mitochondrial respiratory function in the skeletal muscle of aged mice without altering mitochondrial content. These benefits were accompanied by reduced mitochondrial fragmentation, decreased mitochondrial ROS production, and diminished oxidative stress.[175] Mechanistically, improvements in maximal respiratory capacity were independent of PGC-1α, whereas enhancements in mitochondrial ADP-stimulated respiration and suppression of fragmentation appeared to depend on PGC-1α activity, likely involving transcriptional and post-transcriptional regulation of adenine nucleotide translocase 1.[175] Similarly, 8 weeks of treadmill exercise in rats led to an increase in mitochondrial oxygen consumption, hydrogen peroxide generation, and calcium retention capacity while attenuating pro-apoptotic signaling in myocardial tissue.[176] This was accompanied by normalization of mitochondrial dynamics and mitigation of excessive mitophagy, which are frequently dysregulated in the aging heart.[176] In the liver, lifelong treadmill exercise conferred protection against age-associated mitochondrial dysfunction, with extended exercise durations correlating with enhanced mitochondrial efficiency and reduced oxidative stress.[177] Finally, in a study utilizing the model organism *Caenorhabditis elegans*, researchers confirmed the evolutionarily conserved impact of exercise on mitochondrial health.[178] Long-term PA prevented the age-related decline in physical fitness, an effect found to be dependent on proper mitochondrial fission and fusion dynamics in the body wall muscle. This adaptation appeared to be regulated by AMPK signaling, linking energy status to mitochondrial integrity and functional capacity during aging.[178] Taken together, these findings indicate that regular exercise confers protection against aging-related mitochondrial dysfunction.

9.2. *Exercise and mitochondrial microproteins*

Mitochondrial-derived peptides (MDPs), particularly humanin and the mitochondrial open reading frame of the 12S rRNA-c (MOTS-c), have been shown to have protective roles in aging and age-related diseases that parallel those of exercise.[179] MDP levels decline with age, potentially contributing to the deterioration of mitochondrial function and systemic homeostasis in older individuals.[180] Thus, strategies that increase mitochondrial-derived peptide levels might represent a promising treatment to ameliorate aging and age-related diseases. Several human studies have reported that different modalities of exercise (e.g., aerobic exercise, resistance training, HIIT) elevate circulating and skeletal muscle levels of MOTS-c and humanin, even in middle-aged and older adults.[181–184] These findings suggest that exercise may serve as a physiological stimulator of MDPs, contributing to their broad anti-aging effects.

Interestingly, the response of individual MDPs to exercise appears to be differentially regulated depending on exercise intensity and chronic adaptation. One study found that professional athletes exhibited significantly lower serum MOTS-c levels compared to non-athletes, while humanin levels were notably increased.[185] Furthermore, serum humanin levels were inversely associated with training intensity: athletes engaged in high-intensity endurance exercise exhibited significantly lower humanin levels than those performing low- or moderate-intensity training. Similarly, MOTS-c levels were reduced in moderate-intensity endurance athletes compared to those involved in low-intensity regimens.[185] Further investigation should explore the underlying mechanisms as well as the expression changes of mitochondrial-derived peptides in different types of exercise with varying modalities and intensities.

Beyond peptide regulation, mitochondrial proteostasis is closely linked to the maintenance of overall cellular protein homeostasis, or proteostasis. Disruption of mitochondrial protein translation—particularly in the context of aging—has been identified as a critical factor in impaired mitochondrial function. In aged mice, skeletal muscle sarcopenia is associated with deficits in mitochondrial translation, mediated in part by reduced activity of PGC-1α and estrogen-related receptor alpha (ERRα).[186] Notably, long-term exercise training prevents the decline of PGC-1α/ERRα-regulated mitochondrial translation and enhances protein quality control in aged muscle, contributing to improved mitochondrial integrity and function.[186] In elderly individuals, the benefits of exercise on muscle mitochondrial function and hypertrophy were also primarily attributed to the increased translation of mitochondrial proteins, highlighting the translational axis as a conserved and exercise-responsive target for preserving muscle and metabolic health during aging.[187]

10. Exercise reduces aging-induced cellular senescence

Cellular senescence is a hallmark of aging and a major driver of aging-associated tissue dysfunction and chronic disease. Senescent cells accumulate progressively with age and exert deleterious effects through both cell-autonomous mechanisms and paracrine signaling, particularly via the senescence-associated secretory phenotype (SASP).[188] Their elimination, either genetically or pharmacologically, has been shown to improve tissue homeostasis and delay or reverse the progression of numerous age-related diseases, highlighting senescence as a high-priority therapeutic target in aging research. Regular PA has emerged as a promising, non-pharmacological strategy to reduce cellular senescent burden and mitigate associated systemic dysfunction (Fig. 5). Clinical evidence supports the anti-senescent effects of structured exercise interventions. In elderly adults, a 12-week supervised

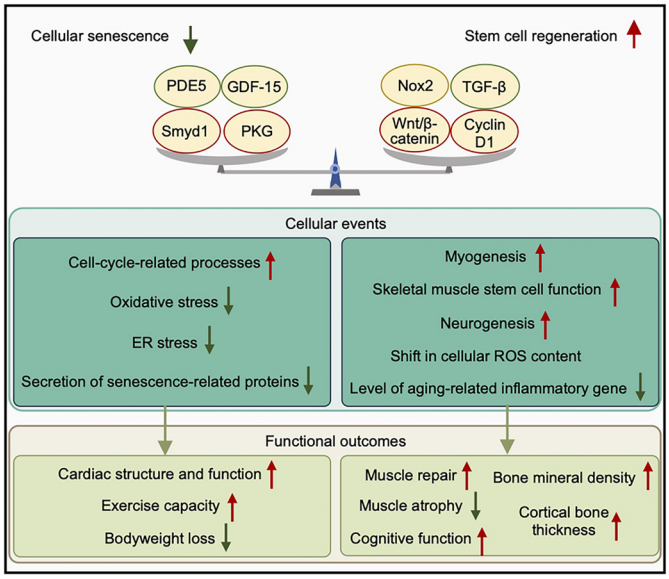

Fig. 5. Exercise can reduce cellular senescence burden and promote stem cell regeneration. The regulators and cellular events through which exercise decreases cellular senescence and enhances stem cell regeneration are included. The functional outcomes of exercise are listed in the lower part of the graph. cGMP = cyclic guanosine monophosphate; ER = endoplasmic reticulum; GDF-15 = growth differentiation factor 15; NADPH = nicotinamide adenine dinucleotide phosphate; Nox2 = NADPH oxidase 2; PDE5 = cGMP-specific phosphodiesterase type 5; PKG = cGMP-protein kinase G; ROS = reactive oxygen species; Smyd1 = SET and MYND domain containing 1; TGF-β = transforming growth factor-β; Wnt/β-catenin = wingless-type MMTV integration site family/beta-catenin.

exercise program significantly reduced markers of cellular senescence in $CD3^+$ T cells, including decreased expression of p16, p21, cyclic GMP-AMP synthase (cGAS), and TNF-α. Additionally, this intervention lowered circulating concentrations of several senescence-related proteins,[189] suggesting a reduction in senescent cell burden.

Mechanistically, cellular senescence is driven by chronic DNA damage signaling, activation of cyclin-dependent kinase inhibitors, cell cycle arrest, anti-apoptotic gene expression, metabolic dysregulation, proinflammatory cytokine production, and ER stress.[190] Regular exercise emerges as a promising senescence-targeting therapy as it can counteract many of these upstream triggers, positioning it as a broadly acting senescence-modifying therapy.[191] In murine models, an 8-week moderate-intensity treadmill exercise attenuated cardiac aging phenotypes related to heart failure with preserved ejection fraction. Exercise improved exercise capacity, systolic strain, diastolic function, contractile reserves, and pulmonary congestion in aged mice.[192] RNAseq analysis revealed that exercise upregulated multiple cell-cycle-related pathways, implicating suppression or reversal of the senescence program, as a contributing mechanism for the observed cardioprotection.[192] Similarly, 8 weeks of swimming exercise improved myocardial structure and function in aged mice by decreasing the oxidative and ER stress responses partly mediated by the activation of myocardial cyclic guanosine monophosphate (cGMP)-protein kinase G signaling and inhibition of cGMP-specific phosphodiesterase type 5 (PDE5).[193] Parallel effects were observed with resistance training, where exercise protected aged mouse hearts against oxidative damage and ER stress via upregulation of SET and MYND domain containing 1 (Smyd1), a muscle-specific histone methyltransferase.[194] Smyd1 activation was shown to blunt D-gal-induced stress in cardiomyocytes, further implicating this pathway in exercise-mediated senescence resistance.[194]

The SASP, a proinflammatory profile secreted by senescent cells, includes cytokines, chemokines, growth factors, and matrix-degrading enzymes, and is known to exacerbate aging-related inflammation and tissue deterioration.[190] Recent longitudinal studies have demonstrated that sustained PA can attenuate key SASP factors. For example, in older individuals, higher levels of PA over a 1-year period were associated with lower circulating growth differentiation factor 15 (GDF-15) and reduced weight loss, the latter being a common adverse outcome in frailty.[195] Moreover, another study revealed that long-term higher PA levels are linked to significantly greater reductions in several senescence-related proteins, such as vascular endothelial growth factor A (VEGFA), tumor necrosis factor receptor 1, and matrix metallopeptidase 7 in elder adults.[196] These findings highlight that maintaining an active lifestyle represents a promising strategy to combat aging and age-related diseases, as GDF-15 and VEGFA are considered biomarkers of senescent cells and are strongly associated with an increased risk of mortality.[197] Collectively, these findings underscore the capacity of regular exercise to mitigate the senescence phenotype, both by reducing the burden of senescent cells and by dampening the proinflammatory SASP environment.

11. Exercise counteracts aging-related extracellular matrix (ECM) remodeling

ECM remodeling is a prominent feature of aging tissues and plays a key role in the progression of multiple pathological conditions, including fibrosis and organ stiffness.[198] Fibrotic processes that occur during aging affect the joint capsules, decreasing the range of movement and promoting characteristic postures such as a stooped posture or *genu recurvatum*. These changes ultimately affect functional capacity and normal gait. For example, in the aging heart, excessive ECM deposition and fibrosis are associated with dysregulation of ECM-related signaling, including reduced activity of matrix metalloproteinases (MMPs) along with upregulation of tissue inhibitors of metalloproteinases (TIMPs) and transforming growth factor-β (TGF-β).[199] Increasing evidence indicates that regular exercise can counteract these detrimental ECM alterations and preserve tissue structure and function. For example, 12 weeks of treadmill exercise in aged rats was able to attenuate aging-induced cardiac fibrosis via reducing collagen type-I accumulation, largely through restoration of MMP activity and suppression of TIMP-1 and TGF-β expression.[200] Similarly, resistance training for 12 weeks significantly reversed the age-related reduction of MMP-2 activity in the lumbar vertebrae and tibia of older

rats, highlighting its beneficial impact on ECM remodeling in aging bone tissue.[201] In addition, in a rabbit model of extending joint contracture, stretching exercise combined with physiotherapy led to an increase in the range of motion by modifying collagen accumulation and modulating TGF-β1 in the articular capsule.[202] Also, stretching exercise modulates FGF2 and FGF6 protein expression in the myotendinous junction.[203]

12. Exercise promotes stem cell regeneration

One of the defining hallmarks of aging is the progressive decline in the regenerative capacity of somatic stem cells, resulting in impaired tissue maintenance and repair.[204] Recent studies demonstrate that exercise has positive effects on the function of multiple types of stem cells and can promote tissue regeneration in aged organisms (Fig. 5). In skeletal muscle, aging is associated with a reduction in satellite cells, particularly those linked to type II fibers.[205–207] Long-term exercise increases the pool of satellite cells, which facilitates muscle repair and prevents sarcopenia.[207,208] Mechanistically, the exercise-induced activation of the Wnt/β-catenin signaling pathway plays a crucial role in promoting satellite cell function.[209] This pathway modulates chromatin accessibility at the promoters of myogenic regulatory factors, such as Myf5 and MyoD, thereby enhancing their transcription and driving satellite cell activation and myogenesis.[209] Moreover, voluntary wheel running has been shown to improve muscle regeneration in aged mice by increasing levels of cyclin D1, which maintains muscle stem cell activation capacity by inhibiting TGF-β signaling.[210] The beneficial effects of exercise on satellite cells may also be linked to metabolic reprogramming. In young adult mice, 5 weeks of treadmill training promoted satellite cell self-renewal by reducing mitochondrial respiration in the resting state, which was associated with enhanced stemness and regenerative potential.[211] However, whether exercise promotes satellite cell self-renewal in aged mice via satellite cell metabolic reprogramming remains to be further investigated.

Beyond its benefits for skeletal muscle, exercise has been associated with enhanced neurogenesis and improved cognitive function in the aging brain.[212] In elderly individuals, 12 weeks of moderate-intensity PA enhanced cognitive performance.[213] In parallel, 4 weeks of moderate-intensity treadmill exercise improved learning and memory in aged mice, accompanied by upregulation of neurogenesis-associated proteins, including hippocalcin, otub1, spectrin-α, and μ-crystallin.[214] Mechanistically, exercise-induced neurogenesis has been linked to modulation of ROS and autophagy integrity within neural stem cells.[215,216] Lower intracellular ROS levels favor a transition toward proliferative and differentiation states, and exercise triggers a transient nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 (NOX2)-dependent ROS surge that recruits quiescent neural stem cells into the active cell cycle.[215] Furthermore, the benefits of exercise on brain health are at least partly mediated by exerkines or exercise-induced metabolic factors, such as BDNF, irisin, cathepsin B, kynurenine, lactate, clusterin, *etc*.[217]

Exercise can also promote hematopoietic and osteogenic stem cell function. For example, 4 weeks of voluntary running significantly increased bone mineral density and cortical bone thickness in aged mice, while restoring the integrity of periarteriolar niches in the bone marrow, which are essential for osteogenesis and lymphopoiesis.[218] The positive impact of exercise on stem cell function might also be mediated by the alterations in the inflammatory profiles within these cells. A single-cell RNA sequencing study analyzing skeletal muscle, neural, and hematopoietic stem cells in young and aged mice with or without voluntary running showed that exercise reverses age-associated inflammatory gene expression and restores youthful intercellular signaling, particularly within skeletal muscle.[115]

13. Exercise modulates intercellular communication

The wide-ranging benefits of exercise are increasingly understood to involve its influence on systemic intercellular communication. In particular, "exerkines"—which are bioactive molecules secreted by tissues such as skeletal muscle, liver, adipose tissue, and the brain during PA—mediate many of the systemic adaptations to exercise and play crucial roles in mitigating aging-related decline (Fig. 6).

13.1. Pro-aging blood-borne factors

Aging is associated with increased systemic levels of several pro-aging circulating factors, including C—C motif chemokine ligand 11, interleukin-6 (IL-6), TGF-β, and complement component C1q, all of which contribute to tissue dysfunction and chronic inflammation.[219,220] Accumulating

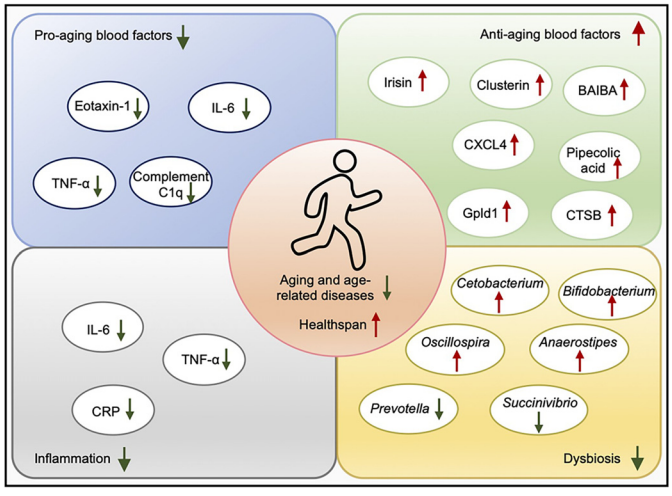

Fig. 6. Effects of exercise on the intercellular communications, inflammation, and gut microbiome. Exercise is associated with decreased pro-aging blood factors, increased anti-aging blood factors, improved inflammation, and reduced dysbiosis. BAIBA = β-aminoisobutyric acid; CRP = C-reactive protein; CTSB = cathepsin B; CXCL4 = C-X-C motif chemokine 4; Gpld1 = glycosylphosphatidylinositol (GPI)-specific phospholipase D1; IL-6 = interleukin-6; TNF-α = tumor necrosis factor-α.

evidence indicates that regular PA can reduce these harmful factors. For example, in obese young men, 8 weeks of aerobic exercise at 70% heart rate reserve reduced plasma eotaxin-1 levels and increased plasma BDNF levels.[221] In elderly individuals with a long-standing history of aerobic training (≥4 h per week for ≥10 years), baseline plasma IL-6 and TNF-α levels were significantly lower compared to sedentary age-matched controls,[222] suggesting that long-term exercise might prevent age-induced increase in plasma IL-6 and TNF-α levels. Furthermore, animal studies have shown that 12 weeks of resistance training could prevent muscle fibrosis and muscle atrophy in aged mice, accompanied by reduced circulating complement C1q levels, potentially through Wnt signaling modulation.[223]

13.2. Anti-aging blood-borne factors

In parallel, the anti-aging effects of exercise are also mediated by increases in beneficial circulating molecules. Recent work highlights the pivotal role of platelets as mediators of exercise-induced neuroprotection.[224] Specifically, the platelet-derived chemokine C-X-C motif chemokine 4 (CXCL4) (also known as platelet factor 4 or PF4) has been identified as both necessary and sufficient to drive hippocampal neurogenesis and enhance cognitive performance in aging brains.[224,225] Remarkably, plasma collected from exercised mice was capable of mimicking the effects of PA by improving neurogenesis and memory and reducing inflammation in models of acute brain injury and AD.[226] The complement inhibitor clusterin was identified as a likely key mediator in this process and, importantly, clusterin levels also increased in humans after a 6-month structured exercise program in patients with cognitive impairment.[226] Furthermore, early-life exercise training, even after extensive detraining, was associated with higher level of pipecolic acid in both serum and liver, which exerted an anti-inflammatory effect via downregulating mechanistic target of rapamycin complex 1 (mTORC1) signaling.[29] Mechanistically, this involved epigenetic remodeling at the Crym promoter, where enhanced H3K4me3 facilitated transcription of the pipecolic acid-generating enzyme Crym. Liver-specific deletion of *Crym* abolished the anti-inflammatory benefits of exercise, underscoring its essential role.[29] Additionally, higher levels of serum pipecolic acid were also observed in young elite athletes compared to sedentary controls, reinforcing its association with long-term PA and metabolic fitness.[29] Collectively, these findings emphasize that exercise profoundly reshapes intercellular communication through the modulation of both detrimental and protective blood-borne signals.

13.3. Long-range and short-range communication systems

It is widely recognized that the systemic benefits of exercise are mediated by both local and distant intercellular signaling mechanisms, primarily orchestrated through the circulation. These include cell-to-cell interactions and organ-to-organ communication via soluble factors, molecules in extracellular vesicles such as miRNA and exerkines—many of which are regulated by exercise. Remarkably, transfusion of plasma from exercised aged mice into sedentary aged counterparts has been shown to enhance hippocampal neurogenesis and cognitive function, demonstrating the sufficiency of exercise-conditioned systemic factors in transmitting rejuvenating effects.[227] These findings indicated that long-term exercise induced the elevation of circulating glycosylphosphatidylinositol-specific phospholipase D1 (Gpld1) in humans,[227] highlighting the role of Gpld1 in exercise-related benefits on age-related cognitive impairments. Irisin is a well-known exercise-induced myokine that represents a promising target for a wide range of age-related diseases, such as obesity, type 2 diabetes, CVDs, and neurodegenerative diseases, among others.[228] Irisin levels decline with age but are upregulated following both acute and chronic exercise interventions. Mechanistically, irisin delays vascular senescence by activating the DnaJb3/Hsp40 chaperone pathway, which stabilizes SIRT6 in an Hsp70-dependent manner, thus preserving endothelial function and vascular integrity.[229] Cathepsin B (CTSB) is another exercise-inducible myokine implicated in cognitive enhancement.[230] CTSB administration has been shown to upregulate BDNF and doublecortin in adult hippocampal progenitor cells, possibly via the adaptor protein P11.[230] In humans, an RCT demonstrated that 26 weeks of aerobic exercise increased circulating CTSB levels in older adults, with levels positively correlating with improvements in cognitive performance.[231] Additionally, exercise can stimulate the secretion of the myokine β-aminoisobutyric acid (BAIBA), which is mediated by PGC-1α. The increase in BAIBA further promotes the induction of white adipose tissue browning and increases β-oxidation in hepatocytes via peroxisome proliferator-activated receptor alpha signaling, highlighting the protective role of BAIBA against metabolic syndrome.[232] Importantly, the circulating BAIBA contents were also elevated in exercised humans and were negatively associated with multiple cardiometabolic risk factors.[232] Together, these findings demonstrate that exercise mediates its protective, regenerative, and anti-aging effects through a network of local and systemic communication pathways.

14. Exercise decreases aging-associated chronic inflammation

Aging is linked to a persistent state of low-grade inflammation, termed “inflammaging”, marked by increased levels of pro-inflammatory cytokines such as C-reactive protein (CRP), IL-6, and TNF-α, among others.[233] This chronic inflammatory state has been strongly associated with the pathogenesis of numerous age-related conditions, including CVD, neurodegeneration, sarcopenia, and metabolic dysfunction.[234] An increasing body of epidemiological research indicates that engaging in regular PA or exercise can reduce aging-related chronic inflammation (Fig. 6). Lifelong aerobic training, with an average duration of over 5 decades, has been shown to suppress age-associated increases in pro-inflammatory gene expression in both peripheral blood and skeletal muscle tissues.[235] Moreover, in elderly individuals with hypertension,

regular exercise was associated with significantly lower IL-6 levels compared to age-matched sedentary controls, further supporting its anti-inflammatory potential in clinical populations.[119] A meta-analysis of RCTs also confirmed that aerobic exercise significantly reduces serum concentrations of CRP, IL-6, and TNF-α in healthy middle-aged and older adults.[236]

The potential mechanisms underlying the protective effects of exercise on aging-related inflammation appear to be multifactorial. In a D-gal-induced aging model, 8 weeks of swimming exercise significantly reduced cardiac inflammation, which was attributed to the upregulation of SIRT1, PGC-1α, and AMPKα1 within cardiac tissues.[237] Moreover, long-term exercise initiated in youth has been found to confer durable enhancements to immune function in middle-aged mice through epigenetic and metabolic reprogramming.[29] Specifically, the long-term benefits of regular exercise in early-life on immune health were primarily attributed to the increased production of pipecolic acid, which correlates with elevated H3K4me3 levels at the *Crym* promoter. Pipecolic acid, as mentioned above, exerted its anti-inflammatory effect by inhibiting the production of pro-inflammatory cytokines in macrophages through downregulating the mTORC1 signaling pathway.[29]

Interestingly, the anti-inflammatory efficacy of exercise may differ by modality. An RCT comparing aerobic and resistance training in elderly adults found that aerobic exercise was superior in modulating immune cell function and reducing inflammatory cytokines.[238] These differential effects underscore the importance of tailoring exercise prescriptions based on both functional goals and inflammatory risk profiles.

15. Exercise ameliorates aging-related dysbiosis

Aging is frequently accompanied by dysbiosis, a disruption in the structure and function of the gut microbiota, which contributes to frailty and the development of age-related conditions.[239,240] For example, evidence has shown that the gut microbiota of old mice could exacerbate neurological outcomes in young mice following cerebral ischemia.[241] Given the emerging role of the gut microbiota in modulating immunity, metabolism, and the brain−gut axis, its manipulation has been proposed as a therapeutic target for a broad spectrum of disorders,[242] including neurological disorders,[243] lung disease,[244] type 2 diabetes,[245] nonalcoholic fatty liver disease,[246] and various cancers.[247,248] Aerobic and resistance exercises affect the gut microbiota differently[249] and can profoundly modulate the composition and function of gut microbiota, thereby influencing host health across the lifespan (Fig. 6).[250−252] This section focuses on how PA counteracts age-related microbial dysbiosis and contributes to disease prevention and healthy aging.

15.1. Exercise can counteract the aging-related alteration in gut microbiota

The gut microbiome plays a central role in host physiology and age-associated phenotypes. Age-related microbial shifts have been implicated in the pathogenesis of numerous chronic conditions, including obesity, CVD, and neurodegenerative diseases.[253,254] In contrast, a more diverse and resilient gut microbiota is associated with increased longevity and reduced frailty.[255] Regular PA has been shown to promote a eubiotic gut environment and support host resilience. Experimental studies have demonstrated that exercise mitigates the deleterious impact of microbiota disruption on neuroplasticity. In particular, voluntary exercise reversed microbiota disturbance-induced impairments in adult hippocampal neurogenesis and reduced anxiety-like behaviors in rats,[256] supporting a key role for the gut−brain axis in mediating the neuroprotective effects of exercise.

In elderly human populations, observational studies suggest a modest but significant correlation between PA levels and gut microbial composition. Among community-dwelling older men, greater daily step counts were associated with an increased abundance of health-promoting bacteria, such as *Cetobacterium,* and reduced levels of potentially pathogenic genera, including *Coprobacillus*, *Adlercreutzia*, and members of the *Erysipelotrichaceae* family.[257] A 24-week exercise intervention combining aerobic and resistance modalities led to further beneficial changes in elderly individuals, including increases in *Bifidobacterium*, *Oscillospira*, and *Anaerostipes*, as well as reductions in *Prevotella* and *Succinivibrio*, which are associated with inflammatory profiles. This shift was accompanied by elevated fecal butyrate, a short-chain fatty acid with well-documented anti-inflammatory and gut barrier-protective effects.[258] Furthermore, 8 weeks of treadmill exercise has been shown to reduce age-related inflammatory markers and significantly attenuate age-related memory decline, accompanied by increased diversity and abundance of beneficial gut microbiota.[259] Taken together, these findings highlight the potential of exercise in reversing age-related dysbiosis and promoting health for elderly adults.

15.2. Exercised fecal microbiota transplantation

The role of gut microbiota in mediating beneficial effects of exercise on aging and age-related diseases has been further substantiated through fecal microbiota transplantation (FMT) experiments. These studies offer causal evidence that exercise-altered gut communities can modulate host physiology and disease susceptibility in recipients. One notable study demonstrated that low-intensity exercise prior to surgery significantly attenuated postoperative cognitive dysfunction (POCD) in both adult and aged mice.[260] Importantly, the beneficial effects of exercise on POCD in old mice were transferable through fecal transplantation: aged sedentary mice that received stool from exercised donors experienced preserved cognitive function following carotid artery surgery, suggesting that changes in the gut microbiota played a critical role in mediating these neuroprotective effects.[260] Mechanistically, exercise was found to prevent surgery-induced reductions in microbial diversity and preserve gut microbiota homeostasis. Intriguingly, administration of valeric acid, a microbial metabolite known to influence neuroplasticity and cognition, abolished the protective effects of exercise, implicating this compound

as a potential mediator of the gut−brain axis in exercise-induced cognitive resilience.[260] Moreover, the preventive effects against POCD were found to be intensity-dependent, as only low- (35%−40% maximal capacity) but not moderate- (55%−60%) or high-intensity (75%−80%) exercise conferred significant neurocognitive benefits.[260]

FMT studies have also highlighted the systemic benefits of exercise-modulated microbiota in cardiac disease. In a mouse model of myocardial infarction (MI), depletion of the gut microbiota abrogated the cardioprotective effects of exercise. Conversely, transplantation of fecal material from exercised MI mice into sedentary MI recipients restored cardiac function, while transplantation from sedentary donors had no such effect,[261] indicating the involvement of gut microbiota in exercise-associated cardio-protection. Exercise-induced changes in the microbial community included increased microbial diversity and a distinct compositional shift. Two key fecal metabolites enriched in exercised mice, 3-Hydroxyphenylacetic acid and 4-Hydroxybenzoic acid, were found to exert protective effects against cardiac dysfunction and apoptosis post-MI via the nuclear factor erythroid 2-related factor 2 (NRF2) pathway.[261]

16. Exercise can induce positive psychosocial adaptations

As individuals age, they often face a gradual contraction in the size and quality of their social network, increasing their vulnerability to social isolation and loneliness. These psychosocial stressors are strongly associated with a heightened risk of numerous adverse health outcomes, including depression, cognitive decline, CVDs, and sleep disturbances.[262,263] Given the high prevalence of social isolation and loneliness among older adults, greater attenuation should be directed toward strategies that promote their psychosocial health.[262,264] Increasing evidence suggests that the mental health of the elderly can be improved through exercise. A systematic review reported that a twice-weekly, 45-min, light-to-moderate-intensity community-based exercise program significantly improved psychological well-being in sedentary individuals aged 65 years or older.[265] Similarly, a large cross-sectional study of 1020 community-dwelling older adults found that regular exercisers exhibited a markedly lower risk of depressive symptoms compared to their sedentary peers,[266] highlighting the positive role of exercise in preventing depressive symptoms in the elderly. Mind-body practices such as tai chi have also demonstrated specific benefits in reducing anxiety and improving quality of life in older adults.[267] In elderly patients diagnosed with anxiety disorder, those receiving tai chi in conjunction with pharmacotherapy experienced greater reductions in anxiety symptoms and higher overall quality of life compared to those receiving medication alone. Continued tai chi practice was also associated with a reduced recurrence rate of anxiety symptoms, suggesting sustained mental health benefits.[267] In addition, 1 RCT showed that a 16-week multicomponent chair-based exercise intervention was able to significantly improve cognitive and motor functions and decrease the symptoms of depression in nursing home residents who are unable to walk.[268] Similarly, structured in-hospital exercise interventions have been shown to enhance multiple domains of intrinsic capacity, including psychological well-being, cognition, vitality, mobility, and sensory function, among hospitalized elderly individuals.[269] Altogether, these findings suggest that exercise might induce positive psychosocial adaptations and improve mental health in the elderly.

17. Exercise optimization for promoting health in older adults

The parameters of exercise, including the modality, intensity, frequency, and duration, are key determinants of its effects. Although experimental data are limited, it is reasonable to infer that the effects of exercise on aging hallmarks are also influenced by these parameters, and more efforts should be devoted to studying the effects of different exercise types and the dose−response relationships between exercise and its outcomes. For example, 1 RCT showed that both aerobic endurance training and HIIT led to increased telomerase activity and telomere length, whereas resistance training had no effect on blood mononuclear cells of healthy adults.[77] Moreover, accumulating evidence has shown that long-term exercise can activate autophagy in aging skeletal muscle. However, the levels of autophagy-related proteins are differentially modulated by different types and intensities of exercise. High-intensity exercise may induce excessive autophagy, whereas low-intensity and short-term exercise (duration $<$ 12 weeks, frequency $<$ 3 times/week) may not be sufficient to activate autophagy.[135] Similarly, there is evidence that retrotransposon LINE1 ORF1 mRNA levels are negatively associated with daily moderate-to-vigorous PA levels in the skeletal muscle of both young and older healthy adults, which underscores the dose-dependent effects of exercise on LINE1 activity.[112] Furthermore, 1 study shows that HIIT exerts more favorable effects than continuous moderate-intensity training on the hearts of old mice, including enhanced cardiac function, increased neovascularization, improved mitochondrial homeostasis, decreased cardiac fibrosis, and reduced aging hallmarks.[270] However, another study indicates that long-term moderate-intensity training, but not HIIT, can significantly decrease age-related cardiac damage, including age-related changes in cardiac function, cardiac hypertrophy, cardiac inflammation, fibrosis, apoptosis, oxidative stress, and levels of aging hallmarks such as P16, P21, and P53 in the heart.[271] The controversy may be due in part to differences in the intervention time and duration of exercise in different studies. Additionally, it is noteworthy that excessive exercise can negatively impact the heart, particularly the atria and right ventricles.[272−274] Animal studies suggest that these effects are driven by inflammatory pathways, leading to atrial fibrosis and increasing the risk of arrhythmias.[273,274] Notably, these pathological changes overlap with those observed in aging.

Older adults are typically associated with progressive functional decline and frequently suffer from various health conditions, making them more vulnerable to frailty and mortality.

To optimize the health outcomes, substantial efforts should be devoted to ensuring the safety and effectiveness of exercise prescriptions for older adults, which should be customized according to exercise type, frequency, intensity, and duration.[37] Additionally, the effects of exercise vary markedly across different tissue. For example, while long-term voluntary wheel running decreases mtDNA mutation load in the skeletal muscle of PolG mice, it has no effect on mtDNA mutation load in the brain or liver.[57,275] Future research that focuses on the tissue-specific response to exercise will provide more targeted recommendations for intended outcomes.

18. Conclusions and prospects

The health-promoting effects of exercise in the elderly are multifactorial, including improvements in physical performance, mental well-being, metabolic regulation, and a reduced incidence of age-associated chronic diseases, including CVD, neurodegenerative disorders, cancer, and type 2 diabetes.[36,276] Current evidence suggests that exercise favorably modulates all 14 hallmarks of aging (Fig. 1), providing further support for using exercise as a non-pharmacologic intervention to promote healthy aging and to delay or prevent the onset of age-related diseases.[277] Accordingly, reducing sedentary behavior and increasing participation in regular PA should be universally encouraged across aging populations. However, most research on how exercise modulates the hallmarks of aging comes from animal studies; well-designed human studies should be conducted to replicate and extend these findings. Future studies are warranted to bridge the gap between pre-clinical and clinical exercise medicine research. For example, the effects of exercise on aging-related mtDNA mutations and age-related alterations in nuclear architecture need to be investigated in humans. Likewise, its impacts on proteostasis, macroautophagy, aging-associated dysregulation of nutrient-sensing signaling, and ECM remodeling in older adults also need to be further examined. Moreover, the molecular mechanisms underlying the protective effects of exercise on these hallmarks remain largely unknown. Long-lived animals, such as the naked mole-rat, may help elucidate the molecular basis of longevity. Comparing the mechanisms responsible for exercise-induced benefits with those found in long-lived animals could clarify which factors promote longevity.

To fully harness the therapeutic potential of exercise, further research is warranted to determine the specific parameters (e.g., modality, intensity, and duration) that are suitable for elderly individuals. A recent global consensus on exercise recommendations for older adults advises that older adults engage in a multifaceted exercise regimen incorporating aerobic, resistance, balance, and flexibility training via structured and incidental activities.[37] Moreover, personalized exercise prescription is emphasized. Exercise programs for older adults should be customized and tailored to achieve specific health-related outcomes, with personalization taking into account the dose−response relationship.[37] This is particularly important for older adults with comorbidities, such as heart diseases, hypertension, type 2 diabetes, metabolic syndrome, or musculoskeletal disorders. However, it is worth noting that more is not necessarily better. Emerging data suggest a potential U-shaped relationship between exercise volume and health outcomes.[278−280] Thus, defining both the minimum effective dose and the upper safety threshold of exercise for different aging phenotypes remains a critical research priority.

Given the heterogeneity of aging and the frequent coexistence of multiple chronic conditions among the elderly, it is essential to deepen our mechanistic understanding of how exercise confers its systemic benefits. Future research should systematically examine how distinct exercise modalities differentially influence the hallmarks of aging and elicit tissue-specific adaptation. For example, well-designed studies are needed to compare the effects of different exercise modalities (such as aerobic, resistance, HIIT, combined aerobic plus resistance training) on telomere length in older individuals. Moreover, the molecular and cellular mechanisms through which exercise modulates telomere biology across diverse tissue systems remain to be fully elucidated.

Additionally, it is noteworthy that early-life exercise can exert long-term health benefits. A recent study reports that 3 months of early-life exercise induces positive effects in both aged male and female mice, including improved systemic metabolism, cardiovascular function, and muscle strength, as well as decreased systemic inflammation and frailty.[281] These findings highlight the importance of regular PA from a young age to improve health outcomes later in life and to promote healthy aging.[281] Further studies exploring the effects of early-life exercise on the major hallmarks of aging in aged animals or older individuals will enhance our mechanistic understanding of how early-life exercise promotes healthy aging and raise public awareness—especially among young adults—of the importance of exercise.

It is important to note that this review has some limitations. It mainly focuses on studies that investigated the effects of exercise on the hallmarks of aging conducted in older individuals or aged animals. As a result, some studies examining the effect of exercise on age-related changes, or those using aging models, may have been missed. Moreover, due to space constraints and the research background of the authors, it is difficult to provide a comprehensive summary of the effects of exercise on each hallmark of aging. Although many aspects remain to be elucidated, mounting evidence indicates that exercise can mitigate aging hallmarks and improve overall health in older adults with various conditions. This review summarizes current knowledge on how exercise modulates each hallmark of aging and outlines future research directions that emphasize the mechanistic basis of exercise medicine strategies and personalized exercise prescription, ultimately aiming to advance evidence-based exercise interventions that promote healthy aging in elderly populations. Advances in high-throughput multimodal omics (e.g., genomics, epigenomics, proteomics, metabolomics) and the application of artificial intelligence and systems biology approaches are expected to accelerate the discovery of key

molecular mediators of exercise-induced health benefits.[282,283] These insights may spur the development of precision exercise prescriptions and facilitate the identification of exercise-mimetic therapeutics, ultimately providing novel strategies for mitigating aging and preventing age-related diseases in populations that are unable or unwilling to engage in PA.

Authors' contributions

YQ and BFG drafted the manuscript; GK, CLO, and JX came up with the idea and edited the manuscript; HIL and GL reviewed and edited the manuscript. All authors have read and approved the final version of this manuscript, and agree with the order of presentation of the authors.

Declaration of competing interest

The authors declare that they have no competing interests. Given the role as associate editor, Junjie Xiao had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to another journal editor.

Acknowledgments

This work was supported by the grants from National Natural Science Foundation of China (82225005 and 82020108002 to JX), the grant from Science and Technology Commission of Shanghai Municipality (23410750100 to JX), the grant from National Natural Science Foundation of China (82200549 to YQ), and the "Chenguang Program" of Shanghai Education Development Foundation and Shanghai Municipal Education Commission (22CGA45 to YQ).

Supplementary materials

Supplementary materials associated with this article can be found in the online version at doi:10.1016/j.jshs.2025.101108.

References

1. World Health Organization (WHO). *Ageing and health*; 2024. Available at: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health/. [accessed 02.06.2025].
2. Partridge L, Deelen J, Slagboom PE. Facing up to the global challenges of ageing. *Nature* 2018;**561**:45–56.
3. Deng Y, Zhang K, Zhu J, Hu X, Liao R. Healthy aging, early screening, and interventions for frailty in the elderly. *Biosci Trends* 2023;**17**:252–61.
4. Sanchez-Sanchez JL, Ortola R, Banegas JR, et al. Association between physical activity and sedentary behaviour and changes in intrinsic capacity in spanish older adults (Seniors- ENRICA-2): A prospective population-based study. *Lancet Healthy Longev* 2025;**6**:100681. doi:10.1016/j.lanhl.2024.100681.
5. Kennedy BK, Berger SL, Brunet A, et al. Geroscience: Linking aging to chronic disease. *Cell* 2014;**159**:709–13.
6. Li Y, Tian X, Luo J, Bao T, Wang S, Wu X. Molecular mechanisms of aging and anti-aging strategies. *Cell Commun Signal* 2024;**22**:285. doi:10.1186/s12964-024-01663-1.
7. Campisi J, Kapahi P, Lithgow GJ, Melov S, Newman JC, Verdin E. From discoveries in ageing research to therapeutics for healthy ageing. *Nature* 2019;**571**:183–92.
8. Gillman MW. Primordial prevention of cardiovascular disease. *Circulation* 2015;**131**:599–601.
9. DeVito LM, Barzilai N, Cuervo AM, et al. Extending human healthspan and longevity: A symposium report. *Ann N Y Acad Sci* 2022;**1507**:70–83.
10. Dogra S, Dunstan DW, Sugiyama T, Stathi A, Gardiner PA, Owen N. Active aging and public health: Evidence, implications, and opportunities. *Annu Rev Public Health* 2022;**43**:439–59.
11. Espinoza SE, Khosla S, Baur JA, de Cabo R, Musi N. Drugs targeting mechanisms of aging to delay age-related disease and promote healthspan: Proceedings of a national institute on aging workshop. *J Gerontol A Biol Sci Med Sci* 2023;**78**:53–60.
12. Kandola A, Ashdown-Franks G, Hendrikse J, Sabiston CM, Stubbs B. Physical activity and depression: Towards understanding the antidepressant mechanisms of physical activity. *Neurosci Biobehav Rev* 2019;**107**:525–39.
13. Qiu Y, Fernandez-Garcia B, Lehmann HI, et al. Exercise sustains the hallmarks of health. *J Sport Health Sci* 2023;**12**:8–35.
14. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002;**346**:793–801.
15. Arem H, Moore SC, Patel A, et al. Leisure time physical activity and mortality: A detailed pooled analysis of the dose−response relationship. *JAMA Intern Med* 2015;**175**:959–67.
16. Ekelund U, Tarp J, Steene-Johannessen J, et al. Dose−response associations between accelerometry measured physical activity and sedentary time and all cause mortality: Systematic review and harmonised meta-analysis. *BMJ* 2019;**366**:l4570. doi:10.1136/bmj.l4570.
17. Shi H, Hu FB, Huang T, et al. Sedentary behaviors, light-intensity physical activity, and healthy aging. *JAMA Netw Open* 2024;**7**:e2416300. doi:10.1001/jamanetworkopen.2024.16300.
18. Huang Y, Jiang C, Xu L, et al. Mortality in relation to changes in physical activity in middle-aged to older Chinese: An 8-year follow-up of the Guangzhou Biobank cohort study. *J Sport Health Sci* 2021;**10**:430–8.
19. Radak Z, Torma F, Berkes I, et al. Exercise effects on physiological function during aging. *Free Radic Biol Med* 2019;**132**:33–41.
20. Pedersen BK, Saltin B. Exercise as medicine−evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports* 2015;**25**:S1–72.
21. Wen CP, Wai JP, Tsai MK, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: A prospective cohort study. *The Lancet* 2011;**378**:1244–53.
22. Mandsager K, Harb S, Cremer P, Phelan D, Nissen SE, Jaber W. Association of cardiorespiratory fitness with long-term mortality among adults undergoing exercise treadmill testing. *JAMA Netw Open* 2018;**1**:e183605. doi:10.1001/jamanetworkopen.2018.3605.
23. Koch LG, Kemi OJ, Qi N, et al. Intrinsic aerobic capacity sets a divide for aging and longevity. *Circ Res* 2011;**109**:1162–72.
24. Imboden MT, Harber MP, Whaley MH, Finch WH, Bishop DL, Kaminsky LA. Cardiorespiratory fitness and mortality in healthy men and women. *J Am Coll Cardiol* 2018;**72**:2283–92.
25. Fujimoto N, Prasad A, Hastings JL, et al. Cardiovascular effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age. *Circulation* 2010;**122**:1797–805.
26. Tarumi T, Patel NR, Tomoto T, et al. Aerobic exercise training and neurocognitive function in cognitively normal older adults: A one-year randomized controlled trial. *J Intern Med* 2022;**292**:788–803.
27. Kemper HC, Monyeki KD. The amsterdam growth and health longitudinal study: How important is physical activity in youth for later health? (ELS 33). *Cardiovasc J Afr* 2019;**30**:138–41.
28. Fernandes RA, Zanesco A. Early physical activity promotes lower prevalence of chronic diseases in adulthood. *Hypertens Res* 2010;**33**:926–31.
29. Zhang N, Wang X, Feng M, et al. Early-life exercise induces immunometabolic epigenetic modification enhancing anti-inflammatory immunity in middle-aged male mice. *Nat Commun* 2024;**15**:3103. doi:10.1038/s41467-024-47458-3.

30. Kokkinos P, Myers J. Exercise and physical activity: Clinical outcomes and applications. *Circulation* 2010;**122**:1637–48.
31. Ueno K, Kaneko H, Kamiya K, et al. Age-dependent relationship of physical inactivity with incident cardiovascular disease: Analysis of a large Japanese cohort. *Can J Cardiol* 2025;**41**:470–7.
32. Lavie CJ, Lin GM, Ross R. Invited commentary: Health benefits associated with an active lifestyle in the elderly population: Unique opportunities associated with light-intensity physical activity. *Can J Cardiol* 2025;**41**:478–80.
33. Bangsbo J, Blackwell J, Boraxbekk CJ, et al. Copenhagen consensus statement 2019: Physical activity and ageing. *Br J Sports Med* 2019;**53**:856–8.
34. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med* 2020;**54**:1451–62.
35. Dempsey PC, Friedenreich CM, Leitzmann MF, et al. Global public health guidelines on physical activity and sedentary behavior for people living with chronic conditions: A call to action. *J Phys Act Health* 2021;**18**:76–85.
36. Izquierdo M, Merchant RA, Morley JE, et al. International Exercise Recommendations in Older Adults (ICFSR): Expert consensus guidelines. *J Nutr Health Aging* 2021;**25**:824–53.
37. Izquierdo M, de Souto, Barreto P, Arai H, et al. Global consensus on optimal exercise recommendations for enhancing healthy longevity in older adults (ICFSR). *J Nutr Health Aging* 2025;**29**:100401. doi:10.1016/j.jnha.2024.100401.
38. Cai Y, Song W, Li J, et al. The landscape of aging. *Sci China Life Sci* 2022;**65**:2354–454.
39. Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. *Cell* 2023;**186**:243–78.
40. Kroemer G, Maier AB, Cuervo AM, et al. From geroscience to precision geromedicine: Understanding and managing aging. *Cell* 2025;**188**:2043–62.
41. Garatachea N, Pareja-Galeano H, Sanchis-Gomar F, et al. Exercise attenuates the major hallmarks of aging. *Rejuvenation Res* 2015;**18**:57–89.
42. Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell* 2013;**153**:1194–217.
43. Lopez-Gil L, Pascual-Ahuir A, Proft M. Genomic instability and epigenetic changes during aging. *Int J Mol Sci* 2023;**24**:14279. doi:10.3390/ijms241814279.
44. Soto-Palma C, Niedernhofer LJ, Faulk CD, Dong X. Epigenetics, DNA damage, and aging. *J Clin Invest* 2022;**132**:e158446. doi:10.1172/JCI158446.
45. Yousefzadeh M, Henpita C, Vyas R, Soto-Palma C, Robbins P, Niedernhofer L. DNA damage-how and why we age? *Elife* 2021;**10**:e62852. doi:10.7554/eLife.62852.
46. Parise G, Brose AN, Tarnopolsky MA. Resistance exercise training decreases oxidative damage to DNA and increases cytochrome oxidase activity in older adults. *Exp Gerontol* 2005;**40**:173–80.
47. Gargallo P, Colado JC, Juesas A, et al. The effect of moderate- versus high-intensity resistance training on systemic redox state and DNA damage in healthy older women. *Biol Res Nurs* 2018;**20**:205–17.
48. Soares JP, Silva AM, Oliveira MM, Peixoto F, Gaivao I, Mota MP. Effects of combined physical exercise training on DNA damage and repair capacity: Role of oxidative stress changes. *Age (Dordr)* 2015;**37**:9799. doi:10.1007/s11357-015-9799-4.
49. Goon JA, Noor Aini AH, Musalmah M, Yasmin Anum MY, Wan Ngah WZ. Long term Tai Chi exercise reduced DNA damage and increased lymphocyte apoptosis and proliferation in older adults. *Med J Malaysia* 2008;**63**:319–24.
50. Nakamoto H, Kaneko T, Tahara S, et al. Regular exercise reduces 8-oxodG in the nuclear and mitochondrial DNA and modulates the DNA repair activity in the liver of old rats. *Exp Gerontol* 2007;**42**:287–95.
51. Tryfidou DV, McClean C, Nikolaidis MG, Davison GW. DNA damage following acute aerobic exercise: A systematic review and meta-analysis. *Sports Med* 2020;**50**:103–27.
52. Schmidt RH, Nickerson JM, Boatright JH. Exercise as gene therapy: BDNF and DNA damage repair. *Asia Pac J Ophthalmol (Phila)* 2016;**5**:309–11.
53. Kumagai H, Miller B, Kim SJ, et al. Novel insights into mitochondrial DNA: Mitochondrial microproteins and mtDNA variants modulate athletic performance and age-related diseases. *Genes (Basel)* 2023;**14**:286. doi:10.3390/genes14020286.
54. Nilsson MI, Tarnopolsky MA. Mitochondria and aging-the role of exercise as a countermeasure. *Biology (Basel)* 2019;**8**:40. doi:10.3390/biology8020040.
55. Trifunovic A, Wredenberg A, Falkenberg M, et al. Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature* 2004;**429**:417–23.
56. Safdar A, Bourgeois JM, Ogborn DI, et al. Endurance exercise rescues progeroid aging and induces systemic mitochondrial rejuvenation in mtDNA mutator mice. *Proc Natl Acad Sci USA* 2011;**108**:4135–40.
57. Ross JM, Coppotelli G, Branca RM, et al. Voluntary exercise normalizes the proteomic landscape in muscle and brain and improves the phenotype of progeroid mice. *Aging Cell* 2019;**18**:e13029. doi:10.1111/acel.13029.
58. Jeppesen TD. Aerobic exercise training in patients with mtDNA-related mitochondrial myopathy. *Front Physiol* 2020;**11**:349. doi:10.3389/fphys.2020.00349.
59. Pathak RU, Soujanya M, Mishra RK. Deterioration of nuclear morphology and architecture: A hallmark of senescence and aging. *Ageing Res Rev* 2021;**67**:101264. doi:10.1016/j.arr.2021.101264.
60. Battey E, Ross JA, Hoang A, et al. Myonuclear alterations associated with exercise are independent of age in humans. *J Physiol* 2025;**603**:3755–75.
61. Blackburn EH. Telomeres and telomerase: Their mechanisms of action and the effects of altering their functions. *FEBS Lett* 2005;**579**:859–62.
62. Lu W, Zhang Y, Liu D, Songyang Z, Wan M. Telomeres-structure, function, and regulation. *Exp Cell Res* 2013;**319**:133–41.
63. Blackburn EH. Switching and signaling at the telomere. *Cell* 2001;**106**:661–73.
64. Bodnar AG, Ouellette M, Frolkis M, et al. Extension of life-span by introduction of telomerase into normal human cells. *Science* 1998;**279**:349–52.
65. Kim JJ, Ahn A, Ying J, Hickman E, Ludlow AT. Exercise as a therapy to maintain telomere function and prevent cellular senescence. *Exerc Sport Sci Rev* 2023;**51**:150–60.
66. Brandao CFC, Nonino CB, de Carvalho FG, et al. The effects of short-term combined exercise training on telomere length in obese women: A prospective, interventional study. *Sports Med Open* 2020;**6**:5. doi:10.1186/s40798-020-0235-7.
67. Sanchez-Gonzalez JL, Sanchez-Rodriguez JL, Martin-Vallejo J, Martel-Martel A, Gonzalez-Sarmiento R. Effects of physical exercise on cognition and telomere length in healthy older women. *Brain Sci* 2021;**11**:1417. doi:10.3390/brainsci11111417.
68. Denham J, O'Brien BJ, Charchar FJ. Telomere length maintenance and cardio-metabolic disease prevention through exercise training. *Sports Med* 2016;**46**:1213–37.
69. Butts B, Hope C, Herring C, Mueller K, Gary RA. The effects of exercise on telomere length in persons with heart failure. *J Cardiovasc Nurs* 2024;**39**:E86–92.
70. Ludlow AT, Witkowski S, Marshall MR, et al. Chronic exercise modifies age-related telomere dynamics in a tissue-specific fashion. *J Gerontol A Biol Sci Med Sci* 2012;**67**:911–26.
71. Sanchez-Gonzalez JL, Sanchez-Rodriguez JL, Varela-Rodriguez S, et al. Effects of physical exercise on telomere length in healthy adults: Systematic review, meta-analysis, and meta-regression. *JMIR Public Health Surveill* 2024;**10**:e46019. doi:10.2196/46019.
72. Schellnegger M, Lin AC, Hammer N, Kamolz LP. Physical activity on telomere length as a biomarker for aging: A systematic review. *Sports Med Open* 2022;**8**:111. doi:10.1186/s40798-022-00503-1.
73. Wang Y, Susac L, Feigon J. Structural biology of telomerase. *Cold Spring Harb Perspect Biol* 2019;**11**:a032383. doi:10.1101/cshperspect.a032383.
74. Semeraro MD, Smith C, Kaiser M, et al. Physical activity, a modulator of aging through effects on telomere biology. *Aging (Albany NY)* 2020;**12**:13803–23. doi:10.18632/aging.103504.
75. Sellami M, Bragazzi N, Prince MS, Denham J, Elrayess M. Regular, intense exercise training as a healthy aging lifestyle strategy: Preventing

DNA damage, telomere shortening and adverse DNA methylation changes over a lifetime. *Front Genet* 2021;**12**:652497. doi:10.3389/fgene.2021.652497.
76. Denham J, Sellami M. Exercise training increases telomerase reverse transcriptase gene expression and telomerase activity: A systematic review and meta-analysis. *Ageing Res Rev* 2021;**70**:101411. doi:10.1016/j.arr.2021.101411.
77. Werner CM, Hecksteden A, Morsch A, et al. Differential effects of endurance, interval, and resistance training on telomerase activity and telomere length in a randomized, controlled study. *Eur Heart J* 2019;**40**:34–46.
78. Saul D, Kosinsky RL. Epigenetics of aging and aging-associated diseases. *Int J Mol Sci* 2021;**22**:401. doi:10.3390/ijms22010401.
79. Wang K, Liu H, Hu Q, et al. Epigenetic regulation of aging: Implications for interventions of aging and diseases. *Signal Transduct Target Ther* 2022;**7**:374. doi:10.1038/s41392-022-01211-8.
80. Yang JH, Hayano M, Griffin PT, et al. Loss of epigenetic information as a cause of mammalian aging. *Cell* 2024;**187**:1312–3.
81. Urdinguio RG, Tejedor JR, Fernandez-Sanjurjo M, et al. Physical exercise shapes the mouse brain epigenome. *Mol Metab* 2021;**54**:101398. doi:10.1016/j.molmet.2021.101398.
82. Noroozi R, Ghafouri-Fard S, Pisarek A, et al. DNA methylation-based age clocks: From age prediction to age reversion. *Ageing Res Rev* 2021;**68**:101314. doi:10.1016/j.arr.2021.101314.
83. Duan R, Fu Q, Sun Y, Li Q. Epigenetic clock: A promising biomarker and practical tool in aging. *Ageing Res Rev* 2022;**81**:101743. doi:10.1016/j.arr.2022.101743.
84. Chen L, Ganz PA, Sehl ME. DNA methylation, aging, and cancer risk: A mini-review. *Front Bioinform* 2022;**2**:847629. doi:10.3389/fbinf.2022.847629.
85. Fox FAU, Liu D, Breteler MMB, Aziz NA. Physical activity is associated with slower epigenetic ageing-findings from the Rhineland study. *Aging Cell* 2023;**22**:e13828. doi:10.1111/acel.13828.
86. Spartano NL, Wang R, Yang Q, et al. Association of accelerometer-measured physical activity and sedentary time with epigenetic markers of aging. *Med Sci Sports Exerc* 2023;**55**:264–72.
87. Fiorito G, Caini S, Palli D, et al. DNA methylation-based biomarkers of aging were slowed down in a two-year diet and physical activity intervention trial: The DAMA study. *Aging Cell* 2021;**20**:e13439. doi:10.1111/acel.13439.
88. Brown WM. Exercise-associated DNA methylation change in skeletal muscle and the importance of imprinted genes: A bioinformatics meta-analysis. *Br J Sports Med* 2015;**49**:1567–78.
89. Murach KA, Dimet-Wiley AL, Wen Y, et al. Late-life exercise mitigates skeletal muscle epigenetic aging. *Aging Cell* 2022;**21**:e13527. doi:10.1111/acel.13527.
90. Ruple BA, Godwin JS, Mesquita PHC, et al. Resistance training rejuvenates the mitochondrial methylome in aged human skeletal muscle. *FASEB J* 2021;**35**:e21864. doi:10.1096/fj.202100873RR.
91. Ferrari L, Vicenzi M, Tarantini L, et al. Effects of physical exercise on endothelial function and DNA methylation. *Int J Environ Res Public Health* 2019;**16**:2530. doi:10.3390/ijerph16142530.
92. Ngwa JS, Nwulia E, Ntekim O, et al. Aerobic exercise training-induced changes on DNA methylation in mild cognitively impaired elderly African Americans: Gene, exercise, and memory study–GEMS-I. *Front Mol Neurosci* 2021;**14**:752403. doi:10.3389/fnmol.2021.752403.
93. Fraga I, Weber C, Galiano WB, et al. Effects of a multimodal exercise protocol on functional outcomes, epigenetic modulation and brain-derived neurotrophic factor levels in institutionalized older adults: A quasi-experimental pilot study. *Neural Regen Res* 2021;**16**:2479–85.
94. de Meireles LC, Bertoldi K, Cechinel LR, et al. Treadmill exercise induces selective changes in hippocampal histone acetylation during the aging process in rats. *Neurosci Lett* 2016;**634**:19–24.
95. Maejima H, Kanemura N, Kokubun T, Murata K, Takayanagi K. Exercise enhances cognitive function and neurotrophin expression in the hippocampus accompanied by changes in epigenetic programming in senescence-accelerated mice. *Neurosci Lett* 2018;**665**:67–73.
96. de Meireles LCF, Galvao Jr F, Walker DM, et al. Exercise modalities improve aversive memory and survival rate in aged rats: Role of hippocampal epigenetic modifications. *Mol Neurobiol* 2019;**56**:8408–19.
97. Liu B, Yip R, Zhou Z. Chromatin remodeling, DNA damage repair and aging. *Curr Genomics* 2012;**13**:533–47.
98. Gillon A, Steel C, Cornwall J, Sheard P. Increased nuclear permeability is a driver for age-related motoneuron loss. *Geroscience* 2020;**42**:833–47.
99. Nemeth K, Bayraktar R, Ferracin M, Calin GA. Non-coding RNAs in disease: From mechanisms to therapeutics. *Nat Rev Genet* 2024;**25**:211–32.
100. Fan SB, Xie XF, Wei W, Hua T. Senescence-related lncRNAs: Pioneering indicators for ovarian cancer outcomes. *Phenomics* 2024;**4**:379–93.
101. Nilwik R, Snijders T, Leenders M, et al. The decline in skeletal muscle mass with aging is mainly attributed to a reduction in type II muscle fiber size. *Exp Gerontol* 2013;**48**:492–8.
102. Leenders M, Verdijk LB, van der Hoeven L, van Kranenburg J, Nilwik R, van Loon LJ. Elderly men and women benefit equally from prolonged resistance-type exercise training. *J Gerontol A Biol Sci Med Sci* 2013;**68**:769–79.
103. Wohlwend M, Laurila PP, Williams K, et al. The exercise-induced long noncoding RNA *CYTOR* promotes fast-twitch myogenesis in aging. *Sci Transl Med* 2021;**13**:eabc7367. doi:10.1126/scitranslmed.abc7367.
104. Liang J, Zhang H, Zeng Z, et al. MicroRNA profiling of different exercise interventions for alleviating skeletal muscle atrophy in naturally aging rats. *J Cachexia Sarcopenia Muscle* 2023;**14**:356–68.
105. Guo M, Qiu J, Shen F, et al. Comprehensive analysis of circular RNA profiles in skeletal muscles of aging mice and after aerobic exercise intervention. *Aging (Albany NY)* 2020;**12**:5071–90.
106. Liang X, Fa W, Wang N, et al. Exosomal miR-532-5p induced by long-term exercise rescues blood-brain barrier function in 5XFAD mice via downregulation of EPHA4. *Aging Cell* 2023;**22**:e13748. doi:10.1111/acel.13748.
107. Kou X, Li J, Liu X, et al. Swimming attenuates D-galactose-induced brain aging via suppressing miR-34a-mediated autophagy impairment and abnormal mitochondrial dynamics. *J Appl Physiol (1985)* 2017;**122**:1462–9.
108. Shen K, Liu X, Chen D, Chang J, Zhang Y, Kou X. Voluntary wheel-running exercise attenuates brain aging of rats through activating miR-130a-mediated autophagy. *Brain Res Bull* 2021;**172**:203–11.
109. Pedraza-Vazquez G, Mena-Montes B, Hernandez-Alvarez D, et al. A low-intensity lifelong exercise routine changes miRNA expression in aging and prevents osteosarcopenic obesity by modulating inflammation. *Arch Gerontol Geriatr* 2023;**105**:104856. doi:10.1016/j.archger.2022.104856.
110. Li Q, Wang L, Cao Y, Wang X, Tang C, Zheng L. Stable expression of dmiR-283 in the brain promises positive effects in endurance exercise on sleep−wake behavior in aging drosophila. *Int J Mol Sci* 2023;**24**:4180. doi:10.3390/ijms24044180.
111. Li X, Yu H, Li D, Liu N. LINE-1 transposable element renaissance in aging and age-related diseases. *Ageing Res Rev* 2024;**100**:102440. doi:10.1016/j.arr.2024.102440.
112. Roberson PA, Romero MA, Osburn SC, et al. Skeletal muscle LINE-1 ORF1 mRNA is higher in older humans but decreases with endurance exercise and is negatively associated with higher physical activity. *J Appl Physiol (1985)* 2019;**127**:895–904.
113. Soci UPR, Melo SFS, Gomes JLP, Silveira AC, Nobrega C, de Oliveira EM. Exercise training and epigenetic regulation: Multilevel modification and regulation of gene expression. *Adv Exp Med Biol* 2017;**1000**:281–322.
114. Endo Y, Zhang Y, Olumi S, et al. Exercise-induced gene expression changes in skeletal muscle of old mice. *Genomics* 2021;**113**:2965–76.
115. Liu L, Kim S, Buckley MT, et al. Exercise reprograms the inflammatory landscape of multiple stem cell compartments during mammalian aging. *Cell Stem Cell* 2023;**30**:689–705.

116. Voisin S, Seale K, Jacques M, et al. Exercise is associated with younger methylome and transcriptome profiles in human skeletal muscle. *Aging Cell* 2024;**23**:e13859. doi:10.1111/acel.13859.
117. Klaips CL, Jayaraj GG, Hartl FU. Pathways of cellular proteostasis in aging and disease. *J Cell Biol* 2018;**217**:51–63.
118. Hipp MS, Kasturi P, Hartl FU. The proteostasis network and its decline in ageing. *Nat Rev Mol Cell Biol* 2019;**20**:421–35.
119. Teixeira M, Gouveia M, Duarte A, et al. Regular exercise participation contributes to better proteostasis, inflammatory profile, and vasoactive profile in patients with hypertension. *Am J Hypertens* 2020;**33**:119–23.
120. Gouveia M, Schmidt C, Basilio PG, et al. Exercise training decreases the load and changes the content of circulating SDS-resistant protein aggregates in patients with heart failure with reduced ejection fraction. *Mol Cell Biochem* 2024;**479**:2711–22.
121. Xia J, Li B, Yin L, Zhao N, Yan Q, Xu B. Treadmill exercise decreases β-amyloid burden in APP/PS1 transgenic mice involving regulation of the unfolded protein response. *Neurosci Lett* 2019;**703**:125–31.
122. Cui K, Li C, Fang G. Aerobic exercise delays Alzheimer's disease by regulating mitochondrial proteostasis in the cerebral cortex and hippocampus. *Life (Basel)* 2023;**13**:1204. doi:10.3390/life13051204.
123. Reimers CD, Knapp G, Reimers AK. Does physical activity increase life expectancy? A review of the literature. *J Aging Res* 2012;**2012**:243958. doi:10.1155/2012/243958.
124. Escobar KA, Cole NH, Mermier CM, VanDusseldorp TA. Autophagy and aging: Maintaining the proteome through exercise and caloric restriction. *Aging Cell* 2019;**18**:e12876. doi:10.1111/acel.12876.
125. Zhou XH, Luo YX, Yao XQ. Exercise-driven cellular autophagy: A bridge to systematic wellness. *J Adv Res* 2025;**76**:271–91.
126. Mancini A, Vitucci D, Randers MB, et al. Lifelong football training: Effects on autophagy and healthy longevity promotion. *Front Physiol* 2019;**10**:132. doi:10.3389/fphys.2019.00132.
127. Mancini A, Vitucci D, Orlandella FM, et al. Regular football training down-regulates miR-1303 muscle expression in veterans. *Eur J Appl Physiol* 2021;**121**:2903–12.
128. Wedel S, Manola M, Cavinato M, Trougakos IP, Jansen-Durr P. Targeting protein quality control mechanisms by natural products to promote healthy ageing. *Molecules* 2018;**23**:1219. doi:10.3390/molecules23051219.
129. Oka K, Yamakawa M, Kawamura Y, Kutsukake N, Miura K. The naked mole-rat as a model for healthy aging. *Annu Rev Anim Biosci* 2023;**11**:207–26.
130. Yang W, Hu Y, Cui S. Fighting with aging: The secret for keeping health and longevity of naked mole rats. *Aging Dis* 2024;**16**:137–45.
131. Tombline G, Gigas J, Macoretta N, et al. Proteomics of long-lived mammals. *Proteomics* 2020;**20**:e1800416. doi:10.1002/pmic.201800416.
132. Nieto-Torres JL, Hansen M. Macroautophagy and aging: The impact of cellular recycling on health and longevity. *Mol Aspects Med* 2021;**82**:101020. doi:10.1016/j.mam.2021.101020.
133. Hansen M, Rubinsztein DC, Walker DW. Autophagy as a promoter of longevity: Insights from model organisms. *Nat Rev Mol Cell Biol* 2018;**19**:579–93.
134. Batatinha HAP, Diniz TA, de Souza Teixeira AA, Kruger K, Rosa-Neto JC. Regulation of autophagy as a therapy for immunosenescence-driven cancer and neurodegenerative diseases: The role of exercise. *J Cell Physiol* 2019;**234**:14883–95.
135. Wang C, Liang J, Ren Y, et al. A preclinical systematic review of the effects of chronic exercise on autophagy-related proteins in aging skeletal muscle. *Front Physiol* 2022;**13**:930185. doi:10.3389/fphys.2022.930185.
136. Wang M, Wu X, Jiao Y, Yin W, Zhang L. Life-long aerobic exercise is a non-pharmacological approach for inducing autophagy and delaying muscle atrophy in the aging population. *Aging Dis* 2024;**16**:1842–52. doi:10.14336/AD.2024.0318.
137. He C, Bassik MC, Moresi V, et al. Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis. *Nature* 2012;**481**:511–5.
138. Gao Y, Zhang W, Zeng LQ, et al. Exercise and dietary intervention ameliorate high-fat diet-induced NAFLD and liver aging by inducing lipophagy. *Redox Biol* 2020;**36**:101635. doi:10.1016/j.redox.2020.101635.
139. Li H, Dun Y, Zhang W, et al. Exercise improves lipid droplet metabolism disorder through activation of AMPK-mediated lipophagy in NAFLD. *Life Sci* 2021;**273**:119314. doi:10.1016/j.lfs.2021.119314.
140. Zhu C, Ding H, Shi L, et al. Exercise improved bone health in aging mice: A role of SIRT1 in regulating autophagy and osteogenic differentiation of BMSCs. *Front Endocrinol (Lausanne)* 2023;**14**:1156637. doi:10.3389/fendo.2023.1156637.
141. Ma L, Li K, Wei W, et al. Exercise protects aged mice against coronary endothelial senescence via FUNDC1-dependent mitophagy. *Redox Biol* 2023;**62**:102693. doi:10.1016/j.redox.2023.102693.
142. Balan E, Schwalm C, Naslain D, Nielens H, Francaux M, Deldicque L. Regular endurance exercise promotes fission, mitophagy, and oxidative phosphorylation in human skeletal muscle independently of age. *Front Physiol* 2019;**10**:1088. doi:10.3389/fphys.2019.01088.
143. Zhang Z, Yang X, Song YQ, Tu J. Autophagy in Alzheimer's disease pathogenesis: Therapeutic potential and future perspectives. *Ageing Res Rev* 2021;**72**:101464. doi:10.1016/j.arr.2021.101464.
144. Wang F, Jia J, Rodrigues B. Autophagy, metabolic disease, and pathogenesis of heart dysfunction. *Can J Cardiol* 2017;**33**:850–9.
145. Wu JJ, Yu H, Bi SG, et al. Aerobic exercise attenuates autophagy-lysosomal flux deficits by ADRB2/β2-adrenergic receptor-mediated V-ATPase assembly factor VMA21 signaling in APP-PSEN1/PS1 mice. *Autophagy* 2024;**20**:1015–31.
146. Sadeghi S, Delphan M, Shams M, Esmaeili F, Shanaki-Bavarsad M, Shanaki M. The high-intensity interval training (HIIT) and curcumin supplementation can positively regulate the autophagy pathway in myocardial cells of STZ-induced diabetic rats. *BMC Res Notes* 2023;**16**:21. doi:10.1186/s13104-023-06295-1.
147. Hu FB. Diet strategies for promoting healthy aging and longevity: An epidemiological perspective. *J Intern Med* 2024;**295**:508–31.
148. Cena H, Calder PC. Defining a healthy diet: Evidence for the role of contemporary dietary patterns in health and disease. *Nutrients* 2020;**12**:334. doi:10.3390/nu12020334.
149. Garcia-Garcia FJ, Monistrol-Mula A, Cardellach F, Garrabou G. Nutrition, bioenergetics, and metabolic syndrome. *Nutrients* 2020;**12**:2785. doi:10.3390/nu12092785.
150. Khemka S, Reddy A, Garcia RI, et al. Role of diet and exercise in aging, Alzheimer's disease, and other chronic diseases. *Ageing Res Rev* 2023;**91**:102091. doi:10.1016/j.arr.2023.102091.
151. Duan H, Pan J, Guo M, Li J, Yu L, Fan L. Dietary strategies with anti-aging potential: Dietary patterns and supplements. *Food Res Int* 2022;**158**:111501. doi:10.1016/j.foodres.2022.111501.
152. Ma J, Li P, Jiang Y, et al. The association between dietary nutrient intake and acceleration of aging: Evidence from NHANES. *Nutrients* 2024;**16**:1635. doi:10.3390/nu16111635.
153. Yang K, Hou R, Zhao J, et al. Lifestyle effects on aging and CVD: A spotlight on the nutrient-sensing network. *Ageing Res Rev* 2023;**92**:102121. doi:10.1016/j.arr.2023.102121.
154. Missong H, Joshi R, Khullar N, et al. Nutrient-epigenome interactions: Implications for personalized nutrition against aging-associated diseases. *J Nutr Biochem* 2024;**127**:109592. doi:10.1016/j.jnutbio.2024.109592.
155. Surugiu R, Iancu MA, Vintilescu SB, et al. Molecular mechanisms of healthy aging: The role of caloric restriction, intermittent fasting, mediterranean diet, and ketogenic diet—A scoping review. *Nutrients* 2024;**16**:2878. doi:10.3390/nu16172878.
156. Raffin J, de Souto Barreto P, Le Traon AP, Vellas B, Aubertin-Leheudre M, Rolland Y. Sedentary behavior and the biological hallmarks of aging. *Ageing Res Rev* 2023;**83**:101807. doi:10.1016/j.arr.2022.101807.
157. Vega RB, Konhilas JP, Kelly DP, Leinwand LA. Molecular mechanisms underlying cardiac adaptation to exercise. *Cell Metab* 2017;**25**:1012–26.
158. Bernardo BC, Ooi JYY, Weeks KL, Patterson NL, McMullen JR. Understanding key mechanisms of exercise-induced cardiac protection to mitigate disease: Current knowledge and emerging concepts. *Physiol Rev* 2018;**98**:419–75.

159. Qiu Y, Pan X, Chen Y, Xiao J. Hallmarks of exercised heart. *J Mol Cell Cardiol* 2022;**164**:126–35.
160. Chen H, Chen C, Spanos M, et al. Exercise training maintains cardiovascular health: Signaling pathways involved and potential therapeutics. *Signal Transduct Target Ther* 2022;**7**:306. doi:10.1038/s41392-022-01153-1.
161. Consitt LA, Dudley C, Saxena G. Impact of endurance and resistance training on skeletal muscle glucose metabolism in older adults. *Nutrients* 2019;**11**:2636. doi:10.3390/nu11112636.
162. Li X, Wei C, Jin Y, et al. Time-resolved map of serum metabolome profiling in D-galactose-induced aging rats with exercise intervention. *iScience* 2024;**27**:108999. doi:10.1016/j.isci.2024.108999.
163. Tzimou A, Benaki D, Nikolaidis S, Mikros E, Taitzoglou I, Mougios V. Effects of lifelong exercise and aging on the blood metabolic fingerprint of rats. *Biogerontology* 2020;**21**:577–91.
164. Kim M, Sujkowski A, Namkoong S, et al. Sestrins are evolutionarily conserved mediators of exercise benefits. *Nat Commun* 2020;**11**:190. doi:10.1038/s41467-019-13442-5.
165. Zong Y, Li H, Liao P, et al. Mitochondrial dysfunction: Mechanisms and advances in therapy. *Signal Transduct Target Ther* 2024;**9**:124. doi:10.1038/s41392-024-01839-8.
166. Malpartida AB, Williamson M, Narendra DP, Wade-Martins R, Ryan BJ. Mitochondrial dysfunction and mitophagy in Parkinson's disease: From mechanism to therapy. *Trends Biochem Sci* 2021;**46**:329–43.
167. Ashleigh T, Swerdlow RH, Beal MF. The role of mitochondrial dysfunction in Alzheimer's disease pathogenesis. *Alzheimers Dement* 2023;**19**:333–42.
168. Apostolova N, Vezza T, Muntane J, Rocha M, Victor VM. Mitochondrial dysfunction and mitophagy in type 2 diabetes: Pathophysiology and therapeutic targets. *Antioxid Redox Signal* 2023;**39**:278–320.
169. Xia D, Liu Y, Wu P, Wei D. Current advances of mitochondrial dysfunction and cardiovascular disease and promising therapeutic strategies. *Am J Pathol* 2023;**193**:1485–500.
170. Amorim JA, Coppotelli G, Rolo AP, Palmeira CM, Ross JM, Sinclair DA. Mitochondrial and metabolic dysfunction in ageing and age-related diseases. *Nat Rev Endocrinol* 2022;**18**:243–58.
171. Guo Y, Guan T, Shafiq K, et al. Mitochondrial dysfunction in aging. *Ageing Res Rev* 2023;**88**:101955. doi:10.1016/j.arr.2023.101955.
172. Grevendonk L, Connell NJ, McCrum C, et al. Impact of aging and exercise on skeletal muscle mitochondrial capacity, energy metabolism, and physical function. *Nat Commun* 2021;**12**:4773. doi:10.1038/s41467-021-24956-2.
173. Gudiksen A, Qoqaj A, Ringholm S, Wojtaszewski J, Plomgaard P, Pilegaard H. Ameliorating effects of lifelong physical activity on healthy aging and mitochondrial function in human white adipose tissue. *J Gerontol A Biol Sci Med Sci* 2022;**77**:1101–11.
174. Flockhart M, Nilsson LC, Tais S, Ekblom B, Apro W, Larsen FJ. Excessive exercise training causes mitochondrial functional impairment and decreases glucose tolerance in healthy volunteers. *Cell Metab* 2021;**33**:957-70.e6.
175. Halling JF, Jessen H, Nohr-Meldgaard J, et al. PGC-1α regulates mitochondrial properties beyond biogenesis with aging and exercise training. *Am J Physiol Endocrinol Metab* 2019;**317**:E513–25.
176. No MH, Heo JW, Yoo SZ, et al. Effects of aging and exercise training on mitochondrial function and apoptosis in the rat heart. *Pflugers Arch* 2020;**472**:179–93.
177. Silva MG, Nunes P, Oliveira P, et al. Long-term aerobic training improves mitochondrial and antioxidant function in the liver of Wistar rats preventing hepatic age-related function decline. *Biology (Basel)* 2022;**11**:1750. doi:10.3390/biology11121750.
178. Campos JC, Marchesi Bozi LH, Krum B, et al. Exercise preserves physical fitness during aging through AMPK and mitochondrial dynamics. *Proc Natl Acad Sci U S A* 2023;**120**:e2204750120. doi:10.1073/pnas.2204750120.
179. Kim SJ, Miller B, Kumagai H, Silverstein AR, Flores M, Yen K. Mitochondrial-derived peptides in aging and age-related diseases. *Geroscience* 2021;**43**:1113–21.
180. Li Y, Li Z, Ren Y, et al. Mitochondrial-derived peptides in cardiovascular disease: Novel insights and therapeutic opportunities. *J Adv Res* 2024;**64**:99–115.
181. Gidlund EK, von Walden F, Venojarvi M, et al. Humanin skeletal muscle protein levels increase after resistance training in men with impaired glucose metabolism. *Physiol Rep* 2016;**4**:e13063. doi:10.14814/phy2.13063.
182. Woodhead JST, D'Souza RF, Hedges CP, et al. High-intensity interval exercise increases humanin, a mitochondrial encoded peptide, in the plasma and muscle of men. *J Appl Physiol (1985)* 2020;**128**:1346–54.
183. Reynolds JC, Lai RW, Woodhead JST, et al. MOTS-c is an exercise-induced mitochondrial-encoded regulator of age-dependent physical decline and muscle homeostasis. *Nat Commun* 2021;**12**:470. doi:10.1038/s41467-020-20790-0.
184. von Walden F, Fernandez-Gonzalo R, Norrbom J, et al. Acute endurance exercise stimulates circulating levels of mitochondrial-derived peptides in humans. *J Appl Physiol (1985)* 2021;**131**:1035–42.
185. Alser M, Ramanjaneya M, Rizwana Anwardeen N, et al. The effect of chronic endurance exercise on serum levels of MOTS-c and humanin in professional athletes. *Rev Cardiovasc Med* 2022;**23**:181. doi:10.31083/j.rcm2305181.
186. de Smalen LM, Borsch A, Leuchtmann AB, et al. Impaired age-associated mitochondrial translation is mitigated by exercise and PGC-1α. *Proc Natl Acad Sci USA* 2023;**120**:e2302360120. doi:10.1073/pnas.2302360120.
187. Robinson MM, Dasari S, Konopka AR, et al. Enhanced protein translation underlies improved metabolic and physical adaptations to different exercise training modes in young and old humans. *Cell Metab* 2017;**25**:581–92.
188. Zhang L, Pitcher LE, Yousefzadeh MJ, Niedernhofer LJ, Robbins PD, Zhu Y. Cellular senescence: A key therapeutic target in aging and diseases. *J Clin Invest* 2022;**132**:e158450. doi:10.1172/JCI158450.
189. Englund DA, Sakamoto AE, Fritsche CM, et al. Exercise reduces circulating biomarkers of cellular senescence in humans. *Aging Cell* 2021;**20**:e13415. doi:10.1111/acel.13415.
190. Hernandez-Segura A, Nehme J, Demaria M. Hallmarks of cellular senescence. *Trends Cell Biol* 2018;**28**:436–53.
191. Zhang X, Englund DA, Aversa Z, Jachim SK, White TA, LeBrasseur NK. Exercise counters the age-related accumulation of senescent cells. *Exerc Sport Sci Rev* 2022;**50**:213–21.
192. Roh JD, Houstis N, Yu A, et al. Exercise training reverses cardiac aging phenotypes associated with heart failure with preserved ejection fraction in male mice. *Aging Cell* 2020;**19**:e13159. doi:10.1111/acel.13159.
193. Chang P, Zhang X, Zhang M, et al. Swimming exercise inhibits myocardial ER stress in the hearts of aged mice by enhancing cGMP-PKG signaling. *Mol Med Rep* 2020;**21**:549–56.
194. Tang J, Wu C, Xu Y, et al. Resistance training up-regulates Smyd1 expression and inhibits oxidative stress and endoplasmic reticulum stress in the heart of middle-aged mice. *Free Radic Biol Med* 2024;**210**:304–17.
195. Raffin J, Rolland Y, Parini A, et al. Association between physical activity, growth differentiation factor 15 and bodyweight in older adults: A longitudinal mediation analysis. *J Cachexia Sarcopenia Muscle* 2023;**14**:771–80.
196. Fielding RA, Atkinson EJ, Aversa Z, et al. Biomarkers of cellular senescence predict the onset of mobility disability and are reduced by physical activity in older adults. *J Gerontol A Biol Sci Med Sci* 2024;**79**:glad257. doi:10.1093/gerona/glad257.
197. St Sauver JL, Weston SA, Atkinson EJ, et al. Biomarkers of cellular senescence and risk of death in humans. *Aging Cell* 2023;**22**:e14006. doi:10.1111/acel.14006.
198. Guvatova ZG, Borisov PV, Alekseev AA, Moskalev AA. Age-related changes in extracellular matrix. *Biochemistry (Mosc)* 2022;**87**:1535–51.
199. Kwak HB. Aging, exercise, and extracellular matrix in the heart. *J Exerc Rehabil* 2013;**9**:338–47.
200. Kwak HB, Kim JH, Joshi K, Yeh A, Martinez DA, Lawler JM. Exercise training reduces fibrosis and matrix metalloproteinase dysregulation in the aging rat heart. *FASEB J* 2011;**25**:1106–17.

201. de Sousa Neto IV, Durigan JLQ, Carreiro de Farias Junior G, et al. Resistance training modulates the matrix metalloproteinase-2 activity in different trabecular bones in aged rats. *Clin Interv Aging* 2021;**16**:71–81.
202. Zhang QB, Zhou Y, Zhong HZ, Liu Y. Effect of stretching combined with ultrashort wave diathermy on joint function and its possible mechanism in a rabbit knee contracture model. *Am J Phys Med Rehabil* 2018;**97**:357–63.
203. Jacob CDS, Barbosa GK, Rodrigues MP, et al. Ultrastructural and molecular development of the myotendinous junction triggered by stretching prior to resistance exercise. *Microsc Microanal* 2022. doi:10.1017/S1431927622000186.
204. Brunet A, Goodell MA, Rando TA. Ageing and rejuvenation of tissue stem cells and their niches. *Nat Rev Mol Cell Biol* 2023;**24**:45–62.
205. Verdijk LB, Koopman R, Schaart G, Meijer K, Savelberg HH, van Loon LJ. Satellite cell content is specifically reduced in type II skeletal muscle fibers in the elderly. *Am J Physiol Endocrinol Metab* 2007;**292**:E151–7.
206. Karlsen A, Bechshoft RL, Malmgaard-Clausen NM, et al. Lack of muscle fibre hypertrophy, myonuclear addition, and satellite cell pool expansion with resistance training in 83−94-year-old men and women. *Acta Physiol (Oxf)* 2019;**227**:e13271. doi:10.1111/apha.13271.
207. Verdijk LB, Snijders T, Drost M, Delhaas T, Kadi F, van Loon LJ. Satellite cells in human skeletal muscle; from birth to old age. *Age (Dordr)* 2014;**36**:545–7.
208. Soendenbroe C, Dahl CL, Meulengracht C, et al. Preserved stem cell content and innervation profile of elderly human skeletal muscle with lifelong recreational exercise. *J Physiol* 2022;**600**:1969–89.
209. Fujimaki S, Hidaka R, Asashima M, Takemasa T, Kuwabara T. WNT protein-mediated satellite cell conversion in adult and aged mice following voluntary wheel running. *J Biol Chem* 2014;**289**:7399–412.
210. Brett JO, Arjona M, Ikeda M, et al. Exercise rejuvenates quiescent skeletal muscle stem cells in old mice through restoration of cyclin D1. *Nat Metab* 2020;**2**:307–17.
211. Abreu P, Kowaltowski AJ. Satellite cell self-renewal in endurance exercise is mediated by inhibition of mitochondrial oxygen consumption. *J Cachexia Sarcopenia Muscle* 2020;**11**:1661–76.
212. Farmand S, Du Preez A, Kim C, et al. Cognition on the move: Examining the role of physical exercise and neurogenesis in counteracting cognitive aging. *Ageing Res Rev* 2025;**107**:102725. doi:10.1016/j.arr.2025.102725.
213. Carta MG, Cossu G, Pintus E, et al. Moderate exercise improves cognitive function in healthy elderly people: Results of a randomized controlled trial. *Clin Pract Epidemiol Ment Health* 2021;**17**:75–80.
214. Kim JH, Liu QF, Urnuhsaikhan E, Jeong HJ, Jeon MY, Jeon S. Moderate-intensity exercise induces neurogenesis and improves cognition in old mice by upregulating hippocampal Hippocalcin, Otub1, and Spectrin-α. *Mol Neurobiol* 2019;**56**:3069–78.
215. Adusumilli VS, Walker TL, Overall RW, et al. ROS dynamics delineate functional states of hippocampal neural stem cells and link to their activity-dependent exit from quiescence. *Cell Stem Cell* 2021;**28**:300–14.
216. Codina-Martinez H, Fernandez-Garcia B, Diez-Planelles C, et al. Autophagy is required for performance adaptive response to resistance training and exercise-induced adult neurogenesis. *Scand J Med Sci Sports* 2020;**30**:238–53.
217. Valenzuela PL, Castillo-Garcia A, Morales JS, et al. Exercise benefits on Alzheimer's disease: State-of-the-science. *Ageing Res Rev* 2020;**62**:101108. doi:10.1016/j.arr.2020.101108.
218. Shen B, Tasdogan A, Ubellacker JM, et al. A mechanosensitive periarteriolar niche for osteogenesis and lymphopoiesis. *Nature* 2021;**591**:438–44.
219. Villeda SA, Luo J, Mosher KI, et al. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature* 2011;**477**:90–4.
220. Naito AT, Sumida T, Nomura S, et al. Complement C1q activates canonical WNT signaling and promotes aging-related phenotypes. *Cell* 2012;**149**:1298–313.
221. Cho SY, Roh HT. Effects of aerobic exercise training on peripheral brain-derived neurotrophic factor and eotaxin-1 levels in obese young men. *J Phys Ther Sci* 2016;**28**:1355–8.
222. MacNeil LG, Tarnopolsky MA, Crane JD. Acute, exercise-induced alterations in cytokines and chemokines in the blood distinguish physically active and sedentary aging. *J Gerontol A Biol Sci Med Sci* 2021;**76**:811–8.
223. Horii N, Uchida M, Hasegawa N, et al. Resistance training prevents muscle fibrosis and atrophy via down-regulation of C1q-induced Wnt signaling in senescent mice. *FASEB J* 2018;**32**:3547–59.
224. Leiter O, Brici D, Fletcher SJ, et al. Platelet-derived exerkine CXCL4/platelet factor 4 rejuvenates hippocampal neurogenesis and restores cognitive function in aged mice. *Nat Commun* 2023;**14**:4375. doi:10.1038/s41467-023-39873-9.
225. Leiter O, Seidemann S, Overall RW, et al. Exercise-induced activated platelets increase adult hippocampal precursor proliferation and promote neuronal differentiation. *Stem Cell Reports* 2019;**12**:667–79.
226. De Miguel Z, Khoury N, Betley MJ, et al. Exercise plasma boosts memory and dampens brain inflammation via clusterin. *Nature* 2021;**600**:494–9.
227. Horowitz AM, Fan X, Bieri G, et al. Blood factors transfer beneficial effects of exercise on neurogenesis and cognition to the aged brain. *Science* 2020;**369**:167–73.
228. Zhang H, Wu X, Liang J, Kirberger M, Chen N. Irisin, an exercise-induced bioactive peptide beneficial for health promotion during aging process. *Ageing Res Rev* 2022;**80**:101680. doi:10.1016/j.arr.2022.101680.
229. Chi C, Fu H, Li YH, et al. Exerkine fibronectin type-III domain-containing protein 5/irisin-enriched extracellular vesicles delay vascular ageing by increasing SIRT6 stability. *Eur Heart J* 2022;**43**:4579–95.
230. Moon HY, Becke A, Berron D, et al. Running-induced systemic cathepsin B secretion is associated with memory function. *Cell Metab* 2016;**24**:332–40.
231. Gaitan JM, Moon HY, Stremlau M, et al. Effects of aerobic exercise training on systemic biomarkers and cognition in late middle-aged adults at risk for Alzheimer's disease. *Front Endocrinol (Lausanne)* 2021;**12**:660181. doi:10.3389/fendo.2021.660181.
232. Roberts LD, Bostrom P, O'Sullivan JF, et al. β-aminoisobutyric acid induces browning of white fat and hepatic β-oxidation and is inversely correlated with cardiometabolic risk factors. *Cell Metab* 2014;**19**:96–108.
233. Nishikawa H, Fukunishi S, Asai A, Yokohama K, Nishiguchi S, Higuchi K. Pathophysiology and mechanisms of primary sarcopenia (Review). *Int J Mol Med* 2021;**48**:156. doi:10.3892/ijmm.2021.4989.
234. El Assar M, Alvarez-Bustos A, Sosa P, Angulo J, Rodriguez-Manas L. Effect of physical activity/exercise on oxidative stress and inflammation in muscle and vascular aging. *Int J Mol Sci* 2022;**23**:8713. doi:10.3390/ijms23158713.3.
235. Lavin KM, Perkins RK, Jemiolo B, Raue U, Trappe SW, Trappe TA. Effects of aging and lifelong aerobic exercise on basal and exercise-induced inflammation. *J Appl Physiol (1985)* 2020;**128**:87–99.
236. Zheng G, Qiu P, Xia R, et al. Effect of aerobic exercise on inflammatory markers in healthy middle-aged and older adults: A systematic review and meta-analysis of randomized controlled trials. *Front Aging Neurosci* 2019;**11**:98. doi:10.3389/fnagi.2019.00098.
237. Chen WK, Tsai YL, Shibu MA, et al. Exercise training augments Sirt1-signaling and attenuates cardiac inflammation in D-galactose induced-aging rats. *Aging (Albany NY)* 2018;**10**:4166–74.
238. Abd El-Kader SM, Al-Shreef FM. Inflammatory cytokines and immune system modulation by aerobic versus resisted exercise training for elderly. *Afr Health Sci* 2018;**18**:120–31.
239. Lim MY, Nam YD. Gut microbiome in healthy aging versus those associated with frailty. *Gut Microbes* 2023;**15**:2278225. doi:10.1080/19490976.2023.2278225.
240. Kim M, Benayoun BA. The microbiome: An emerging key player in aging and longevity. *Transl Med Aging* 2020;**4**:103–16.
241. Zeng X, Li J, Shan W, Lai Z, Zuo Z. Gut microbiota of old mice worsens neurological outcome after brain ischemia via increased valeric acid and IL-17 in the blood. *Microbiome* 2023;**11**:204. doi:10.1186/s40168-023-01648-1.
242. Du Y, Gao Y, Zeng B, Fan X, Yang D, Yang M. Effects of anti-aging interventions on intestinal microbiota. *Gut Microbes* 2021;**13**:1994835. doi:10.1080/19490976.2021.1994835.

243. Sorboni SG, Moghaddam HS, Jafarzadeh-Esfehani R, Soleimanpour S. A comprehensive review on the role of the gut microbiome in human neurological disorders. *Clin Microbiol Rev* 2022;**35**:e0033820. doi:10.1128/CMR.00338-20.
244. Ma PJ, Wang MM, Wang Y. Gut microbiota: A new insight into lung diseases. *Biomed Pharmacother* 2022;**155**:113810. doi:10.1016/j.biopha.2022.113810.
245. Zhou Z, Sun B, Yu D, Zhu C. Gut microbiota: An important player in type 2 diabetes mellitus. *Front Cell Infect Microbiol* 2022;**12**:834485. doi:10.3389/fcimb.2022.834485.
246. Fang J, Yu CH, Li XJ, et al. Gut dysbiosis in nonalcoholic fatty liver disease: Pathogenesis, diagnosis, and therapeutic implications. *Front Cell Infect Microbiol* 2022;**12**:997018. doi:10.3389/fcimb.2022.997018.
247. Wong CC, Yu J. Gut microbiota in colorectal cancer development and therapy. *Nat Rev Clin Oncol* 2023;**20**:429–52.
248. Fernandes MR, Aggarwal P, Costa RGF, Cole AM, Trinchieri G. Targeting the gut microbiota for cancer therapy. *Nat Rev Cancer* 2022;**22**:703–22.
249. Fernandez J, Fernandez-Sanjurjo M, Iglesias-Gutierrez E, et al. Resistance and endurance exercise training induce differential changes in gut microbiota composition in murine models. *Front Physiol* 2021;**12**:748854. doi:10.3389/fphys.2021.748854.
250. Souza PB, de Araujo Borba L, Castro de Jesus L, Valverde AP, Gil-Mohapel J, Rodrigues ALS. Major depressive disorder and gut microbiota: Role of physical exercise. *Int J Mol Sci* 2023;**24**:16870. doi:10.3390/ijms242316870.
251. Wegierska AE, Charitos IA, Topi S, Potenza MA, Montagnani M, Santacroce L. The connection between physical exercise and gut microbiota: Implications for competitive sports athletes. *Sports Med* 2022;**52**:2355–69.
252. Silva JSC, Seguro CS, Naves MMV. Gut microbiota and physical exercise in obesity and diabetes: A systematic review. *Nutr Metab Cardiovasc Dis* 2022;**32**:863–77.
253. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol* 2021;**19**:55–71.
254. Halverson T, Alagiakrishnan K. Gut microbes in neurocognitive and mental health disorders. *Ann Med* 2020;**52**:423–43.
255. Badal VD, Vaccariello ED, Murray ER, et al. The gut microbiome, aging, and longevity: A systematic review. *Nutrients* 2020;**12**:3759. doi:10.3390/nu12123759.
256. Nicolas S, Dohm-Hansen S, Lavelle A, et al. Exercise mitigates a gut microbiota-mediated reduction in adult hippocampal neurogenesis and associated behaviours in rats. *Transl Psychiatry* 2024;**14**:195. doi:10.1038/s41398-024-02904-0.
257. Langsetmo L, Johnson A, Demmer RT, et al. The association between objectively measured physical activity and the gut microbiome among older community dwelling men. *J Nutr Health Aging* 2019;**23**:538–46.
258. Erlandson KM, Liu J, Johnson R, et al. An exercise intervention alters stool microbiota and metabolites among older, sedentary adults. *Ther Adv Infect Dis* 2021;**8**:20499361211027067. doi:10.1177/20499361211027067.
259. Park SS, Park SH, Jeong HT, et al. The effect of treadmill exercise on memory function and gut microbiota composition in old rats. *J Exerc Rehabil* 2024;**20**:205–12.
260. Lai Z, Shan W, Li J, Min J, Zeng X, Zuo Z. Appropriate exercise level attenuates gut dysbiosis and valeric acid increase to improve neuroplasticity and cognitive function after surgery in mice. *Mol Psychiatry* 2021;**26**:7167–87.
261. Zhou Q, Deng J, Pan X, et al. Gut microbiome mediates the protective effects of exercise after myocardial infarction. *Microbiome* 2022;**10**:82. doi:10.1186/s40168-022-01271-6.
262. Ran Z, Wei J, Yang G, Yang C. Prevalence of social isolation in the elderly: A systematic review and meta-analysis. *Geriatr Nurs* 2024;**58**:87–97.
263. Tragantzopoulou P, Giannouli V. Social isolation and loneliness in old age: Exploring their role in mental and physical health. *Psychiatriki* 2021;**32**:59–66.
264. Hajek A, Volkmar A, Konig HH. Prevalence and correlates of loneliness and social isolation in the oldest old: A systematic review, meta-analysis and meta-regression. *Soc Psychiatry Psychiatr Epidemiol* 2025;**60**:993–1015.
265. Windle G, Hughes D, Linck P, Russell I, Woods B. Is exercise effective in promoting mental well-being in older age? A systematic review. *Aging Ment Health* 2010;**14**:652–69.
266. Chang SH, Chien NH, Chen MC. Regular exercise and depressive symptoms in community-dwelling elders in northern Taiwan. *J Nurs Res* 2016;**24**:329–36.
267. Song QH, Shen GQ, Xu RM, et al. Effect of Tai Chi exercise on the physical and mental health of the elder patients suffered from anxiety disorder. *Int J Physiol Pathophysiol Pharmacol* 2014;**6**:55–60.
268. Cordes T, Zwingmann K, Rudisch J, Voelcker-Rehage C, Wollesen B. Multicomponent exercise to improve motor functions, cognition and well-being for nursing home residents who are unable to walk: A randomized controlled trial. *Exp Gerontol* 2021;**153**:111484. doi:10.1016/j.exger.2021.111484.
269. Valenzuela PL, Izquierdo M, Martinez-Velilla N, et al. Exercise effects on intrinsic capacity in acutely hospitalised older adults: A pooled analysis of two randomised controlled trials. *Age Ageing* 2025;**54**:afaf082. doi:10.1093/ageing/afaf082.
270. Li Q, Liu Q, Lin Z, et al. Comparison between the effect of mid-late-life high-intensity interval training and continuous moderate-intensity training in old mouse hearts. *J Gerontol A Biol Sci Med Sci* 2025;**80**:glaf025. doi:10.1093/gerona/glaf025.
271. Pei Z, Yang C, Guo Y, Dong M, Wang F. Effect of different exercise training intensities on age-related cardiac damage in male mice. *Aging (Albany NY)* 2021;**13**:21700–11.
272. Wandell P, Enarsson M, Feldreich T, Lind L, Arnlov J, Carlsson AC. High physical activity level and the long-term risk of atrial fibrillation in two Swedish cohorts. *Geriatrics (Basel)* 2025;**10**:80. doi:10.3390/geriatrics10030080.
273. Gorman RA, Yakobov S, Polidovitch N, et al. The effects of daily dose of intense exercise on cardiac responses and atrial fibrillation. *J Physiol* 2024;**602**:569–96.
274. Alcarraz A, Meza-Ramos A, Rubies C, et al. From moderate to strenuous training: Unravelling mechanistic contributors and biomarkers for atrial fibrillation in exercise. *Europace* 2025;**27**:euaf098. doi:10.1093/europace/euaf098.
275. Maclaine KD, Stebbings KA, Llano DA, Rhodes JS. Voluntary wheel running has no impact on brain and liver mitochondrial DNA copy number or mutation measures in the PolG mouse model of aging. *PLoS One* 2020;**15**:e0226860. doi:10.1371/journal.pone.0226860.
276. Liu-Ambrose T, Barha C, Falck RS. Active body, healthy brain: Exercise for healthy cognitive aging. *Int Rev Neurobiol* 2019;**147**:95–120.
277. Herrmann SD, Conger SA, Willis EA, Ainsworth BE. Promoting public health through the 2024 compendium of physical activities: Strategies for adults, older adults, and wheelchair users. *J Sport Health Sci* 2024;**13**:739–42.
278. O'Keefe EL, Torres-Acosta N, O'Keefe JH, Lavie CJ. Training for longevity: The reverse J-curve for exercise. *Mo Med* 2020;**117**:355–61.
279. Burtscher J, Strasser B, D'Antona G, Millet GP, Burtscher M. How much resistance exercise is beneficial for healthy aging and longevity? *J Sport Health Sci* 2023;**12**:284–6.
280. Lee DC, Lee IM. Optimum dose of resistance exercise for cardiovascular health and longevity: Is more better? *Curr Cardiol Rep* 2023;**25**:1573–80.
281. Feng M, Li M, Lou J, et al. Early-life exercise extends healthspan but not lifespan in mice. *Nat Commun* 2025;**16**:6328. doi:10.1038/s41467-025-61443-4.
282. Ji Q, Jiang X, Wang M, et al. Multimodal omics approaches to aging and age-related diseases. *Phenomics* 2024;**4**:56–71.
283. Ying W. Phenomic studies on diseases: Potential and challenges. *Phenomics* 2023;**3**:285–99.