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Exercise-regulated bone–brain axis: A novel perspective on age-related cognitive decline

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Facts

- Physical exercise is a key non-pharmacological intervention protecting against cognitive aging and reducing dementia risk.
- Exercise activates brain-derived neurotrophic factor pathways in the brain, promoting neurogenesis & synaptic plasticity while reducing neuroinflammation.
- The bone–brain axis is a bidirectional network where bone factors (osteocalcin, FGF23) cross the blood–brain barrier to influence cognition.
- Exercise benefits cognition partly by stimulating bone signals (osteocalcin, irisin), thus engaging the bone–brain axis to improve emotional & cognitive states.

Open questions

- Is exercise-induced release of bone factors a primary cause of cognitive gains or a secondary correlate of other dominant mechanisms?
- What exercise type, intensity, and duration best modulates the bone–brain axis for optimal cognitive protection in aging?
- How does the bone–brain axis interact with other systems (e.g., gut–brain, immune) to collectively influence brain health during aging?
- Can bone–brain axis insights translate into novel therapies (e.g., drug mimetics) for cognitive health in exercise-ineligible individuals?

Abstract

Aging is a significant risk factor for cognitive decline, non-pharmacological interventions such as exercise have demonstrated a protective role in delaying cognitive decline and reducing dementia risk. Exercise activates key signaling pathways, including brain-derived neurotrophic factor and vascular endothelial growth factor, promoting neurogenesis and synaptic plasticity while reducing neuroinflammation. Recent studies have highlighted the bone–brain axis, a bidirectional regulatory network where bone-derived factors, such as osteocalcin and fibroblast growth factor 23 cross the blood–brain barrier, influencing brain function and cognition. Exercise has been shown to enhance the release of bone-derived signals, such as osteocalcin and irisin, further improving cognitive and emotional states, providing new physiological mechanisms for exercise's role in cognitive protection. This review summarizes the progress of research on the bone–brain axis, emphasizing the interplay between bone, brain, and other systems in the context of aging and cognitive decline. Additionally, it explores how exercise can modulate the bone–brain axis to provide potential therapeutic avenues for preventing cognitive decline. Future studies should focus on personalized exercise interventions and combining exercise with other strategies to optimize cognitive health in aging populations.

Key Words: aging; bone–brain axis; brain-derived neurotrophic factor; cognitive decline; dementia; exercise; neuroregeneration; osteocalcin

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Introduction

Aging is one of the major risk factors for cognitive decline. Cognitive decline is a chronic, progressive process, and approximately 40% of its onset or progression has been attributed to modifiable lifestyle-related factors, including physical activity, dietary habits, cognitive engagement, sleep quality, and psychological well-being. Among these factors, exercise intervention has emerged as one of the most effective and widely applicable non-pharmacological strategies for delaying neurodegeneration and reducing dementia risk (Ahlskog et al., 2011; Sofi et al., 2011; de Souto Barreto et al., 2018; Li et al., 2025c). Compared with drug therapies, exercise is low-cost, has minimal side effects, and benefits multiple physiological systems simultaneously.

At the mechanistic level, accumulating evidence demonstrates that exercise promotes brain health by activating key signaling pathways, such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor, which jointly enhance hippocampal neurogenesis, synaptic plasticity, and cerebral blood flow (Ballard, 2017; Liang et al., 2021; Kraemer and Kraemer, 2023; Khalil, 2024; Oyovwi et al., 2025). Exercise also exerts anti-inflammatory and antioxidative effects, attenuating microglial overactivation and chronic neuroinflammation, both of which are strongly implicated in age-related cognitive decline. In addition, recent studies highlight that exercise may regulate gene transcription through epigenetic pathways, such as increasing Bdnf promoter methylation or histone H3 acetylation, thereby contributing to long-term memory maintenance and attenuating cognitive deterioration (Liang et al., 2021; Zheng et al., 2025). These findings provide convincing biological evidence supporting exercise as a neuroprotective intervention.

In recent years, the skeletal system has been redefined as a crucial endocrine organ. The discovery of the bone-brain axis has expanded the traditional view of bone as merely a structural tissue and revealed a dynamic bidirectional communication network between the skeletal system and the central nervous system (CNS) (Liu et al., 2024; Zhang and Zhang, 2024; Li et al., 2025a, b; Shi et al., 2025). Bone tissue secretes multiple bone-derived endocrine factors, including osteocalcin (OCN) and fibroblast growth factor 23 (FGF23), which can enter the bloodstream, cross the blood–brain barrier (BBB), and influence neuronal activity, neurotransmitter synthesis, learning, memory performance, and emotional regulation (Rousseaud et al., 2016; Shi and Chen, 2024). In turn, the CNS regulates bone remodeling through pathways, such as the sympathetic nervous system and hypothalamic neuropeptides, forming a sophisticated feedback loop that links brain function with skeletal homeostasis (Liang et al., 2025).

Emerging evidence further suggests that exercise

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strengthens bone-derived signaling. Mechanical loading and muscle-bone crosstalk during exercise can stimulate osteocytes to release key endocrine molecules, such as OCN and irisin. These circulating signals have been shown to enhance hippocampal plasticity, improve mood states, and alleviate cognitive impairment, thereby providing a novel mechanistic explanation for the neuroprotective benefits of exercise beyond its classical effects on the cardiovascular and nervous systems (Schurman et al., 2023). This expanding line of research suggests that bone-derived hormones may serve as important molecular mediators connecting exercise with improved brain function.

Therefore, this review aims to comprehensively summarize the regulatory mechanisms and recent research progress regarding how exercise influences the bone–brain axis and its multi-organ network. By integrating evidence from molecular biology, neuroscience, endocrinology, and exercise physiology, this work seeks to deepen the mechanistic understanding of exercise-induced neuroprotection. Such knowledge will not only help refine exercise-based prevention strategies for cognitive decline but also provide theoretical foundations and new research directions for future mechanistic studies and clinical interventions targeting the bone-brain axis (**Figure 1**).

Search Strategy

To comprehensively review the current evidence on the role of exercise in regulating the bone-brain axis and its impact on age-related cognitive decline, a systematic literature search was performed. The search focused on English-language publications from January 2010 to August 2025, covering both foundational studies and the most recent advances. Four major international databases were selected to ensure comprehensive coverage of biomedical and exercise-related literature: PubMed/MEDLINE, Web of Science Core Collection, Embase, and Cochrane Library. A combination of Medical Subject Headings (MeSH) and free-text keywords was applied to capture relevant studies across three main domains: Exercise intervention ("exercise," "physical activity," "aerobic exercise," and "resistance training"), bone-brain axis factors ("osteocalcin," "sclerostin," "bone-derived factor," "bone–brain axis," "FGF23," and "osteopontin"), and Cognitive decline or neurodegenerative diseases ("cognitive decline," "mild cognitive impairment," "dementia," and "Alzheimer's disease").

Mechanisms of Age-Related Cognitive Decline

As age increases, cognitive function inevitably undergoes gradual and progressive deterioration, typically manifested as memory loss, executive dysfunction, reduced attention, and slower information processing speeds. This decline is not merely the result of structural brain atrophy but is instead a multifactorial process influenced by neurological, biochemical, and molecular alterations occurring throughout the aging brain. Neuroaging is characterized by prominent volume reduction in critical cognitive regions, such as the prefrontal cortex and hippocampus, along with decreased gray matter thickness and reduced white matter integrity. In particular, age-related degeneration of white matter fiber tracts disrupts neural signal transmission efficiency and contributes to disorganized brain network communication. These structural abnormalities are closely associated with a decline in functional network connectivity, ultimately impairing the brain's capacity for information processing, storage, and integration (Voicu et al., 2025).

At the cellular and synaptic level, aging is accompanied by marked reductions in synaptic plasticity, decreased dendritic spine density, and diminished rates of adult hippocampal neurogenesis. Synaptic weakening results in impaired long-term potentiation, a core basis for learning and memory. Multiple intrinsic aging mechanisms are believed to underlie these changes, including the progressive accumulation of DNA damage, telomere shortening, genomic instability, and epigenetic drift, such as aberrant histone methylation or acetylation patterns, that alter gene transcription profiles necessary for neuronal survival and plasticity. In addition, disruptions in autophagy and proteostasis compromise the removal of misfolded or aggregated proteins, imposing further stress on neurons and weakening their ability to repair, regenerate, and maintain synaptic integrity (Soares et al., 2014; Toricelli et al., 2021). Over time, these cellular deficits interact and amplify one another, forming a self-reinforcing cycle of neurodegeneration.

At the molecular level, oxidative stress and chronic, low-grade neuroinflammation are widely recognized as key drivers of age-associated cognitive decline. With aging, mitochondrial respiratory efficiency gradually decreases, resulting in excessive reactive oxygen species production and oxidative damage to lipids, proteins, and nucleic acids. This increase in reactive oxygen species, coupled with impaired antioxidant defenses, accelerates neuronal injury and disrupts intracellular signaling, further impairing synaptic communication and cellular metabolism (Bondy, 2024). Meanwhile, microglia, which play essential roles in immune surveillance and synaptic maintenance, undergo phenotypic aging and exhibit a pro-inflammatory profile. Senescent microglia secrete elevated levels of inflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor α (TNF-α), leading to chronic neuroinflammation that suppresses synaptic plasticity, disrupts neurogenesis, and exacerbates neurodegenerative cascades (Cui et al., 2012).

In addition to central inflammation, increased permeability of the aging BBB allows peripheral pro-inflammatory molecules to infiltrate brain tissue, creating a feed-forward inflammatory loop that further amplifies neural damage. Together, oxidative stress, neuroinflammation, impaired vascular function, and disrupted homeostatic signaling synergistically accelerate neuronal dysfunction and structural brain degeneration. These interconnected mechanisms ultimately heighten the vulnerability of the aging brain and contribute to the progressive decline of cognitive capacity observed in older adults.

Biological Basis of the Bone–Brain Axis

Bone-derived factors and their impact on cognition

Bone is not only a structural support organ but also an important and dynamic endocrine system that secretes a series of "bone-derived hormones," such as OCN, FGF23, and sclerostin (SOST), which exert systemic regulatory functions far beyond the skeletal system itself (Shi et al., 2024; Chang et al., 2025; Li et al., 2025a). In recent years, emerging evidence has revealed that these bone-derived endocrine factors not only participate in bone remodeling and mineral homeostasis, but can also cross the BBB and directly influence neuronal excitability, neurotransmitter synthesis, synaptic plasticity, and neuroinflammation. These findings have established bone as a vital component of the bone–brain axis, positioning it as a key regulator in maintaining cognitive health and resisting neurodegenerative decline. As aging, osteoporosis, and neurodegenerative diseases frequently coexist, research on bone-derived signaling molecules offers an important theoretical foundation for understanding how skeletal dysregulation may exacerbate cognitive impairment.

OCN is one of the most widely studied bone-derived hormones, secreted predominantly by osteoblasts. Among its molecular forms, the uncarboxylated OCN (ucOCN) is regarded as the biologically active subtype with potent endocrine activity. Earlier research demonstrated that ucOCN is involved in metabolic regulation, including insulin secretion, glucose utilization, adipose metabolism, muscle function, and reproductive signaling. However, accumulating breakthroughs have expanded its functional role into the CNS. OCN knockout mouse models exhibit pronounced spatial learning deficits, memory impairments, and anxiety-like behaviors, accompanied by altered hippocampal circuitry and reduced synaptic plasticity. Conversely, exogenous administration of ucOCN can significantly ameliorate age-related cognitive deficits, restore synaptic function, and increase hippocampal BDNF expression, suggesting that OCN is both necessary and sufficient to maintain cognitive competence (Chang et al., 2025; Li et al., 2025a).

OCN is able to cross the BBB and act on multiple neuronal targets in the brain. Research indicates that OCN enters the brain by binding to the GPR158 receptor on the BBB, which is highly expressed in the hippocampus and prefrontal cortex—regions closely associated with learning, memory, and emotional regulation. Once in the brain, OCN promotes cognitive function by modulating neurotransmitter systems. Specifically, OCN enhances the synthesis of dopamine, serotonin, and norepinephrine, which are neurotransmitters closely related to mood, learning, and memory. In addition, OCN plays an important role in neurogenesis. Studies have found that OCN promotes neurogenesis in the hippocampal region by activating the BDNF and TrkB signaling pathways. This process is critical for cognitive function, particularly in the formation and maintenance of memory. OCN also enhances synaptic plasticity, especially by promoting long-term potentiation, which improves synaptic transmission efficacy and further enhances learning and memory abilities (Li et al., 2025a). Through these mechanisms, OCN acts as a powerful anti-aging signal, helping to preserve neuronal survival, promote synaptic resilience, and prevent cognitive decline during aging.

In contrast to OCN's protective role, SOST, a glycoprotein secreted mainly by osteocytes, serves as a potent inhibitor of bone formation by antagonizing the Wnt/β-catenin signaling pathway. While originally studied in the context of skeletal metabolism, recent findings indicate that SOST can also enter the CNS and exert detrimental effects on cognitive function. A study from Nanjing University reported that SOST levels in cerebrospinal fluid increase with age in cognitively normal elderly individuals, and blood concentrations of SOST are negatively correlated with cognitive performance in AD patients (Shi et al., 2024). The animal work further demonstrated that SOST secreted by aging osteocytes can cross the BBB, bind to neuronal lipoprotein receptor-related protein 6 receptors, suppress Wnt signaling, and elevate beta-site amyloid precursor protein cleaving enzyme 1 enzyme activity. This upregulation promotes the cleavage of amyloid precursor protein and accelerates amyloid β accumulation, leading to synaptic dysfunction and plaque deposition. In AD mouse models, SOST overexpression worsens amyloid pathology and cognitive deterioration, whereas osteocyte-specific SOST knockout restores Wnt activity, decreases amyloid β production, and protects synaptic plasticity. This discovery provides a compelling mechanistic explanation for why osteoporosis and AD often coexist: high SOST levels may serve as a molecular bridge through which skeletal aging exacerbates neurodegeneration.

Osteopontin (OPN), secreted by osteoblasts, osteoclasts, and bone marrow-derived macrophages, represents another multifunctional bone-derived cytokine with diverse immunological and neurological roles (Yu et al.,

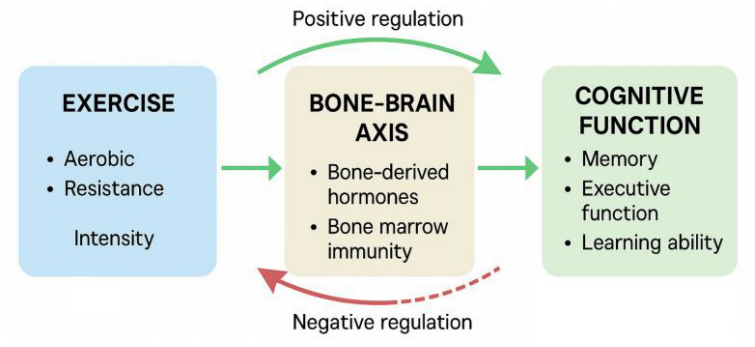

Figure 1 | **Interaction of exercise on cognitive function through the bone–brain axis.**

2020). OPN is expressed in several brain regions, including the basal ganglia, hippocampus, and cortex. However, unlike OCN and SOST, OPN exhibits a dualistic function whose effects depend on disease state and inflammatory context. In multiple sclerosis, for example, OPN promotes inflammatory cascades, enhances immune cell infiltration, and accelerates demyelination, thereby aggravating disease progression (Comabella et al., 2005; Agah et al., 2018; Alrafiah et al., 2019; González-Jiménez et al., 2025). By contrast, in certain models of Parkinson's disease, OPN fragments have been found to protect dopaminergic neurons against toxin-induced degeneration, suggesting a context-dependent neuroprotective role. In AD mouse models, OPN has been implicated in facilitating amyloid β clearance by mobilizing macrophages or microglia. Treatment with Glatiramer acetate, for instance, increases systemic OPN levels and promotes an anti-inflammatory macrophage phenotype capable of enhanced amyloid β phagocytosis, resulting in fewer amyloid plaques and improved cognition (Wang et al., 2020). Thus, OPN may contribute to either neuroprotection or neurodegeneration depending on the balance of inflammatory signals, highlighting the complexity of bone-immune-brain crosstalk. Further research is needed to clarify whether OPN can be therapeutically targeted through exercise, drugs, or bone remodeling interventions.

FGF23 is another crucial bone-derived endocrine hormone involved primarily in phosphate homeostasis, vitamin D metabolism, and mineral regulation. Its biological activity requires the co-receptor α-Klotho, which exists in both membrane-bound and soluble forms (Chen et al., 2018; Desbiens et al., 2022). Interestingly, α-Klotho itself has emerged as a potent anti-aging protein with antioxidative, anti-inflammatory, and pro-cognitive properties. An experimental study showed that Klotho supplementation enhances synaptic function, promotes oligodendrocyte maturation, mitigates neuronal oxidative stress, and improves learning and memory in non-human primates (Urakawa et al., 2006). In the bone–brain axis, the FGF23/Klotho system is believed to influence neuronal calcium-phosphate equilibrium, membrane potential stability, and myelination processes, suggesting a potential link to age-related cognitive decline (Cardoso et al., 2018; Matei et al., 2022; Prud'homme et al., 2022). Elevated FGF23 levels, commonly seen in chronic kidney disease and mineral imbalance, have been associated with cognitive impairment, possibly due to disrupted phosphate metabolism and cerebrovascular dysfunction. Meanwhile, Klotho deficiency accelerates oxidative injury, neuroinflammation, and synaptic loss. These findings imply that maintaining a balanced FGF23/Klotho axis may be essential for long-term preservation of brain function.

SOST, which negatively regulates Wnt signaling and is strongly upregulated under conditions of bone resorption and mechanical unloading, has recently attracted attention as a therapeutic target due to its dual role in skeletal and cognitive aging (Jiao et al., 2023). Mouse experiments demonstrate that excessive SOST is associated with memory impairment and network dysfunction, while SOST inhibition restores Wnt signaling, enhances synaptic resilience, and partially reverses cognitive decline (Yuan et al., 2023; Nagarajan et al., 2024). Taken together, these findings highlight that bone-derived hormones do not act in isolation, but rather form an interconnected signaling network that shapes brain homeostasis, either promoting neural integrity (as in OCN and Klotho) or accelerating degeneration (as in SOST excess).

In summary, bone-derived factors exert profound effects on brain aging by modulating synaptic plasticity, amyloid metabolism, neuroinflammation, oxidative stress, and energy homeostasis. OCN appears to be a major protective signal that sustains cognitive function, whereas SOST serves as a pro-degenerative mediator linking osteoporosis with neuroinflammation and amyloid pathology. OPN acts as a bidirectional regulator of neuroimmune responses, while the FGF23/Klotho axis influences phosphate metabolism, oxidative stress tolerance, and neuronal resilience. These discoveries collectively reshape the traditional understanding of bone as a passive scaffold and instead position it as a pivotal endocrine regulator of cognition. As research advances, bone-derived hormones are expected to become promising biomarkers and intervention targets for preventing age-related cognitive decline and neurodegenerative diseases.

Measuring bone-derived factors in human trials faces several challenges. First, individual differences, such as age, sex, and exercise habits, significantly affect the levels of these factors. Secondly, current measurement methods like enzyme-linked immunosorbent assay and mass spectrometry have limited sensitivity, especially for detecting low-concentration factors, and are prone to interference from physiological states and environmental factors. Additionally, the impact of exercise type, intensity, and duration on the release of bone-derived factors varies, making it challenging to determine the optimal time window for measurement. When translating findings from animal models to human applications, species differences and experimental conditions may not align. Animal studies often use higher intensity exercise, which is difficult to replicate in human trials. Future research needs multi-center, standardized clinical trials, combined with multi-omics data, to improve the translation of animal model findings.

OCN promotes neurogenesis and enhances synaptic plasticity by activating the BDNF signaling pathway, thereby positively impacting brain function. Therefore, recombinant OCN is considered to have potential as an alternative treatment for patients who are unable to engage in high-intensity exercise. However, applying bone-derived factors in clinical treatment still presents some challenges. First, the biological activity of OCN in the body is complex, and its mechanisms of action are not yet fully understood, especially in different disease contexts. Secondly, long-term use of OCN may lead to some side effects, such as impacts on bone metabolism and immune system function. Therefore, more clinical trials are needed to validate its safety and efficacy, and further assess its potential for use in patients unable to exercise.

Interaction between bone signals and the central nervous system

The interaction between the skeletal system and the CNS forms a complex bidirectional regulatory network that extends beyond traditional concepts of motor control and mechanical adaptation. The CNS regulates bone remodeling through neural and hormonal pathways, while bone-derived endocrine signals, in turn, influence neuronal activity, synaptic plasticity, emotion, and cognition. Together, these interconnected regulatory circuits form a functional bone–brain axis that integrates skeletal homeostasis with higher-order brain functions and systemic energy metabolism (Kosmidis et al., 2018; Patricia da Silva et al., 2023; Chen et al., 2025; Li et al., 2025a).

On the efferent side of this axis, the CNS modulates bone remodeling primarily through the autonomic nervous system and hypothalamic neuropeptide signaling. Sympathetic outflow, for instance, plays a major role in bone metabolism: norepinephrine released from sympathetic nerve terminals binds to β2-adrenergic receptors on osteoblasts, inhibiting bone formation and enhancing bone resorption. Meanwhile, hypothalamic neuropeptides, such as neuropeptide Y, agouti-related peptide, and pro-opiomelanocortin–derived peptides, can influence osteoblast and osteoclast activity by regulating both systemic hormones and local bone remodeling signals. Through these neural circuits, the hypothalamus integrates metabolic cues, circadian rhythms, and emotional stress to shape bone turnover, forming a CNS→bone regulatory loop that links skeletal homeostasis to whole-body physiological states. These mechanisms demonstrate that bone remodeling is not merely a passive process driven by mechanical loading, but a dynamic, centrally regulated process influenced by neuroendocrine commands.

Conversely, a growing body of evidence has demonstrated that bone-derived hormones act as afferent signals that transmit skeletal status back to the brain, forming the reciprocal bone→CNS axis. OCN, particularly its uncarboxylated form (ucOCN), is the most well-characterized afferent messenger in this system. ucOCN can efficiently cross the BBB and accumulate in key cognitive regions, such as the hippocampus, brainstem, and midbrain (Freus et al., 2025). Once in the CNS, ucOCN promotes the synthesis of monoamine neurotransmitters, including dopamine, serotonin, and norepinephrine, while reducing γ-aminobutyric acid synthesis. By shifting the balance toward excitatory and modulatory neurotransmission, OCN enhances learning, memory consolidation, and emotional resilience. Behaviorally, this hormone has been shown to reduce anxiety-like symptoms and improve hippocampal-dependent spatial learning, highlighting its neurotrophic and psychoregulatory functions. Through these mechanisms, OCN acts as a molecular mediator that couples skeletal activity to cognitive and emotional outcomes.

In addition to monoamine regulation, OCN also modulates intracellular signaling pathways implicated in cognitive aging, particularly insulin signaling and the phosphatidylinositol 3-kinase/protein kinase B cascade. By improving neuronal glucose utilization and mitochondrial energy metabolism, OCN enhances the metabolic efficiency of hippocampal neurons and protects them from age-related decline. This metabolic role may be especially relevant in neurodegenerative disorders, such as AD, in which insulin resistance and impaired glucose metabolism are prominent pathogenic features.

Beyond OCN, the FGF23–Klotho signaling axis represents another important bone-derived regulatory pathway influencing CNS function. FGF23, produced by osteocytes, requires the co-receptor Klotho for downstream activity. Notably, Klotho is expressed in selected brain regions and exhibits a wide range of neuroprotective properties, including antioxidative effects, anti-inflammatory functions, and synaptic maintenance. Experimental studies have shown that Klotho preserves calcium homeostasis, promotes oligodendrocyte maturation, and stabilizes neuronal networks, thereby supporting cognitive performance. In animal models, enhanced Klotho expression improves learning and memory, whereas Klotho deficiency results in premature cognitive decline. Meanwhile, FGF23 may influence neuronal excitability and vascular function, potentially linking mineral dysregulation to cognitive impairment.

Taken together, these findings demonstrate that bone signals and CNS circuits maintain a continuous feedback loop in which neural pathways guide skeletal remodeling, and bone-derived factors reciprocally shape brain physiology. This bidirectional bone–brain communication network challenges the traditional view of bone as merely a mechanical organ, instead placing it at the center of neuroendocrine regulation of cognition, metabolism, and aging. Understanding these pathways provides new theoretical foundations for interventions targeting neurodegeneration, emphasizing that strategies aimed at improving skeletal health, through exercise, endocrine modulation, or metabolic regulation, may also serve as promising approaches for preserving cognitive function across the lifespan (**Figure 2**).

Changes in the bone–brain axis in aging and cognitive decline

With advancing age, the regulatory balance of the bone-brain axis becomes progressively disrupted, leading to declines in both skeletal integrity and cognitive performance. A growing number of clinical and experimental studies have demonstrated that circulating levels of key bone-derived hormones, including OCN and the anti-aging protein α-Klotho, decrease markedly after middle age in both humans and animal models. These reductions show a strong negative correlation with the degree of cognitive impairment, suggesting that the age-related weakening of bone endocrine function contributes directly to neurodegenerative processes (Bradburn et al., 2016; Gerosa and Lombardi, 2021). Interestingly, population-based studies indicate that the relationship between OCN levels and cognitive outcomes is more pronounced in females, possibly due to sex hormone–dependent differences in osteoblast activity, metabolic regulation, and postmenopausal bone loss. In contrast, findings in males remain inconsistent, implying that sex-specific endocrine interactions may modulate how skeletal aging influences brain function.

Aging is accompanied by osteoporosis, reduced bone mineral density, and impaired bone remodeling, conditions that frequently coexist with cognitive decline and dementia. In patients with AD, abnormalities in bone metabolism are commonly observed, including disrupted calcium–phosphate balance, altered osteoblast/osteoclast activity, and decreased OCN and Klotho concentrations (Ruggiero et al., 2024). These observations support the concept that the bidirectional regulatory pathways between bone and the brain become dysregulated with age. When CNS-derived signals that normally guide bone turnover weaken, skeletal homeostasis deteriorates; meanwhile, the decline in bone-derived endocrine

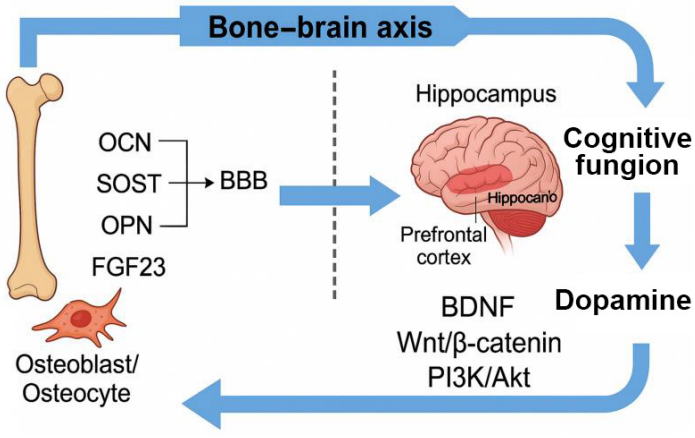

Figure 2 | **Effect of bone–brain axis on cognitive function via osteoblast-derived factors.**
Akt: Protein kinase B; BBB: blood–brain barrier; BDNF: brain-derived neurotrophic factor; FGF23: fibroblast growth factor 23; OCN: osteocalcin; OPN: osteopontin; PI3K: phosphatidylinositol 3-kinase.

signals reduces neuroprotection, forming a pathological feedback loop that accelerates neurodegeneration. This reciprocal impairment suggests that osteoporosis and cognitive decline are not merely parallel aging outcomes, but interconnected manifestations of a failing bone–brain communication system.

Multiple age-related biological stressors further aggravate this decline. Chronic low-grade inflammation, oxidative stress, mitochondrial dysfunction, and bone marrow stromal cell senescence collectively impair the synthesis and secretion of key hormones, such as OCN and Klotho. In aged bone tissue, inflammatory cytokines and senescence-associated secretory phenotypes suppress osteoblast function and reduce endocrine signaling output, thereby weakening the bone's ability to regulate neurotransmission, synaptic plasticity, and neuronal survival. Simultaneously, reduced Klotho availability diminishes antioxidant defenses in the brain, disrupts calcium homeostasis, and compromises neuronal energy metabolism, making the CNS more vulnerable to age-related insults and protein aggregation.

Experimental evidence strongly supports the causal role of bone-derived factors in cognitive aging. In aged OCN-knockout mice, hippocampal-dependent learning and memory deteriorate rapidly, and anxiety-like behaviors increase. However, supplementation with exogenous OCN can restore cognitive function, normalize neurotransmitter synthesis, and alleviate anxiety phenotypes, demonstrating that maintaining OCN signaling is essential for preserving brain health (Khrimian et al., 2017; Gerosa and Lombardi, 2021). Similarly, genetic or pharmacological enhancement of Klotho expression in mice leads to improved synaptic function, enhanced learning and memory performance, and delayed onset of cognitive aging, reinforcing its role as a central neuroprotective factor within the bone–brain axis (Laszczyk et al., 2017). These findings suggest that age-related declines in OCN and Klotho are not merely biomarkers of aging, but active drivers of neurodegeneration.

In summary, aging disrupts the homeostatic feedback mechanisms of the bone–brain axis through hormonal decline, inflammation, oxidative stress, and skeletal degeneration. The resulting reduction in bone-derived endocrine signals removes an important layer of neuroprotection, increasing susceptibility to cognitive decline and neurodegenerative diseases, such as AD. Understanding these age-dependent alterations highlights the bone–brain axis as a promising therapeutic target and suggests that restoring bone endocrine function, through exercise, pharmacological modulation, or metabolic interventions, may offer new strategies to prevent or slow cognitive aging.

New Detection and Analytical Methods for Bone–Brain Axis

Multi-omics in exercise-regulated bone-brain axis

Multi-omics technologies have become powerful tools for dissecting the complex regulatory networks through which exercise influences the bone–brain axis (**Additional Table 1**). In longitudinal exercise intervention cohorts and animal models, the integration of single-cell and spatial transcriptomics, mass-spectrometry-based proteomics, and targeted or untargeted metabolomics enables researchers to map pathway-level reprogramming across the bone–bone marrow–circulation–brain continuum. These approaches allow for a systems-level understanding of how exercise reshapes multi-organ communication, providing molecular evidence for the coordinated benefits of physical activity on skeletal homeostasis and cognitive function (Aebersold and Mann, 2003; Patti et al., 2012; Hasin et al., 2017).

Transcriptomic profiling of bone tissue, bone marrow niches, and distinct brain regions, such as the hippocampus, hypothalamus, and cortex, can reveal exercise-driven changes in gene expression networks that regulate osteogenesis, neuroplasticity, inflammation, and neuroendocrine signaling. Single-cell RNA sequencing further enables the identification of cell-type-specific regulatory programs, uncovering how osteoblasts, osteocytes, microglia, astrocytes, and neuronal subpopulations respond heterogeneously to exercise stimuli. Spatial transcriptomics extends these findings by preserving anatomical context, allowing researchers to visualize the localized expression of bone–brain axis-related genes and signaling receptors within intact tissue architecture. For instance, the spatial transcriptomics platform developed by Ståhl et al. (2016), enables three-dimensional visualization of exercise-responsive molecular pathways at near-cellular resolution.

Proteomics provides complementary information by quantifying changes in protein abundance, secretion, and receptor-mediated signaling pathways. Mass-spectrometry-based secretome and plasma proteomics are particularly valuable for clarifying the endocrine dimension of the bone–brain axis, including the exercise-induced modulation of OCN, SOST, FGF23, and their downstream receptor networks. These datasets can help determine how exercise intensity, duration, and mechanical loading influence bone-derived hormone release, post-translational modifications, and ligand–receptor signaling cascades within the CNS. In addition, brain proteomics captures exercise-induced changes in synaptic proteins, mitochondrial enzymes, and neurotrophic signaling pathways, offering mechanistic insight into how skeletal endocrine signals translate into improved synaptic plasticity and cognitive resilience.

Metabolomics further enriches this multi-omics framework by characterizing exercise-regulated shifts in metabolic pathways, including energy metabolism, oxidative stress responses, amino acid turnover, lipid signaling, and inflammatory mediators. Since metabolic dysfunction is a shared pathogenic feature of osteoporosis and cognitive decline, metabolomic profiling serves as a critical bridge linking exercise physiology to bone–brain crosstalk. Combined analysis of circulating metabolites, bone marrow metabolic flux, and brain metabolic reprogramming can reveal how exercise restores systemic homeostasis and supports neuronal survival through improved mitochondrial efficiency, reduced reactive oxygen species, and suppression of chronic inflammation.

By integrating transcriptomic, proteomic, and metabolomic datasets, multi-omics approaches enable the construction of causal inference networks and quantitative models that describe the dose–response relationship between exercise type or intensity and the strength of bone–brain signaling. Advanced computational tools, including multi-omics factor analysis, Bayesian network inference, and machine-learning-based trajectory modeling, allow researchers to identify core regulatory hubs, predict exercise-responsive biomarkers, and discover candidate therapeutic targets.

In addition to canonical omics layers, extracellular vesicle (EV) omics has emerged as a new dimension in bone–brain axis research (Yáñez-Mó et al., 2015). Exercise has been shown to alter the molecular cargo of bone-derived EVs, including microRNAs, lipids, and peptides, which can enter the circulation and influence brain function by modulating gene expression and cell–cell communication at distant sites. EV-mediated signaling thus represents a crucial mechanism of inter-organ communication that multi-omics approaches are uniquely suited to decode.

High-resolution molecular imaging and cross-organ signal tracing

High-resolution molecular imaging has become an indispensable strategy for visualizing and decoding the dynamic interactions of the bone–brain axis *in vivo*. These technologies allow researchers to monitor exercise-induced remodeling of skeletal tissue while simultaneously assessing functional and pathological changes in the CNS. By integrating imaging signals across organs, it becomes possible to construct a synchronized "bone activity–brain network" map, thereby providing direct evidence for how peripheral skeletal signals influence neural circuits and cognitive outcomes in real time (Even-Sapir et al., 2007).

On the skeletal side, ^{18}F-NaF positron emission tomography (PET)/computed tomography offers quantitative insight into bone remodeling, mineralization status, and microdamage repair. This modality is highly sensitive to osteoblastic activity, making it well-suited for evaluating how different exercise paradigms modulate bone turnover and mechanical adaptation. When paired with micro-computed tomography or high-resolution peripheral quantitative computed tomography, researchers can visualize bone microarchitecture, cortical porosity, and trabecular integrity with exceptional anatomical precision. These assessments provide the structural foundation for studying how mechanical loading and exercise-induced bone signals originate.

In parallel, multimodal brain PET imaging enables the simultaneous examination of amyloid deposition, glucose metabolism, neuroinflammation, and neurotransmitter system changes. Amyloid PET and tau PET allow direct monitoring of AD-related pathology, while ^{18}F-fluorodeoxyglucose-PET reflects neuronal energy metabolism, and emerging tracers targeting 18-kDa translocator protein or microglial activation map inflammatory processes within the CNS. Complementing PET, functional magnetic resonance imaging provides information on neural activity, brain connectivity, and exercise-related enhancement of hippocampal and cortical network efficiency. When bone and brain scans are acquired longitudinally, cross-organ imaging correlations can be established to reveal whether increases in bone remodeling parallel improvements in neural network connectivity or cognitive performance.

In animal models, high-resolution near-infrared fluorescence imaging and *in vivo* imaging system offer powerful tools for tracing molecular messengers along the bone–brain axis. By fluorescently labeling bone-derived EVs, OCN, or recombinant bone-secreted proteins, researchers can directly visualize their biodistribution, including their ability to cross the BBB. This approach provides real-time kinetic information about the timing, intensity, and tissue selectivity of skeletal signals after exercise or pharmacological stimulation. These methods are especially valuable for demonstrating causal directionality, showing that bone-derived factors do not merely correlate with CNS changes, but actively reach and influence brain regions involved in cognition and emotion.

At the mechanistic level, bone-specific Cre transgenic mouse models (such as OCN-Cre or DMP1-Cre lines) enable cell-type-specific labeling or manipulation of skeletal endocrine pathways. When combined with reporter systems, these models make it possible to identify which bone cell populations release specific

signaling molecules during exercise. Likewise, stable isotope pulse–chase tracing provides quantitative measurements of molecular half-life, turnover rates, and cross-organ transport flux of bone-derived hormones within the CNS (Morishita et al., 2015; Turkheimer et al., 2015). By applying these techniques in aging or disease models, investigators can determine whether exercise accelerates the delivery of beneficial bone signals to the brain, prolongs their retention, or alters BBB transport efficiency.

Together, high-resolution imaging and cross-organ tracing technologies provide a multidimensional framework for uncovering how skeletal endocrine signals travel, where they accumulate, and how they reshape neural circuits. When integrated with multi-omics data and behavioral phenotyping, these tools can ultimately clarify the temporal sequence of exercise-induced adaptations, enabling a mechanistic understanding of how maintaining bone health contributes to cognitive resilience across the lifespan.

Wearable and remote monitoring for dynamic assessment of bone-brain axis

With the advancement of digital health technologies, wearable sensors, remote sampling platforms, and telemetric monitoring systems have opened new possibilities for dynamically studying the bone–brain axis in real-world environments. Unlike traditional laboratory-centered approaches, which capture only limited time points, digital health tools enable continuous, multi-dimensional acquisition of behavioral, physiological, and biochemical signals, offering an unprecedented opportunity to investigate how exercise modulates cross-organ communication over time. For example, wrist-worn accelerometers can continuously quantify physical activity intensity, step count, gait parameters, and sedentary duration, allowing objective assessment of habitual movement patterns rather than relying on self-reported data. Meanwhile, measures, such as heart rate variability, sleep staging, respiration rate, and peripheral body temperature collected through wearable trackers provide real-time insights into the "exercise dose–autonomic nervous system–sleep" axis, which is closely linked to both skeletal remodeling and cognitive function (Piwek et al., 2016; Doherty et al., 2017).

In parallel, remote biological sampling technologies are reshaping biomarker research related to the bone–brain axis. Home-based collection of dried blood spot samples makes it feasible to monitor circulating concentrations of key bone-derived hormones, including OCN, SOST, and FGF23, at multiple time points without requiring frequent hospital visits. By synchronizing biomarker fluctuations with wearable-derived behavioral rhythms, researchers can characterize temporal coupling between exercise, bone endocrine output, and downstream effects on brain function. In addition, digital cognitive assessment platforms administered via smartphone or tablet enable repeated testing of memory, attention, reaction time, and executive function in natural home settings. When integrated with bone biomarker trajectories and exercise behavior metrics, this approach makes it possible to construct individualized, longitudinal datasets that capture the dynamic behavior of the bone–brain axis rather than relying on static snapshots.

The next transformative step lies in computational integration. By applying artificial intelligence and machine-learning algorithms to multi-source digital datasets, researchers can build personalized predictive models that identify which individuals are "high responders" or "low responders" to specific exercise interventions. Multimodal data fusion techniques, such as deep learning, Bayesian inference, and network-based modeling, enable mapping of causal relationships among exercise dose, autonomic regulation, sleep rhythms, bone hormone secretion, and cognitive trajectories. This approach provides a framework for optimizing individualized exercise prescriptions tailored to maximize bone-endocrine benefits and cognitive protection. Moreover, predictive modeling can aid in determining exercise thresholds or "minimum effective doses" required to trigger beneficial bone-derived endocrine responses, thereby facilitating precision exercise medicine.

Digital health technologies also support long-term follow-up and closed-loop management systems, allowing real-time feedback and adaptive intervention strategies. For instance, wearable-triggered alerts or app-based coaching can adjust exercise intensity when heart rate variability decreases, sleep quality deteriorates, or physical activity drops below personalized thresholds. Over months or years, such closed-loop systems can generate high-resolution trajectories of bone-derived hormone dynamics, brain function markers, and behavioral adaptations, offering valuable insights into the sustained effects of exercise on the bone–brain axis and aging-related cognitive resilience (Demirev, 2013). Ultimately, the integration of wearables, remote biomarkers, digital cognition, and AI-driven analytics represents a powerful paradigm for advancing mechanistic research, guiding individualized interventions, and enabling large-scale, population-level monitoring of exercise–bone–brain interactions in daily life.

Mechanisms of Exercise on the Bone–Brain Axis

Physical activity and exercise, as non-pharmacological interventions, have been shown to provide multiple benefits for both the skeleton and the brain. The traditional view holds that exercise enhances cognitive function by improving cerebral blood flow, promoting neuroplasticity, and increasing the levels of neurotrophic factors (such as BDNF) (Walsh and Tschakovsky, 2018; Liu et al., 2020; Gaitán et al., 2021). More recent studies, however, reveal that the positive effects of exercise on cognition also involve endocrine pathways mediated by the bone-brain axis.

The role of the bone–brain axis is reflected in multiple aspects. First, exercise stimulates bone cells to release bone-derived factors, such as OCN and irisin, through mechanical loading and muscle-bone communication. These factors can enter the brain via the bloodstream and promote neurogenesis, enhance synaptic plasticity, and thus improve cognitive functions like learning and memory. Additionally, bone-derived factors also have anti-inflammatory effects, which can reduce neuroinflammation, a crucial process for slowing age-related cognitive decline. Studies have shown that OCN can enhance synaptic transmission efficacy by activating the BDNF signaling pathway, promoting neurogenesis in the hippocampal region, and playing a role in cognitive protection (**Figure 3**).

Exercise enhances bone-derived hormone secretion

Regular exercise is now recognized not only as a mechanical stimulus for bone remodeling but also as a powerful endocrine regulator that enhances the secretion of bone-derived hormones with systemic benefits. Repetitive mechanical loading during exercise activates osteoblasts and osteocytes, improving bone formation, mineralization, and paracrine and endocrine signaling. Numerous animal studies have demonstrated that aerobic and resistance exercise training significantly elevate circulating levels of ucOCN, which in turn improves whole-body energy metabolism, skeletal muscle performance, and cognitive outcomes (Miyamoto et al., 2018; Nicolini et al., 2020). This endocrine response positions the skeleton as an active participant in exercise-induced health benefits rather than a passive load-bearing structure.

Growing evidence suggests that the cognitive benefits of exercise may be partly attributed to increased OCN secretion. OCN can cross the BBB, bind to neuronal receptors, and enhance synaptic plasticity and neurotransmitter synthesis. To explain these coordinated changes, researchers have proposed the "IL-6/gp130/OCN axis" hypothesis, which integrates skeletal muscle activity with bone endocrine output and brain function. During exercise, contracting skeletal muscle releases myokines, most notably IL-6. IL-6 acts in an endocrine manner and binds to the gp130 co-receptor expressed on osteoblast and osteocyte surfaces, stimulating intracellular pathways that promote OCN synthesis and secretion (Chowdhury et al., 2020; Zhao et al., 2023; Li et al., 2025a). This mechanism highlights a muscle–bone communication loop whereby myokines serve as upstream exercise responders that entrain bone endocrine output.

Once released, OCN acts on the brain to improve glucose utilization, mitochondrial efficiency, and neuronal firing stability. These effects are particularly prominent in the hippocampus, a brain region essential for learning and memory. OCN has been shown to enhance long-term potentiation, regulate monoamine neurotransmitters, and support hippocampal neurogenesis, mechanisms consistent with improved cognitive flexibility and memory encoding. Shan et al. (2023) demonstrated that activation of this muscle–bone–brain signaling cascade contributes to exercise-induced cognitive improvements in obese animal models, suggesting that OCN serves as a critical molecular bridge linking metabolic health and brain function.

This process can be summarized as a positive feedback loop: skeletal muscle contraction → IL-6 secretion → activation of gp130 signaling in bone → stimulation of OCN release → OCN acting on the brain to enhance synaptic plasticity and metabolic efficiency. Through this loop, exercise amplifies its systemic impact, coordinating metabolic, skeletal, and neural adaptations that collectively support cognitive resilience. Importantly, this mechanism provides a theoretical framework to explain why exercise remains one of the most effective non-pharmacological strategies for preventing age-related cognitive decline.

Moreover, OCN secretion appears to be sensitive to exercise modality and intensity. Weight-bearing activities and high-impact mechanical loading generally produce greater osteogenic signaling than low-impact aerobic exercise, suggesting that specific exercise prescriptions may optimize endocrine outcomes. As research continues to expand, the IL-6/gp130/OCN axis is emerging as a promising therapeutic target for designing precision exercise interventions aimed at improving both skeletal and cognitive health.

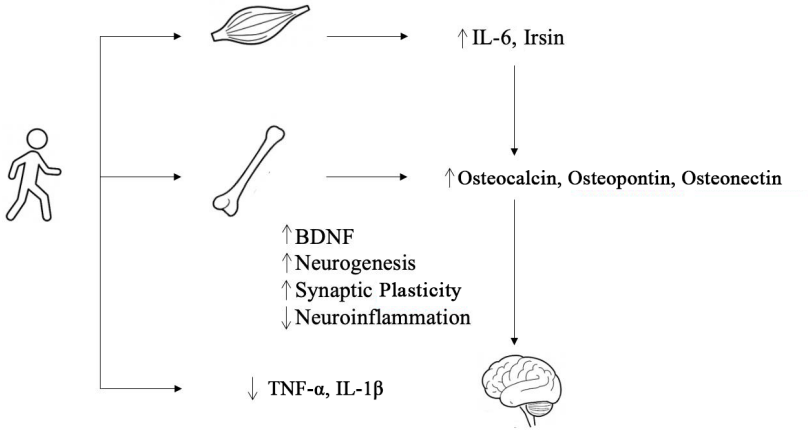

Figure 3 | **Mechanisms of exercise on the bone–brain axis.**
BDNF: Brain-derived neurotrophic factor; IL: interleukin; TNF-α: tumor necrosis factor α.

Synergy between exercise-induced myokines and bone-derived factors

During exercise, skeletal muscle functions as a powerful endocrine organ, secreting a wide range of myokines that exert systemic effects on metabolism, bone remodeling, and brain function. Among these factors, irisin, a cleavage fragment of the membrane protein FNDC5, has attracted particular attention for its neuroprotective and pro-cognitive effects. Exercise upregulates FNDC5 expression in skeletal muscle, leading to increased irisin release into the bloodstream. Once circulating, irisin can cross the BBB and act directly on hippocampal neurons to increase BDNF expression, promote adult neurogenesis, and enhance synaptic adaptability (Jo and Song, 2021; Inyushkin et al., 2023; Villamil-Parra and Moscoso-Loaiza, 2024; Choi and Balakrishnan, 2026). These effects contribute to improved learning, memory, and emotional stability, making irisin one of the most important molecular mediators of exercise-induced cognitive enhancement.

Recent findings suggest that irisin does not act alone, but instead forms a synergistic endocrine network with bone-derived OCN, linking muscle activity to skeletal endocrine output and ultimately to brain function. On one hand, irisin has been shown to enhance osteoblastic differentiation and bone formation, which may further promote OCN secretion from bone tissue. On the other hand, OCN improves skeletal muscle energy utilization by facilitating glucose and fatty acid uptake, thereby enhancing muscle endurance and increasing the capacity for sustained exercise. This creates a reciprocal feedback loop in which muscle-derived signals promote bone endocrine activity, and bone-derived hormones, in turn, optimize muscle metabolic efficiency, collectively amplifying the systemic benefits of exercise (Kirk et al., 2020). Through this bidirectional relationship, irisin and OCN co-regulate metabolic homeostasis, cognitive function, and neuroplasticity, forming the core of a muscle–bone–brain communication axis.

Shi et al. (2025) highlighted that exercise-induced OCN and irisin are central mediators of the bone–muscle–brain axis, emphasizing their cooperative roles in supporting neuroplasticity, emotional regulation, and cognitive resilience. By jointly increasing BDNF signaling, improving neuronal energy metabolism, and suppressing neuroinflammation, these molecules offer a mechanistic explanation for why exercise is particularly effective in delaying age-related cognitive decline and neurodegenerative progression. The synergy between myokines and bone-derived endocrine factors also illustrates why exercise outperforms single-target pharmacological treatments: exercise simultaneously engages multiple organs that reinforce one another through shared molecular pathways.

Experimental evidence further supports this synergistic model. In aged or metabolically impaired animal models, interventions that enhance both bone and muscle signaling yield superior outcomes compared to single-tissue strategies. For example, studies combining creatine supplementation with exercise demonstrated synergistic improvements in both muscle performance and bone integrity, while also producing measurable benefits in hippocampal function and behavior (Kreider et al., 2017; Stares and Bains, 2020; Forbes et al., 2022). These findings suggest that therapeutic strategies targeting the muscle–bone–brain axis, rather than treating organs in isolation, may unlock more effective approaches for preventing or reversing cognitive decline.

In summary, the interaction between exercise-induced myokines and bone-derived hormones represents a highly coordinated endocrine network that supports systemic adaptation to physical activity. Irisin enhances OCN secretion and neuroplasticity, while OCN improves muscle metabolic efficiency and endurance, together forming a positive feedback loop that amplifies the health benefits of exercise at the molecular, cellular, and behavioral levels. Understanding this synergy provides a critical conceptual foundation for the development of multi-target exercise interventions and combined therapeutics designed to simultaneously preserve musculoskeletal health and protect cognitive function throughout aging.

Exercise regulates bone marrow immunity and inflammation

Exercise exerts profound anti-inflammatory and immunoregulatory effects, and an emerging body of evidence suggests that these benefits are mediated, at least in part, through the bone–immune–brain axis. The bone marrow serves as the primary hematopoietic and immune organ, continuously producing hematopoietic stem cells, immune progenitors, and circulating immune cells that influence systemic and central immune homeostasis. Moderate and sustained physical exercise has been shown to enhance the renewal capacity of hematopoietic stem cells and mesenchymal stem cells within the bone marrow, improving the marrow microenvironment and restoring balanced immune function (Scheffer and Latini, 2020; Peng et al., 2022; Yang et al., 2022; Xiang et al., 2024). By modulating hematopoietic activity, exercise influences downstream immune signaling that reaches the brain via both humoral and cellular pathways, thereby contributing to neuroprotection.

One of the hallmark features of aging is chronic low-grade inflammation, often termed "inflammaging," characterized by persistently elevated levels of pro-inflammatory cytokines, such as TNF-α and IL-1β. This inflammatory state disrupts tissue homeostasis throughout the body, accelerates skeletal aging, and promotes neuroinflammation that contributes to cognitive decline. Exercise counteracts this process through multiple mechanisms. First, exercise reduces visceral fat mass and improves systemic metabolism, thereby decreasing adipose-derived pro-inflammatory cytokines. Second, regular training increases circulating anti-inflammatory mediators, including IL-10, helping to restore a healthier immune balance in elderly individuals (Shan et al., 2019). Through these processes, exercise attenuates chronic inflammation at its source, both within the bone marrow niche and in peripheral tissues, ultimately reducing inflammatory signals that reach and activate microglia in the brain.

In addition to systemic cytokine modulation, exercise-induced changes in bone-derived endocrine factors further reinforce anti-inflammatory protection. OCN, which increases in response to exercise, has been reported to exert direct immunomodulatory effects. For instance, in Parkinson's disease models, OCN suppresses microglial and astrocytic activation, leading to reduced production of TNF-α and IL-1β in affected brain regions (Guo et al., 2018). By limiting glial overactivation, OCN helps maintain synaptic integrity and neuronal survival. Thus, OCN functions not only as a metabolic and neuroplasticity regulator but also as an anti-inflammatory mediator that acts on both the immune system and the CNS.

Taken together, these findings indicate that the bone marrow plays a central intermediary role: exercise improves marrow hematopoiesis → restores immune balance → reduces systemic inflammation → suppresses neuroinflammation → protects cognition. This multi-step cascade demonstrates how exercise generates dual benefits for the brain, directly through bone-derived hormones and indirectly through inflammatory regulation. Reduced neuroinflammation is especially critical for preventing age-related cognitive decline, since chronic activation of microglia and astrocytes is known to impair synaptic plasticity, disrupt neuronal metabolism, and accelerate neurodegenerative pathology.

In summary, exercise acts on the bone–immune–brain axis by rejuvenating bone marrow immunity, reducing pro-inflammatory signaling, and enhancing the anti-inflammatory capacity of bone-derived endocrine factors. By simultaneously targeting inflammation at peripheral, skeletal, and central levels, exercise provides a powerful multi-system defense that supports cognitive resilience across the lifespan.

Exercise promotes neuroregeneration

Bone-derived factors, such as OCN, OPN, and osteonectin, are involved not only in bone metabolism but also in crossing the BBB. They act on receptors in cognitive-related brain regions, such as the hippocampus and prefrontal cortex, to regulate the expression of key molecules like BDNF and vascular endothelial growth factor, thereby promoting neuronal axon growth, synaptic remodeling, and hippocampal-dependent learning and memory (Morland et al., 2017; Sayyah et al., 2022; Lee et al., 2023). Exercise is an important exogenous stimulus that activates the bone-brain axis. Numerous animal and clinical studies have shown that aerobic exercise can significantly increase the levels of bone-derived factors, enhance OCN secretion, and activate the Wnt/β-catenin and TrkB-cyclic adenosine monophosphate response element binding protein signaling pathways, promoting hippocampal dentate gyrus neurogenesis, increasing the number of newborn neurons, and enhancing synaptic plasticity (Woo et al., 2013; Cheng et al., 2020; Ying et al., 2021; Sullivan et al., 2022; Park et al., 2023). At the same time, exercise-induced upregulation of bone-derived factors can increase BDNF concentrations, which play a critical role in neurogenesis, axon guidance, and synaptic stabilization. Long-term regular exercise can increase hippocampal volume and improve spatial memory. Additionally, exercise also has a positive effect on regulating neuroinflammation and optimizing the neuronal microenvironment. Exercise reduces excessive activation of microglia, increases the secretion of anti-inflammatory factors (such as IL-6 and IL-10), thereby alleviating neuroinflammation and improving the neurogenic environment (Su et al., 2022; Li et al., 2023; Pahlavani, 2023). In AD models, exercise-induced secreted proteins, such as Clusterin, can significantly reduce inflammation levels, promote the survival of newborn neurons, and improve cognitive function.

At the cellular protection level, moderate exercise can reduce the apoptosis rate of hippocampal neurons and delay the loss of neuronal cells in aging and pathological conditions. Studies have shown that moderate-intensity treadmill exercise can reduce stress-induced hippocampal cell apoptosis by about 40%, while swimming training inhibits Fas-dependent and mitochondrial-dependent apoptotic pathways, and reduces the activation of inflammatory signaling, thus enhancing hippocampal neuron survival (Lin et al., 2020; Amirazodi et al., 2022). This neuronal protection provides a stable cellular foundation for neuroregeneration and works synergistically with synaptic repair.

Overall, exercise plays multiple roles in the intervention of age-related cognitive decline through the bone-brain axis: on one hand, exercise increases the levels of bone-derived factors, mobilizing neurotrophic factors, such as BDNF, to promote neurogenesis and synaptic plasticity; on the other hand, exercise reduces neuroinflammation and decreases apoptosis, optimizing the microenvironment for neuroregeneration. These mechanisms work together to delay the process of cognitive decline and improve the cognitive function of patients with neurodegenerative diseases.

Multi-Organ Networks in Cognitive Function Regulation

Age-related cognitive decline does not occur in isolation but is the result of changes in multiple systems. There are complex interactions between bone, muscle, immune, endocrine, and other multi-organ networks, which play an important role in maintaining cognitive function. In recent years, interdisciplinary research has emerged to explore how various systems in the body collectively influence the aging process of the brain.

Bone-muscle coupling and cognition

The skeleton and skeletal muscles form an integrated musculoskeletal unit that supports locomotion, postural stability, and metabolic homeostasis. However, beyond their mechanical partnership, accumulating evidence indicates that bone and muscle engage in constant biochemical crosstalk, releasing endocrine factors that influence each other's physiology and, indirectly, brain function (Shi et al., 2025). With advancing age, osteoporosis and sarcopenia commonly develop in parallel, a condition referred to as "osteosarcopenia," characterized by decreased bone density, reduced muscle mass, and impaired muscle strength. Osteosarcopenia is closely associated with elevated risks of falls, fractures, frailty, disability, and cognitive decline, underscoring the interdependence of bone, muscle, and brain aging.

During physical activity, mechanical stress and muscle contractions stimulate bone formation through both biomechanical forces and endocrine pathways. Myokines released from contracting muscle, such as irisin, IL-6, and BDNF, promote osteoblastic activity, enhance bone remodeling, and improve skeletal microarchitecture (Kim, 2022; Kang et al., 2025). In turn, healthy bone tissue secretes hormones, such as OCN, that enhance muscle glucose uptake, mitochondrial function, and endurance capacity. This creates a reciprocal muscle–bone signaling loop that allows both tissues to adapt synergistically

to exercise. When this loop is disrupted during aging, declines in muscle force production can reduce skeletal loading, accelerating bone loss, while impaired bone endocrine signaling further diminishes muscle function, creating a downward spiral that contributes to frailty and cognitive vulnerability.

The musculoskeletal system also communicates with the brain through multiple endocrine and neural channels. Exercise-induced release of BDNF is well known for its central effects on hippocampal neurogenesis, synaptic plasticity, and memory formation. However, emerging studies suggest that BDNF may also act on bone cells via the muscle–bone axis, influencing bone remodeling and linking neuromuscular activity to skeletal adaptation. Meanwhile, bone-derived OCN acts on the brain to enhance learning, memory, and neurotransmitter synthesis, illustrating that bone is not merely a passive mechanical structure but an active endocrine organ contributing to cognitive maintenance. These interconnected pathways support the concept that musculoskeletal health is tightly coupled to brain health across the lifespan.

Because bone and muscle degeneration frequently progress simultaneously, interventions targeting only one tissue may fail to prevent cognitive decline. Therefore, understanding bone–muscle–brain synergy is essential for developing strategies against cognitive aging. Resistance and strength training, for example, can increase muscle mass, boost myokine release, and impose osteogenic loading on the skeleton, thereby improving bone mineral density and reducing osteoporotic risk. Clinical studies in older adults show that resistance exercise not only preserves musculoskeletal integrity but also improves executive function, attention, gait stability, and overall quality of life. These benefits highlight that cognitive protection may be optimized when exercise prescriptions are designed to simultaneously stimulate both muscle and bone rather than focusing on aerobic training alone.

In summary, bone–muscle coupling represents a critical biological bridge linking physical function and cognitive health. Aging-related musculoskeletal degeneration contributes to neurodegeneration through reduced endocrine signaling, chronic inflammation, impaired metabolism, and decreased physical activity. Conversely, enhancing muscle strength and protecting bone integrity through targeted exercise can activate beneficial bone- and muscle-derived factors, helping maintain cognitive resilience in aging populations. This integrated perspective supports a multisystem approach to healthy aging, positioning musculoskeletal training as a cornerstone for preventing both physical frailty and cognitive decline.

Bone marrow immunity and neuroinflammation

Bone marrow is a central hub of immune cell production, and its functional state plays a decisive role in shaping inflammatory responses throughout the body, including within the CNS. With aging, the bone marrow undergoes profound structural and functional alterations, including increased adipogenesis, reduced hematopoietic stem cell function, immune cell dysregulation, and chronic low-grade inflammation. These changes can trigger excessive output of pro-inflammatory cytokines and aberrant immune cell phenotypes, which in turn contribute to neuroinflammation and neuronal vulnerability. Mononuclear macrophages originating from the bone marrow are capable of infiltrating the CNS and differentiating into microglia-like cells, where they participate in immune surveillance and inflammatory responses in the brain (Han et al., 2018). When the bone marrow immune system becomes imbalanced, these peripheral immune cells can exacerbate microglial activation and amplify neuroinflammatory cascades.

Bone marrow aging, also termed "immune senescence," is associated with increased production of TNF-α, IL-1β, and other inflammatory mediators, along with impaired regulation of adaptive immunity. These systemic inflammatory signals can reach the brain through humoral pathways or through infiltrating immune cells, promoting glial overactivation and synaptic dysfunction. Neurodegenerative diseases, such as AD, are often accompanied by pathological changes in the bone marrow microenvironment, including dysfunctional hematopoiesis and an imbalance between pro- and anti-inflammatory immune cell populations (Leimkühler and Schneider, 2019; Wu et al., 2019). As a result, aging bone marrow indirectly accelerates cognitive decline by fueling chronic neuroinflammation, which disrupts neuronal homeostasis, weakens synaptic integrity, and diminishes neurogenesis.

Meanwhile, the communication between bone marrow and the CNS is bidirectional, meaning that pathological changes in brain function can feed back to impair bone marrow immunity. Stress, depression, chronic sympathetic activation, and elevated glucocorticoid levels can suppress bone marrow hematopoietic activity, impair immune cell renewal, and decrease bone mass through altered autonomic signaling. This creates a vicious feedback loop in which CNS dysfunction worsens bone marrow impairment, and bone-derived immune abnormalities further aggravate neuroinflammation. Therefore, bone and brain aging are not isolated phenomena but are intertwined through a shared immune network.

Hormonal changes provide another key link in this tri-network. For example, estrogen decline after menopause leads to both accelerated bone loss and heightened inflammatory responses, conditions strongly associated with increased risk of cognitive impairment (Russell et al., 2019; Stefanowski et al., 2023). The simultaneous onset of osteoporosis and neuroinflammation in postmenopausal women illustrates how endocrine imbalance destabilizes the bone–immune–brain axis. Therefore, bone marrow–derived immune dysregulation becomes an important contributor to long-term neurodegenerative progression.
In summary, maintaining bone marrow immune balance is crucial for controlling neuroinflammation and protecting cognitive function during aging. When any component of the bone–immune–brain network is disrupted, whether through bone loss, immune imbalance, or neuroinflammatory overload, systemic homeostasis collapses, accelerating brain aging and cognitive decline. Therapies that target immune regulation in the bone marrow, combined with strategies that preserve skeletal health, may therefore represent effective approaches for preventing neuroinflammation-driven neurodegeneration.

Endocrine system changes

In advanced age, multiple endocrine axes undergo functional decline, and these hormonal alterations exert profound, simultaneous effects on bone density, muscle mass, metabolism, and cognitive function. Among the most affected systems are the growth hormone–IGF-1 axis and the gonadal axis, both of which play essential roles in maintaining skeletal integrity, neuromuscular health, and brain plasticity. For example, age-related reductions in growth hormone, IGF-1, estrogen, and testosterone weaken osteoblast activity and accelerate bone loss, while also contributing to sarcopenia and diminished physical performance. At the neural level, these hormonal declines correlate with reduced synaptic plasticity, impaired executive function, and increased vulnerability to anxiety and depressive symptoms (Braverman et al., 2009; Islam et al., 2019). This multi-organ decline demonstrates how endocrine aging is a critical upstream driver of musculoskeletal degeneration and cognitive impairment.

Beyond sex hormones and growth hormone–IGF-1, metabolic endocrine dysfunction exerts an equally strong influence on brain aging. Insulin resistance and glucose metabolism disorders, commonly seen in elderly individuals with type II diabetes, are well established as risk factors for cognitive decline, hippocampal atrophy, and AD–related pathology. The brain is a metabolically demanding organ, and disruptions in insulin signaling impair neuronal glucose utilization, mitochondrial function, and long-term potentiation. These changes promote oxidative stress, neuroinflammation, and synaptic degeneration. Importantly, OCN serves as an endocrine modulator linking bone metabolism to glucose regulation, as it enhances insulin sensitivity and stimulates pancreatic insulin secretion. Thus, OCN deficiency in aging may help explain why metabolic disorders and cognitive impairment frequently coexist, forming a shared pathophysiological pathway that connects bone, endocrine, and brain aging.

In light of these observations, some researchers have proposed the concept of "OCN syndrome," which postulates that OCN deficiency acts as a unifying mechanism underlying several age-related comorbidities, including osteoporosis, cognitive impairment, and impaired glucose tolerance (Shan et al., 2019). Although this hypothesis remains under investigation, it underscores the importance of multi-system interactions and highlights OCN as a central endocrine signal bridging metabolism and neurobiology. If validated, this framework could reshape clinical strategies by emphasizing interventions that restore bone-derived endocrine function as a means to simultaneously target metabolic and cognitive decline.

In addition to OCN, hormonal changes in cortisol, thyroid hormones, and adipokines also influence brain aging and the bone–brain axis. Chronic stress and elevated cortisol, for instance, suppress bone formation and impair hippocampal neurogenesis, while abnormal thyroid function alters both skeletal turnover and cognitive speed. These endocrine disturbances contribute to a vicious cycle, where hormonal decline accelerates bone fragility and neurodegeneration, which in turn worsen systemic stress responses and autonomic imbalance. This cyclical deterioration illustrates that endocrine aging is not an isolated process but part of a tightly interconnected network.

Collectively, these findings highlight that maintaining endocrine balance is essential for preserving musculoskeletal and cognitive health in old age. Exercise, nutritional strategies, and targeted endocrine therapies may help restore or compensate for aging-related hormonal decline, thereby protecting both the skeleton and the brain. As research advances, endocrine modulation of the bone–brain axis is likely to emerge as a promising intervention target for preventing neurodegenerative processes and promoting healthy aging.

Role of Exercise in the Prevention and Treatment of Cognitive Decline

With the deepening research on the bone-brain axis, the traditional "one-size-fits-all" exercise prescription is no longer sufficient to meet the diverse needs of aging populations for cognitive protection. In recent years, the concept of precision medicine has gradually been integrated into exercise interventions (**Additional Table 2**). By leveraging biomarkers, digital technologies, and combination therapies, innovative strategies are emerging to delay cognitive decline and optimize treatment outcomes.

Personalized exercise prescription based on biomarkers

Bone-brain axis–related factors, such as OCN, SOST secreted by osteocytes, FGF23, and the muscle-derived myokine irisin, are considered important biomarkers that reflect the interaction between bone and brain functions (Gerosa and Lombardi, 2021; Shi et al., 2025). By dynamically measuring the levels of these factors in plasma or EVs, it is possible to evaluate individual bone-brain axis activity and predict responsiveness to exercise interventions. For instance, Bradburn et al. (2016) reported that serum OCN levels in older adults were positively correlated with hippocampal volume and cognitive performance, suggesting that OCN could serve as a monitoring indicator for exercise-induced cognitive benefits. In the future, a "test–intervene–feedback" loop can be established to continuously adjust exercise type and intensity, thereby achieving a truly personalized and precise exercise prescription. Furthermore, combining genetic and epigenetic analyses, such as BDNF gene polymorphisms or exercise-related DNA methylation sites (Liu et al., 2020), can help stratify individuals into high- and low-response groups. This approach allows for maximizing the benefits of exercise interventions while minimizing ineffective physical burdens.

Integrating virtual reality with neurorehabilitation training

The emergence of virtual reality and augmented reality technologies has expanded the scope of exercise training beyond traditional physical environments, offering older adults an immersive, multisensory rehabilitation experience (Valmaggia et al., 2016). Exercise tasks performed within virtual reality environments can simultaneously improve balance, gait, and muscle strength while activating neural circuits in the prefrontal cortex and hippocampus, thereby reinforcing both motor and cognitive pathways. For example, in a randomized controlled trial, Liao et al. (2020) found that combining virtual reality with aerobic exercise significantly enhanced executive function and memory in individuals with mild cognitive impairment. Furthermore, integrating virtual reality with brain-computer interfaces and neurofeedback

systems enables real-time monitoring of brain activity and personalized adjustment of training protocols. This promotes neural plasticity and cognitive recovery. Such approaches may also enhance bone-brain axis interventions by strengthening the stimulation of OCN or BDNF signaling pathways during exercise to optimize cognitive outcomes.

Combined optimization of exercise with nutrition and pharmacotherapy

In some elderly populations, exercise alone may not achieve sufficient therapeutic effects, especially among individuals with rapid progression of osteoporosis or cognitive impairment. As a result, combined strategies that integrate exercise with nutritional and pharmacological interventions have gained increasing attention. From a nutritional perspective, supplementation with vitamin D, calcium, and omega-3 fatty acids has been shown to synergistically enhance the effects of exercise on bone metabolism and neuroprotection (Canhada et al., 2018). For instance, a meta-analysis by Fischer et al. (2023) demonstrated that exercise combined with vitamin D supplementation significantly improved bone mineral density and indirectly enhanced cognitive function.

On the pharmacological side, modulators targeting bone-derived factors, such as anti-SOST monoclonal antibodies or FGF23 regulators, may be used alongside exercise in the future to achieve dual activation of the bone-brain axis (Shi et al., 2024).

Additionally, certain anti-inflammatory and neurotrophic drugs, such as IL-6 inhibitors and BDNF sensitizers, combined with exercise, have shown potential for reducing neuroinflammation and promoting neuronal regeneration (Walsh and Tschakovsky, 2018).

Limitations

This review has several limitations that should be acknowledged. First, although extensive literature searches were conducted across multiple international databases, relevant studies may have been missed, especially those published in non-English languages, which could introduce language bias. Second, most of the included studies are preclinical or small-scale clinical trials, and there is a lack of large, multicenter randomized controlled trials to provide high-level evidence for the role of exercise in regulating the bone-brain axis. Third, many mechanistic findings are derived from animal models, which may not fully translate to human physiology and disease processes. Additionally, heterogeneity in exercise protocols, intensity, and participant characteristics among studies makes direct comparisons challenging. Finally, this review did not include unpublished or ongoing studies, which might have led to publication bias and limited the comprehensiveness of the conclusions. Therefore, future research should focus on standardized methodologies, longitudinal human studies, and multi-omics approaches to validate and expand upon these findings.

Conclusion and Future Perspectives

This review comprehensively summarizes the recent progress in understanding how exercise regulates the bone-brain axis and its impact on age-related cognitive decline. The findings highlight that bone is not merely a structural organ but also an active endocrine regulator involved in neurocognitive health. Exercise enhances the secretion of bone-derived factors, such as OCN, SOST, FGF23, and OPN, which cross the BBB and modulate neuronal metabolism, synaptic plasticity, and neurogenesis. These insights provide a novel perspective on the systemic mechanisms through which exercise protects cognitive function and delays neurodegeneration.

Traditionally, studies on exercise and cognition have focused on central mechanisms, such as neurotrophic factors (e.g., BDNF, vascular endothelial growth factor) and cerebral blood flow. This review expands the field by introducing the concept of the bone-brain axis, emphasizing the role of peripheral endocrine signals in cognitive regulation. Compared with previous reviews, this work integrates recent findings from molecular biology, multi-omics research, and imaging studies, including the discovery of OCN's effects via GPR158 signaling and the involvement of SOST in AD pathology. These new insights provide a more comprehensive framework for understanding cross-organ communication in cognitive aging.

Moreover, this review highlights emerging technologies, such as spatial transcriptomics, exosome analysis, and molecular imaging, which allow dynamic tracking of bone-derived signals and their effects on brain function. This interdisciplinary approach offers a deeper mechanistic understanding and supports the development of targeted interventions.

From an application standpoint, identifying bone-derived biomarkers, such as OCN and SOST, enables personalized exercise prescriptions. By monitoring changes in these biomarkers, clinicians can predict individual responsiveness to exercise and adjust interventions accordingly. This biomarker-driven strategy moves beyond generalized recommendations and toward precision healthcare.

Clinically, the strong associations between osteoporosis, bone fragility, and dementia underscore the need to integrate bone health into cognitive care. Early screening and treatment of bone disorders may help reduce the risk of cognitive decline. Furthermore, combining exercise with nutritional supplements (e.g., vitamin D, omega-3 fatty acids) or drugs targeting bone-derived pathways could synergistically enhance therapeutic effects.

Earlier research primarily considered exercise as acting directly on the brain. This review demonstrates that bone-derived signals form a crucial intermediary, explaining why bone diseases and cognitive decline often co-occur. By integrating findings across molecular, systemic, and behavioral levels, this review introduces a multi-organ network perspective that bridges gaps in previous knowledge. The inclusion of novel experimental methods, such as high-resolution imaging and wearable monitoring, represents a forward-looking framework not seen in earlier reviews.

The bone–brain axis concept has broad relevance beyond cognitive decline, potentially impacting other conditions, such as depression, Parkinson's disease, and metabolic disorders. The mechanisms and interventions discussed here are globally applicable, offering a foundation for cost-effective, scalable strategies to promote healthy aging. Exercise-based interventions, particularly when guided by biomarkers and digital health tools, are accessible and adaptable across diverse healthcare systems worldwide.

Future research should focus on large-scale, multicenter trials to validate these findings in diverse populations. Standardizing methods for measuring bone-derived factors and integrating multi-omics data will improve comparability across studies. Additionally, precision interventions that combine exercise, nutrition, and pharmacotherapy should be developed and tested to achieve optimal cognitive protection.

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Additional files:

Additional Table 1: *Emerging research methodologies on the bone–brain axis.*

Additional Table 2: *Summary of exercise-based strategies for cognitive decline from bone–brain axis perspective.*

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