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REVIEW

THE EXERCISE-INDUCED IRISIN–BDNF AXIS: A SYSTEMATIC REVIEW OF EVIDENCE AND TRANSLATIONAL IMPLICATIONS

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ABSTRACT

Background: Exercise is a central regulator of metabolic and neurotrophic processes, in which irisin and brain-derived neurotrophic factor (BDNF) play key roles in mediating muscle–brain communication.
Objective: This systematic review aimed to summarize the effects of different exercise modalities and immobilization on irisin and BDNF expression, focusing on the PGC-1α–FNDC5–irisin signaling pathway.
Methods: The review followed the PRISMA 2020 guidelines. Studies published between January 1995 and September 2025 were identified through PubMed, Scopus, Web of Science, and Google Scholar using Boolean search combinations ('irisin' AND 'BDNF' AND 'exercise'). Inclusion criteria covered human and animal studies exploring the irisin–BDNF axis. Data were extracted independently and synthesized qualitatively. Risk of bias was assessed using Cochrane domains. *Results:* Evidence indicates endurance, resistance, and high-intensity interval training increase circulating irisin and hippocampal BDNF levels. Acute exercise induces transient increases, whereas chronic training produces sustained adaptations. Immobilization reduces both irisin and BDNF expression.
Conclusions: Current evidence suggests the PGC-1α–FNDC5–irisin–BDNF axis may constitute a molecular link between skeletal muscle activity and brain health; causal conclusions are limited by the associative and largely preclinical nature of the evidence. This review was not prospectively registered. Methodological heterogeneity precluded meta-analysis. Data extraction sheets and full search strings are available as supplementary material.

KEYWORDS

Irisin, BDNF, exercise, neuroplasticity, FNDC5, PGC-1α, hippocampus, resistance training

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INTRODUCTION

Regular exercise is widely acknowledged as a significant protective factor against various pathological processes, including cardiovascular diseases and neurodegenerative disorders linked to cognitive impairments and decline[1]. When it comes to brain health, all forms of exercise positively impact cerebral plasticity, leading to improved cognitive performance in areas such as learning and memory, while also promoting psychological and physical well-being[2,3].

Irisin and brain-derived neurotrophic factor (BDNF), the focus of this systematic review, are myokines that play significant roles in muscle metabolism[2]. Irisin, a myokine dependent on peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α), is a proteolytic product of fibronectin domain-containing protein[4] (FNDC5), which is a membrane protein found in muscles. Following aerobic exercise, irisin activates the PGC-1α - FNDC5/irisin pathway, leading to the browning of white adipose tissue[5].

On the other hand, BDNF is a member of the neurotrophin family, which includes nerve growth factor (NGF) and neurotrophins NT-3, NT-4/5, NT-6, and NT-7. Neurotrophins are crucial for the regulation of various neural processes[5]. Among the neurotrophins, BDNF exhibits the highest expression in the brain and serves as a key mediator of the beneficial effects of exercise on brain health[5-6].

Recent studies suggest that two myokines may interact with each other following exercise, establishing a connection between PGC1α, a nuclear transcriptional coactivator (not a secreted/circulating protein) that is upregulated in skeletal muscle during exercise and drives FNDC5/irisin expression, and the roles of FNDC5 and BDNF in hippocampal expression[7]. It is proposed that elevated levels of irisin in the circulation due to exercise can cross the blood-brain barrier and subsequently stimulate brain-derived neurotrophic factor (BDNF) production in the hippocampus. This interaction between irisin and BDNF appears to enhance neuronal proliferation and neural differentiation (including dendritic remodeling) in the hippocampus[6]. Furthermore, it contributes to synaptic plasticity and neurogenesis, ultimately influencing reward, learning, and motivation. These findings imply that the brain is instrumental in promoting plasticity in memory and learning processes, with potential implications for both physiological and pathological conditions, such as Alzheimer's disease[8-11].

The present review aims to systematically evaluate the effects of various exercise modalities on the irisin–BDNF signaling pathway, following PRISMA guidelines. Based on the data in the literature, the critical question in our study is to detect how exercise can activate the PGC1α – FNDC5 – BDNF pathway neurologically in the brain and muscle.

Exercise and BDNF

Brain-derived neurotrophic factor (BDNF) is a vital neurotrophin that significantly influences neuronal survival, synaptic plasticity, and cognitive function. It operates as a key player in maintaining the health of neurons and supporting the mechanisms that underlie learning and memory processes[12]. In the realm of exercise physiology, BDNF has emerged as an essential molecular mediator that links physical activity with neuroplastic adaptations—changes in the brain's structure and function that enhance its ability to adapt and reorganize[13]. Research has shown that both acute bouts of exercise, such as a single session of vigorous activity, and chronic exercise, which refers to regular physical activity over an extended period, can elevate levels of BDNF in both the bloodstream and the brain[14-18].

This elevation in BDNF levels is believed to facilitate several important physiological processes:

Neurogenesis: Exercise stimulates the production of new neurons from neural stem cells, particularly in the hippocampus, an area of the brain crucial for learning and memory. This process is associated with improved cognitive functions and emotional regulation[19].

Long-term potentiation (LTP): LTP is a persistent strengthening of synapses based on recent patterns of activity and is fundamentally important for learning and memory. Increased BDNF promotes LTP, thereby enhancing synaptic efficiency and connectivity[20-22].

Improving learning and memory: Enhanced BDNF levels correlate positively with improved cognitive performance, indicating a direct role of BDNF in the consolidation and retrieval of memories[23,24].

The underlying mechanisms through which exercise influences BDNF levels are multi-faceted.

Increased neuronal activity: Physical activity raises the functional demands on neural circuits, resulting in increased neurotrophin expression, including BDNF[25,26].

PGC-1α/FNDC5 signaling: Exercise can upregulate the expression of PGC-1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha) and its downstream effector FNDC5 in skeletal muscle. This signaling pathway is crucial for the release of irisin, a hormone that may promote BDNF expression in the brain[27-30].

Enhanced cerebral blood flow: Physical activity increases blood flow to the brain, which may aid in delivering essential nutrients and oxygen necessary for neuronal health and could facilitate the transport of BDNF. In contrast, physical inactivity or immobilization is linked to a significant reduction in BDNF expression[31]. Low levels of BDNF may contribute to impaired synaptic plasticity, decreased neurogenesis, and a heightened risk of cognitive decline, making it essential to promote regular physical activity. Understanding the bidirectional relationship between exercise and BDNF is crucial not only for appreciating the neurophysiological benefits of physical activity but also for developing targeted interventions aimed at preserving neuromuscular and cognitive health across the lifespan[32]. Such strategies can play a significant role in mitigating age-related cognitive decline and in the

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treatment of various neurodegenerative disorders[33]. In summary, the relationship between exercise and BDNF underscores the importance of maintaining an active lifestyle for cognitive health, and continues to be a vital area of research in neuroscience and exercise physiology[34-36].

Exercise and irisin

Irisin is a myokine derived from the proteolytic cleavage of fibronectin type III domain-containing protein 5 (FNDC5). It serves as a crucial molecular bridge connecting the dynamism of skeletal muscle activity to the vast landscape of systemic metabolic regulation[37]. Engaging in exercise—especially endurance and resistance training—stirs the expression of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) within skeletal muscle. This cascade triggers the transcription of FNDC5, culminating in the release of irisin into the bloodstream[35-37]. Irisin exerts several reported physiological effects. It actively promotes the browning of white adipose tissue, igniting increased thermogenesis through the upregulation of uncoupling protein-1 (UCP1), and enhances overall energy expenditure across the body[35]. Additional reported effects include modulation of hypertrophy signaling, attenuation of oxidative stress, and promotion of mitochondrial biogenesis[36]. Preclinical evidence suggests irisin may cross the blood-brain barrier and stimulate BDNF expression, potentially contributing to neuroplasticity and cognitive function; this remains to be confirmed in well-controlled human studies[37]. Importantly, irisin measurement via commercial ELISA kits lacks standardization, warranting caution in cross-study comparisons. However, a decline in physical activity or periods of immobilization trigger a reduction in PGC-1α and FNDC5 expression, leading to diminished circulating levels of irisin.

This drop may hinder essential processes such as muscle remodeling, disrupt metabolic balance, and ultimately impact brain health, reflecting the potential importance of physical activity for metabolic and neurological health[38] *(Fig. 1)*.

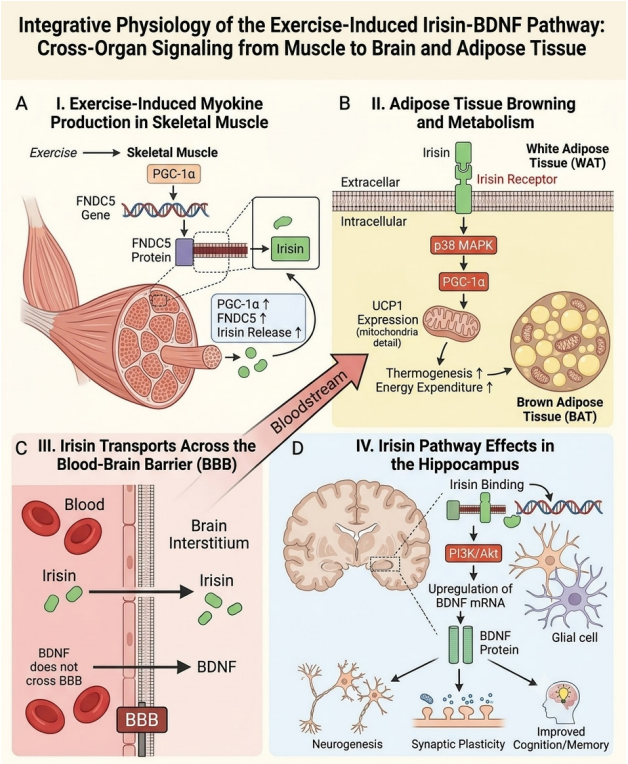


Figure 1. *Integrative physiology of the exercise-induced irisin-bdnf pathway: cross-organ signaling from muscle to brain and adipose tissue. A) Physical exercise stimulates the activation of PGC-1α in skeletal muscle, driving FNDC5 gene expression and subsequent synthesis of FNDC5 pro-peptide. Proteolytic cleavage of FNDC5 releases the myokine irisin into the bloodstream. B) In white adipose tissue (WAT), circulating irisin binds to its receptor, activating the p38 MAPK/PGC-1\alpha axis. This upregulates mitochondrial UCP1 expression, inducing adipose tissue browning, thermogenesis, and enhanced energy expenditure. C) Peripheral irisin successfully crosses the blood-brain barrier (BBB) into the brain interstitium, whereas peripheral BDNF does not readily cross the BBB. D) Within the hippocampus, irisin binding triggers the PI3K/Akt downstream pathway, leading to the upregulation of BDNF mRNA and protein expression. This cascade promotes neurogenesis, synaptic plasticity, and glial cell support, ultimately improving cognition and memory.*

BDNF-PGC-1α-FNDC5-irisin pathway

Engaging in endurance and resistance exercises serves as a powerful stimulus for both neuronal and muscular activation, leading to the induction of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) expression in skeletal muscle[39] PGC-1α acts as a transcriptional coactivator, regulating genes involved in mitochondrial biogenesis and energy metabolism, thereby serving as a key coordinator of exercise-induced muscle adaptation. One of its primary downstream targets is fibronectin type III domain-containing protein 5 (FNDC5), the transcription of which is enhanced by PGC-1α. FNDC5 then undergoes proteolytic cleavage, resulting in the release of irisin, a soluble myokine, into the bloodstream[37-42].

Once secreted, irisin may exert effects peripherally and centrally. Preclinical evidence suggests it can cross the blood-brain barrier, where it has been shown to upregulate BDNF expression, particularly in the hippocampus, though this mechanism requires confirmation in human studies[43]. Elevated BDNF levels are associated with neurogenesis, enhanced synaptic plasticity, and improved cognitive performance in preclinical and human studies, suggesting a link between peripheral muscle activity and brain health. Concurrently, circulating irisin facilitates the browning of white adipose tissue by upregulating uncoupling protein-1 (UCP1), which increases thermogenesis and systemic energy expenditure. This integrated pathway highlights the role of exercise as a systemic regulator of both metabolic and neurotrophic balance[29,33,44] *(Fig. 1)*.

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Author (Year)	Focus	Key findings	Implications
Leger (2024)[4]	Exercise intensity and FNDC5/ Irisin–BDNF interaction	High-intensity exercise ↑ FNDC5/ Irisin & hippocampal BDNF; suggests muscle-brain signaling.	Supports exercise prescription targeting intensity for cognitive/ neurological benefits.
Farshbaf (2021)[20]	Skeletal muscle-brain axis, mental health	Exercise can enhance brain function and mental health via irisin-mediated pathways.	Potential therapeutic role of exercise in neuropsychiatric disorders.
Xu (2024)[1]	T2DM mice, hippocampal neurogenesis	Exercise ↓ inflammation, ↑ hippocampal neurogenesis & memory; mediated by irisin signaling.	Highlights therapeutic potential of exercise for T2DM-related cognitive impairment.
Chen (2017)[2]	Epigenetic regulation of BDNF expression	Exercise alters epigenetic marks at BDNF promoters, influencing expression in brain disorders.	Reveals epigenetic basis for exercise effects on BDNF in neurodegeneration.
Kaus (2017)[48]	Early-life exercise and histone modifications	Early-life exercise programs alter histone modifications → long-term ↑ BDNF expression.	Suggests early-life exercise can reprogram brain development for long-term benefit.
Dicarlo (2023)[21]	Irisin effects on neurotrophins, depression	Irisin modulates neurotrophin/ cytokine expression in hippocampus & prefrontal cortex.	Implications for depression treatment and neuroinflammation modulation via irisin.
Kazeminasab (2022)[22]	Acute vs chronic exercise, aerobic vs anaerobic	Acute exercise ↑ irisin more than chronic; aerobic > anaerobic; resistance training shows additive effects.	Design of exercise interventions must consider type, intensity, and duration to optimize irisin release.
Farshbaf (2021)[20]	Irisin treatment on stress-related behavior	Irisin administration blocks stress-induced anxiety-like behavior & memory deficits in male mice.	Potential use of irisin as a therapeutic target for stress-related disorders.
Liu (2020)[23]	Ischemic stroke and neuroprotection	Exercise-induced irisin alleviates ischemic brain injury via neuroprotection mechanisms.	Supports exercise as adjunct therapy for stroke rehabilitation and recovery.
Ceylan (2024)[24]	Sex, obesity, cognitive impairment and exercise prescription	Contextual factors (sex, obesity, age) influence irisin/BDNF dynamics; calls for personalized exercise protocols.	Calls for sex- and disease-specific exercise programs to maximize neurotrophic effects.

Table 1. *Epigenetic regulation of irisin & BDNF post-exercise.*

Author (year)	Focus	Key findings	Implications
Vaynman (2004)[26]	Exercise-induced memory and cognitive function (MWM test in animals)	Exercise ↑ BDNF → improved memory/cognition; BDNF critical mediator post-immobilization.	Supports BDNF as a therapeutic target for post-immobilization cognitive deficits.
Patterson (1996)[27]	BDNF knockout mice, hippocampal synaptic plasticity	Recombinant BDNF rescues synaptic transmission & hippocampal LTP deficits in knockout mice.	Highlights BDNF replacement strategies for neurodegenerative or cognitive disorders.
Moreno-Navarrete (2013) [28]	Diabetic human subjects, irisin levels	Irisin levels ↓ in diabetics; indicates loss of beige/brown fat characteristics; therapeutic target potential.	Potential for irisin-targeted interventions to improve insulin sensitivity & metabolic health.
Martinowich (2003)[29]	Epigenetic regulation of Bdnf gene (CpG methylation)	↑ BDNF synthesis correlates with ↓ CpG methylation in Bdnf regulatory region → epigenetic control.	Epigenetic therapies may be used to boost BDNF levels for neural repair and plasticity.
Nibuya (1995)[30]	ECS and antidepressant drug treatment, neuronal survival	ECS & antidepressants ↑ BDNF and trkB mRNA → enhanced neuroprotection & neuronal survival.	Suggests combined exercise & pharmacological modulation to maximize neurotrophic benefits.

Table 2. *Bioinformatics modeling of irisin/BDNF pathways post-immobilization.*

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Author (year)	Focus	Key findings	Implications
Cosio (2021)[31]	Older adults, progressive resistance training programs	Resistance training ↑ brain and circulating irisin levels, especially in progressive programs.	Supports progressive resistance training as a tool to enhance irisin and promote healthy aging.
Belviranli (2018)[32]	Aging-induced decreases in BDNF/irisin (cardiac, hepatic, plasma)	Resistance training mitigates aging-induced ↓ in BDNF & irisin levels across tissues.	Highlights systemic benefits of resistance training in reversing age-related decline in neurotrophins.
Eidukaitė (2023)[33]	Elderly individuals, 12-week resistance training pilot study	12-week resistance training ↑ total BDNF levels; beneficial for exercise outcomes.	Encourages inclusion of resistance training in elderly populations for cognitive health.
Afshar (2025)[34]	Strength training effects on myokines (irisin, BDNF, follistatin, myostatin)	Strength training ↑ irisin, BDNF, follistatin; ↓ myostatin, suggesting anabolic & neuroprotective effects.	Potential clinical use of strength training to enhance neuroplasticity and muscle-brain crosstalk.
Trombeta (2021)[35]	Cognitive function, dementia risk, HIV-associated dementia	↑ BDNF levels linked with ↓ risk of cognitive disorders; resistance training may reduce dementia risk.	Suggests resistance training as a non-pharmacological intervention for dementia prevention.

Table 3. *Influence of resistance training on brain irisin levels.*

MATERIALS AND METHODS

The review adhered to PRISMA 2020 standards. Databases searched included PubMed, Scopus, Web of Science, and Google Scholar, covering the period from January 1995 to September 2025. Boolean operators (AND, OR) were applied to combine: 'irisin', 'BDNF', 'exercise', 'resistance training', 'FNDC5', 'PGC-1α', 'neuroplasticity', 'cognitive function'. Full database-specific search strings are provided as supplementary material. Studies eligible for inclusion comprised experimental or clinical research linking exercise to the expression of irisin or BDNF. *In vitro*-only studies, pharmacological interventions, and incomplete datasets were excluded from consideration. The study selection process was conducted by the primary reviewer (E.M.), with a second independent reviewer validating all screening and selection decisions; disagreements were resolved by consensus. Data extraction employed standardized templates, and the risk of bias was assessed qualitatively using domains adapted from the Cochrane risk of bias tool. Given the heterogeneity of study designs (RCTs, observational, animal experiments), design-appropriate considerations were applied to each study type rather than a single universal instrument. Due to heterogeneity, effect measures were not statistically pooled; instead, results were synthesized narratively. Certainty of evidence was not formally graded using the GRADE framework. Qualitatively, it is considered low to moderate, reflecting heterogeneity in study designs and the predominantly preclinical nature of mechanistic evidence. This review was not prospectively registered. The findings of this review were organized under thematic headings and classified according to factors such as exercise intensity, type (aerobic or resistance), duration (acute or chronic), and population characteristics. Data are presented in three distinct tables *(Table 1, 2, and 3)*.

Risk of bias in studies

The methodological quality and risk of bias of the included studies were assessed qualitatively based on key domains adapted from the Cochrane risk of bias tool. These domains included:

1) randomization and allocation procedures;
2) blinding of participants and outcome assessors;
3) completeness of outcome data;
4) selective reporting;
5) other potential sources of bias such as conflicts of interest.

As the included studies varied substantially in design and purpose, a formal scoring system was not applied. Instead, the evaluation emphasized transparency in methods and reliability of reported outcomes to inform the qualitative synthesis.

RESULTS

The initial search identified 661 records. After duplicate removal (n = 153) and title/abstract screening (n = 298 excluded), 161 full-texts were assessed, and 24 studies met inclusion criteria. The PRISMA flow diagram *(Fig. 2)* summarizes the selection process. *Tables 1, 2 and 3* report study characteristics, key findings, and implications. Formal publication bias assessment was not conducted (meta-analysis was not performed; funnel plots were not applicable). Accordingly, publication bias cannot be excluded. Certainty of evidence is qualitatively considered low to moderate given heterogeneity in methodology and the predominantly associative and preclinical evidence base. This review underscores the impact of exercise, especially resistance and high-intensity protocols, on the expression of irisin and BDNF. The key findings can be summarized as follows:

Exercise intensity: High-intensity exercise significantly

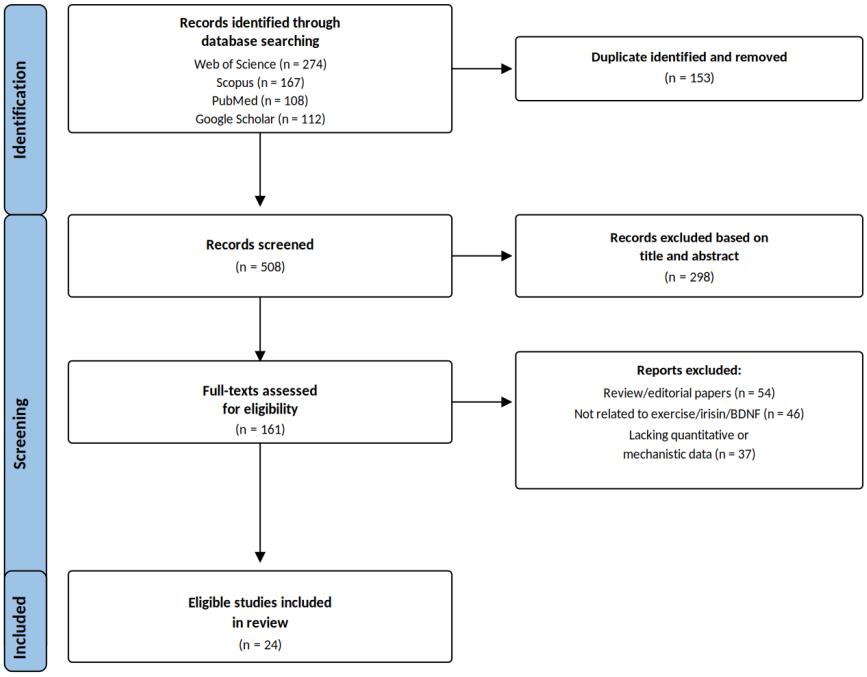


Figure 2. *Flow chart illustrating the selection process for all included and excluded studies.*

enhances levels of FNDC5/irisin and hippocampal BDNF, emphasizing the role of the muscle-brain axis in neuroplasticity.

Resistance training: Participation in resistance and strength training is associated with considerable increases in irisin and BDNF levels, which may be crucial for maintaining cognitive function, particularly among older adults.

Epigenetic regulation: Exercise has been shown to decrease DNA methylation in the promoter regions of the BDNF gene and to increase histone acetylation, resulting in long-lasting alterations in gene expression.

Clinical implications: Elevations in irisin and BDNF may contribute positively to the pathophysiology of conditions such as depression, diabetes, cognitive disorders, and neurodegenerative diseases. *Multifactorial effect:* Factors such as gender, age, obesity, and disease status influence the dynamics of irisin and BDNF; thus, exercise prescriptions should be tailored to individual needs.

In summary, current evidence suggests that exercise activates the muscle-brain axis, which in turn regulates the pathways of irisin and BDNF, culminating in long-term neuroprotective, anti-inflammatory, and cognitive enhancement effects.

DISCUSSION

Exercise, particularly resistance and high-intensity training, is associated with upregulation of the irisin–BDNF axis, with potential benefits for brain and metabolic health. In contrast, immobilization is associated with suppression of this pathway. These findings suggest potential therapeutic relevance of exercise-based interventions; causal conclusions remain premature given the predominantly associative and preclinical evidence base. In recent years, the impact of exercise on irisin and brain-derived neurotrophic factor (BDNF) levels has been the subject of extensive investigation. Systematic reviews and meta-analyses, particularly focusing on high-intensity interval training (HIIT) and resistance training, reinforce the idea that both peripheral and central release of irisin, along with enhanced hippocampal BDNF levels, contribute positively to neuroplasticity and cognitive performance[45-47].

Mechanistic insights: the irisin-BDNF axis

Recent research has indicated that the expression of BDNF within the hippocampus is closely tied to the intensity of physical exercise. Findings reveal that higher exercise intensities lead to a substantial increase in the release of BDNF from muscle tissue, showcasing a dynamic interplay between physical activity and neurochemical responses. Specifically, a study examining the effects of four weeks of HIIT on rats demonstrated significant enhancements in spatial memory, elevated levels of hippocampal BDNF, and increased neurogenesis—surpassing MICT outcomes[48]. Note: hippocampal tissue BDNF and peripheral serum BDNF are not interchangeable measures and should not be conflated across studies. Moreover, another investigation comparing high-intensity aerobic exercise with HIIT revealed a progressive rise in BDNF expression in the brain as exercise intensity escalated. This protocol spanned six weeks and included six training sessions per week, reinforcing the premise that the degree of exertion is a crucial factor in determining neurotrophic factor levels[25]. Intriguingly, findings from additional research indicate that serum levels of irisin, a myokine released during physical activity, exhibit a similar trend to that of hippocampal BDNF expression. Specifically, after engaging in HIIT, serum irisin levels were significantly elevated compared to those recorded following moderate-intensity continuous training conducted five times per week for eight weeks or for six

weeks[2]. Furthermore, when researchers plotted circulating irisin levels against hippocampal BDNF expression, they discovered a noteworthy positive correlation between these two biological markers. Collectively, these studies suggest an association between exercise intensity, circulating irisin, and hippocampal BDNF levels, consistent with the hypothesis that the FNDC5/irisin pathway contributes to exercise-induced neurobiological effects. Causal attribution in humans requires further controlled investigation.

Comparative effects of exercise modalities

The intricate relationship between physical activity, periods of immobilization, and their subsequent impact on the levels of irisin and brain-derived neurotrophic factor (BDNF) represents a vital domain of research, with far-reaching implications for both muscle structure and cognitive function. Recent studies have illuminated how varying levels of exercise intensity and the specific types of physical activities undertaken can greatly affect these critical molecular markers[25]. Notably, high-intensity exercise has been shown to elicit particularly strong responses, leading to significant increases in peripheral FNDC5/irisin concentrations, as well as enhanced expression of BDNF in the hippocampus—an area of the brain essential for memory and learning[8].These findings underscore the importance of exercise in promoting not only muscular health but also neuroplasticity and overall brain health.

The epigenetic regulation of irisin and BDNF expression following exercise has emerged as a crucial mechanism underlying these adaptations. Research indicates that exercise-induced changes in BDNF expression involve complex epigenetic modifications, particularly at BDNF promoters. The skeletal muscle-brain axis, mediated by irisin, plays a fundamental role in exercise-dependent improvements in brain function and mental health, with evidence suggesting that exercise training can reduce inflammation and enhance hippocampal neurogenesis through irisin signaling pathway activation[48-50].

Exercise-induced changes in irisin and BDNF differ between acute and chronic interventions. Acute exercise is associated with transient increases in circulating irisin, with aerobic exercise appearing particularly effective for these short-term responses [51-54]. In stark contrast, the steady rhythm of chronic resistance training appears to cultivate a more profound and enduring accumulation of irisin levels, hinting at distinct biological pathways that govern the adaptations elicited by short bursts versus sustained efforts. Among training modalities, HIIT has been shown in several studies to produce greater increases in circulating irisin compared to moderate-intensity continuous training, with more pronounced effects in younger individuals and those with type 2 diabetes mellitus[55]. These findings may have clinical relevance for individuals with obesity or metabolic disorders, as HIIT has shown favorable effects on irisin in overweight young men in some studies[56].

Effects of immobilization on irisin and brain-derived neurotrophic factor (BDNF) pathways

The effects of immobilization on the irisin–BDNF pathway represent an important, though comparatively understudied, area of this literature[57]. Irisin, a myokine released in response to physical exercise, plays a vital role in regulating metabolism and enhancing cognitive function. It facilitates the conversion of white adipose tissue into brown fat, promoting energy expenditure and improving insulin sensitivity[58-60].

Research has demonstrated that individuals leading sedentary lifestyles tend to exhibit significantly lower levels of irisin in their bloodstream. This decline may contribute to a variety of detrimental health outcomes, particularly in terms of cognitive performance and metabolic health[47]. For instance, reduced irisin levels have been associated with an increased risk of obesity, diabetes, and cognitive decline, including conditions such as dementia. Therefore, understanding the role of irisin within the context of physical activity is crucial for addressing the potential health risks tied to prolonged inactivity and promoting strategies for a more active lifestyle[57-60].

Interplay between irisin and brain-derived neurotrophic factor (BDNF): implications for metabolic and neurodegenerative diseases

The relationship between irisin and metabolic diseases is particularly critical, as low levels of this myokine are linked to several serious health conditions, including type 2 diabetes mellitus, obesity, and cardiovascular disease[59]. For instance, in the context of type 2 diabetes, lower irisin levels have been associated with insulin resistance, highlighting its potential role in glucose metabolism. Similarly, in cases of obesity, impaired irisin signaling may affect the body's energy expenditure, contributing to weight gain and associated health complications[60].

Furthermore, from a neurological perspective, reduced levels of BDNF have been linked to cognitive decline and mood disorders, with irisin being suggested to have a protective effect on neuronal health. The interplay between these two pathways-irisin and BDNF-suggests that lack of physical activity not only hampers metabolic processes but may also have detrimental effects on cognitive functioning, leading to an increased risk of neurodegenerative diseases[42]. Resistance training has demonstrated significant potential for increasing brain irisin levels, particularly in older adults engaging in progressive training programs[26]. Regular resistance exercise is associated with attenuation of aging-related decreases in plasma and tissue BDNF and irisin levels, as well as improvements in strength and favorable myokine profiles including follistatin. These findings are primarily from animal and small human studies and require replication in larger controlled trials[32,53]. The therapeutic implications of these findings are substantial, particularly for neurodegenerative diseases and cognitive decline. Exercise-induced

enhancement of memory appears to be mediated by BDNF with BDNF playing a crucial role in neuronal function and plasticity[45]. The relationship between exercise, irisin, and BDNF suggests potential therapeutic applications for conditions ranging from depression to metabolic disorders, though further research is needed to fully understand the molecular mechanisms involved. Most included studies were small and heterogeneous, limiting the ability to generalize findings.

Limitations and future directions

Due to considerable heterogeneity in study design, sample characteristics, and measurement methodologies, a quantitative meta-analysis could not be performed. Most of the included studies were small and methodologically diverse, which limits the generalizability of the findings. Nevertheless, this comprehensive qualitative analysis reveals the intricate relationships between exercise, immobilization, and their respective effects on irisin and BDNF levels. The evidence consistently supports the beneficial influence of various exercise modalities—particularly high-intensity interval training (HIIT) and resistance training—while highlighting the detrimental impact of immobilization. Collectively, these findings hold significant implications for future research directions and for the development of targeted therapeutic strategies aimed at enhancing neuroplasticity and metabolic health. Exercise, particularly resistance and high-intensity training, is associated with upregulation of the irisin–BDNF axis and potential benefits for neuroplasticity and metabolic health. Physical inactivity is associated with reductions in both markers. Limitations:

1) Substantial heterogeneity precluded meta-analysis;
2) Most mechanistic findings derive from animal models;
3) Human and animal evidence were not always clearly stratified;
4) Irisin assay standardization is lacking;
5) Circulating and hippocampal BDNF were not consistently distinguished;
6) This review was not prospectively registered.

Future research should prioritize standardized protocols, validated assay platforms, adequately powered human trials, and formal GRADE evidence grading.

CONCLUSION

This systematic review synthesizes evidence suggesting the irisin–BDNF axis may mediate exercise-induced effects on muscular and neurological health. Resistance training and HIIT are among the modalities most consistently associated with increased circulating irisin and, in preclinical models, enhanced hippocampal BDNF expression. Epigenetic regulation of BDNF represents a plausible mechanism for sustained neuroplastic adaptations. Conversely, physical inactivity is associated with reductions in both biomarkers. Important caveats: Causal conclusions remain premature — most mechanistic evidence derives from animal studies, human data are heterogeneous and largely associative, and irisin measurement is methodologically challenged. Claimed therapeutic implications for neurodegenerative and metabolic diseases require validation through well-powered prospective human trials with standardized protocols and validated biomarker platforms.

REFERENCES

1. Xu H, Tian X, Wang Y, Lin J, Zhu B, Zhao C, et al. Exercise promotes hippocampal neurogenesis in T2DM mice via the irisin/TLR4/MyD88/NF-κB-mediated neuroinflammation pathway. Biol (Basel). 2024;13:100809. doi: 10.3390/biology13100809.
2. Chen KW, Chen L. Epigenetic regulation of BDNF gene during development and diseases. Int J Mol Sci. 2017;18:30571. doi: 10.3390/ijms18030571.
3. Leger C, Quirie A, Meloux A, Fontanier E, Chaney R, Basset C, et al. Impact of exercise intensity on cerebral BDNF levels: role of FNDC5/irisin. Int J Mol Sci. 2024;25:2121. doi: 10.3390/ijms2502121.
4. Jones KR, Farinas I, Backus C, Reichardt LF. Targeted disruption of the BDNF gene perturbs brain and sensory neuron development but not motor neuron development. Cell. 1994;76:989–99. doi: 10.1016/0092-8674(94)90377-8.
5. Lindsay RM. Nerve growth factors (NGF, BDNF) enhance axonal regeneration but are not required for survival of adult sensory neurons. J Neurosci. 1988;8:2394–405.
6. Poduslo JF, Curran GL. Permeability at the blood–brain and blood–nerve barriers of the neurotrophic factors: NGF, CNTF, NT-3, BDNF. Brain Res Mol Brain Res. 1996;36:280–6. doi: 10.1016/0169-328x(95)00250-v.
7. Aid T, Kazantseva A, Piirsoo M, Palm K, Timmusk T. Mouse and rat BDNF gene structure and expression revisited. J Neurosci Res. 2007;85:525–35. doi: 10.1002/jnr.21139.
8. Pruunsild P, Kazantseva A, Aid T, Palm K, Timmusk T. Dissecting the human BDNF locus: bidirectional transcription, complex splicing, and multiple promoters. Genomics. 2007;90:397–406. doi: 10.1016/j.ygeno.2007.05.004.
9. Halbach OV. BDNF effects on dendritic spine morphology and hippocampal function. Cell Tissue Res. 2018;373:729–41. doi: 10.1007/s00441-017-2782-x.
10. Calabrese F, Molteni R, Racagni G, Riva MA. Neuronal plasticity: a link between stress and mood disorders. Psychoneuroendocrinology. 2009;34(Suppl 1):S208–16. doi: 10.1016/j.psyneuen.2009.05.014.
11. Schwartz PM, Borghesani PR, Levy RL, Pomeroy SL, Segal RA. Abnormal cerebellar development and foliation in BDNF–/– mice reveals a role for neurotrophins in CNS patterning. Neuron. 1997;19:269–81. doi: 10.1016/S0896-6273(00)80938-1.
12. Gharami K, Xie Y, An JJ, Tonegawa S, Xu B. Brain-derived neurotrophic factor overexpression in the forebrain ameliorates Huntington's disease phenotypes in mice. J Neurochem. 2008;105:369–79. doi: 10.1111/j.1471-4159.2007.05137.
13. Wrann CD. FNDC5/irisin – their role in the nervous system and as a mediator for beneficial effects of exercise on the brain. Brain Plast. 2015;1:55–61. doi: 10.3233/BPL-150019.
14. Panja D, Bramham CR. BDNF mechanisms in late LTP formation: a synthesis and breakdown.Neuropharmacology.2014;76:66476.doi: 10.1016/j.neuropharm.2013.06.024.
15. Baj G, Del Turco D, Schlaudraff J, Torelli L, Deller T, Tongiorgi E. Regulation of the spatial code for BDNF mRNA isoforms in the rat hippocampus following pilocarpine treatment. Hippocampus. 2013;23:413–22. doi: 10.1002/hipo.22100.
16. Schmolesky MT, Webb DL, Hansen RA. The effects of aerobic exercise intensity and duration on levels of brain-derived neurotrophic factor in healthy men. J Sports Sci Med. 2013;12:502–11.
17. Jaberi S, Fahnestock M. Mechanisms of the beneficial effects of exercise on brain-derived neurotrophic factor expression in Alzheimer's disease. Biomolecules. 2023;13:11577. doi: 10.3390/biom13111577.
18. El Hayek L, Khalifeh M, Zibara V, Abi Assaad R, Emmanuel N, Karnib N, et al. Lactate mediates the effects of exercise on learning and memory through SIRT1-dependent activation of hippocampal BDNF. J Neurosci. 2019;39:2369–82. doi: 10.1523/JNEUROSCI.1661-18.2019.
19. Adziqa A, Qiantori PTR, Lesmana R, Defi IR, Kastella F, Tarawan V, et al. Exercise-enhanced neurogenesis: a potential remedy for malnourished rat brains. eJ Kedokteran Indones. 2025;12:657–238. doi:

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10.23886/ejki.12.657.238.
20. Farshbaf MJ. Multiple roles in neuroprotection for the exercise-derived myokine irisin. Front Aging Neurosci. 2021;13:649929. doi: 10.3389/fnagi.2021.649929.
21. Dicarlo M, Zerlotin R, Zecca C, Dell'Abate MT, Buccoliero G, Logroscino S, et al. Short-term irisin treatment enhanced neurotrophin expression differently in the hippocampus and the prefrontal cortex of young mice. Int J Mol Sci. 2023;24:6715. doi: 10.3390/ijms24119111
22. Kazeminasab F, Sadeghi E, Afshari-Safavi A. Comparative impact of various exercises on circulating irisin in healthy subjects: a systematic review and network meta-analysis. Oxid Med Cell Longev. 2022;2022:8235809. doi: 10.1155/2022/8235809.
23. Liu Y. The neuroprotective effect of irisin in ischemic stroke. Front Aging Neurosci. 2020;12:588958. doi: 10.3389/fnagi.2020.588958.
24. Ceylan HI, Silva AF, Ramirez-Campillo R, Murawska-Cialowicz E. Exploring the effect of acute and regular physical exercise on circulating brain-derived neurotrophic factor levels in individuals with obesity: a comprehensive systematic review and meta-analysis. Biol (Basel). 2024;13:323. doi: 10.3390/biology13050323.
25. Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur J Neurosci. 2004;20:2580–90. doi: 10.1111/j.1460-9568.2004.03720.x.
26. Patterson SL, Abel T, Deuel TA, Martin KC, Rose JC, Kandel ER. Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. Neuron. 1996;16:1137–45. doi: 10.1016/S0896-6273(00)80140-3.
27. Moreno-Navarrete JM, Ortega F, Serrano M, et al. Irisin is expressed and produced by human muscle and adipose tissue in association with obesity and insulin resistance. J Clin Endocrinol Metab. 2013;98:E769–75. doi: 10.1210/jc.2012-2749.
28. Martinowich K, Hattori D, Wu H, Fouse S, He F, Hu Y, et al. DNA methylation-related chromatin remodeling in activity-dependent BDNF gene regulation. Neuron. 2003;38:943–54. doi: 10.1126/science.1090842.
29. Nibuya M, Morinobu S, Duman RS. Regulation of BDNF and TrkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J Neurosci. 1995;15:7539–47. doi: 10.1523/JNEUROSCI.15-11-07539.1995.
30. Cosio PL, Crespo-Posadas M. Effect of chronic resistance training on circulating irisin: systematic review and meta-analysis of randomized controlled trials. Int J Environ Res Public Health. 2021;18:2021. doi: 10.3390/ijerph18052476.
31. Belviranli M, Okudan N. Exercise training protects against aging-induced cognitive dysfunction via activation of the hippocampal PGC-1α/FNDC5/BDNF pathway. Neurobiol Aging. 2018;70:1–8. doi: 10.1007/s12017-018-8500-3.
32. Eidukaite S, Masiulis N, Kvedaras M. Exploring the preliminary effects of resistance training on total brain-derived neurotrophic factor (BDNF) levels in elderly individuals: a pilot study. Balt J Sport Health Sci. 2023;2:4–10. doi: 10.33607/bjshs.v2i129.1377.
33. Afshar R, Rahmati M, Mirnasouri R. The effect of 12 weeks of strength training on muscular strength, body fat percentage, irisin and BDNF in active middle-aged women. J Arak Univ Med Sci. 2025;28:1–8. doi:10.61186/jams.28.1.1 doi: 10.61186/jams.28.1.1.
34. Trombeta JC, Cavaglieri CR, Bonfante ILP, et al. Combined physical training increases plasma brain-derived neurotrophic factor levels, but not irisin, in people living with HIV/AIDS. Int J Exerc Sci. 2021;14:1004–17. doi: 10.70252/HOMO5275.
35. Afzalpour ME, Chadorneshin HT, Foadoddini M, Eivari HA. Comparing interval and continuous exercise training regimens on neurotrophic factors in rat brain. Physiol Behav. 2015;147:78–83. doi: 10.1016/j.physbeh.2015.04.012.
36. Shirvani H, Arabzadeh E. Metabolic cross-talk between skeletal muscle and adipose tissue in high-intensity interval training vs moderate-intensity continuous training by regulation of PGC-1α. Eat Weight Disord. 2020;25:17–24. doi:10.1007/s40519-018-0491-4.
37. Arabzadeh E, Shirvani H, Ebadi Zahmatkesh M, Riyahi Malayeri S, Meftahi GH, Rostamkhani F. Irisin/FNDC5 influences myogenic markers on skeletal muscle following high- and moderate-intensity exercise training in STZ-diabetic rats. 3 Biotech. 2022;12:193. doi: 10.1007/s13205-022-03253-9.
38. Pignataro M, Dicarlo M, Zerlotin R, Zecca C, Dell'Abate MT, Buccoliero G, et al. FNDC5/Irisin system in neuroinflammation and neurodegenerative diseases: update and novel perspective. Int J Mol Sci. 2021;22:1605. doi: 10.3390/ijms22041605.
39. Radikova Z, Mosna L, Eckerstorfer C, Bajer B, Havranova A, Imrich R, et al. Plasma irisin and brain-derived neurotrophic factor levels in sedentary subjects: effect of 8-week lifestyle intervention. Endocr Regul. 2024;58:115–28. doi: 10.2478/enr-2024-0013.
40. De Sousa R. Molecular crosstalk for longevity: exercise and the AMPK/SIRT1/PGC-1α/Irisin/BDNF axis. Mol Biol Rep. 2025;53(1):142. doi: 10.1007/s11033-025-11315-3.
41. Okamoto M, Mizuuchi D, Omura K, Lee M, Oharazawa A, Yook JS, et al. High-intensity intermittent training enhances spatial memory and hippocampal neurogenesis associated with BDNF signaling in rats. Cereb Cortex. 2021;31:4386–97. doi: 10.1093/cercor/bhab093.
42. Shotaro I, Nishii K, Aizu N, Kito T, Iwata D, Chihara T, et al. Effects of aerobic exercise and resistance training on cognitive function: comparative study based on FNDC5/Irisin/BDNF pathway. Dement Geriatr Cogn Disord. 2024;53:329–37. doi: 10.1159/000541093.
43. Autry AE. Function of brain-derived neurotrophic factor in the hypothalamus: implications for depression pathology. Front Mol Neurosci. 2022;15:1028223.
44. Tilp M, Scharf C, Payer G, et al. Physical exercise during the morning school-break improves basic cognitive functions. Mind Brain Educ. 2020;14(1):24–31. doi:10.1111/mbe.12228
45. Zhai Q, Zeng Y, Gu Y, et al. Time-restricted feeding entrains long-term behavioral changes through the IGF2KCC2 pathway. iScience. 2022;25(5):104267.
46. Jodeir M, Alvi K. Multiple roles in neuroprotection for the exercise-derived myokine irisin. Front Aging Neurosci. 2021;13:649929. doi: 10.3389/fnagi.2021.649929.
47. Michel S, Clark JP, Ding JM, et al. Brain-derived neurotrophic factor and neurotrophin receptors modulate glutamate-induced phase shifts of the suprachiasmatic nucleus. Eur J Neurosci. 2006;24(4):1109–16. doi: 10.1111/j.1460-9568.2006.04972.x.
48. Kraus C, Castren E, Kasper S, Lanzenberger R. Neurosci Biobehav Rev. 2017;77:317–26. doi: 10.1016/j.neubiorev.2017.03.007.
49. Liang X, Ding Y, Lin F, Zhang Y, Zhou X, Meng Q, et al. Overexpression of ERBB4 rejuvenates aged mesenchymal stem cells and enhances angiogenesis via PI3K/AKT and MAPK/ERK pathways. FASEB J. 2019;33(3):4559–70. doi: 10.2478/enr-2024-0013.
50. Arosio B, Calvani R, Ferri E, Coelho-Junior HJ, Carandina A, Campanelli F, et al. Sarcopenia and cognitive decline in older adults: targeting the muscle–brain axis. Nutrients. 2023;15:1853.doi: 10.3390/nu15081853.
51. Azimi M, Gharakhanlou R, Naghdi N, Khodadadi D, Heysieattalab S. Moderate treadmill exercise ameliorates amyloid-β-induced learning and memory impairment possibly via increasing AMPK activity and upregulation of the PGC-1α/FNDC5/BDNF pathway. Peptides. 2018;102:78–88. doi: 10.1016/j.peptides.2017.12.027.
52. Gomes G, Cieszczyk P. Exercise – a unique endogenous regulator of irisin, BDNF, leptin and cortisol against depression. Balt J Health Phys Act. 2020;12(4):1.
53. Pesce M, La Fratta I, Paolucci T, Grilli A, Patruno A, Agostini F, et al. From exercise to cognitive performance: role of irisin. Appl Sci. 2021;11(15):7120. doi: 10.3390/app11157120.
54. Bi J, Zhang J, Ren Y, et al. Irisin reverses intestinal epithelial barrier dysfunction during intestinal injury via binding to the integrin αVβ5 receptor. J Cell Mol Med. 2020;24(1):996–1009. doi: 10.1111/jcmm.14811.
55. Zsuga J, More E, Erdei T, Papp G, Harsanyi S, et al. Blind spot for sedentarism: redefining the diseasome of physical inactivity in view of circadian system and the irisin/BDNF axis. Front Neurol. 2018;9:818. doi: 10.3390/app11157120.
56. Nakashima D, Fujie S, Togo M, Takeshita S, Hasegawa K, et al. Effect of acute high-intensity intermittent exercise on serum brain-derived neurotrophic factor concentrations. J Sports Med Phys Fitness. 2023;63(6):731–8. doi: 10.23736/S0022-4707.23.14596-8.
57. Taylor S, Eklund R, Arthur C. Fear of failure in sport, exercise, and physical activity: a scoping review. Int Rev Sport Exerc Psychol. 2021;16:500–28. doi: 10.1007/s11482-020-09866-7.
58. Mutz M, Reimers AK, Demetriou Y. Leisure time sports activities and life satisfaction: deeper insights based on a representative survey from Germany. Appl Res Qual Life. 2021;16:2155–7. doi: 10.1016/j.isci.2022.104267.
59. Cheng L, Lu Q, Liu B. BDNF pathway regulates TrkB expression in hippocampus of iron-deficient young rats. Minerva Med. 2020;111(6):609–11. doi: 10.1007/s11482-020-09866-7.
60. Chow L, Gerszten R, Taylor J, et al. Exerkines in health, resilience and disease. Nat Rev Endocrinol. 2022;18(5):273–89. doi: 10.1038/s41574-022-00641-2.