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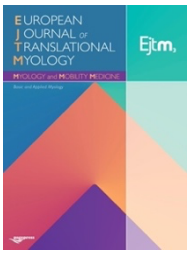

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Exercise-induced irisin–BDNF signaling in aging: implications for cognitive decline, sarcopenia, and neurodegeneration. A narrative review

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Abstract

Age-related cognitive decline is closely associated with diminished neuroplasticity and disrupted neurotrophic signaling. Exercise is a potent modulator of the irisin–BDNF axis, a molecular pathway with emerging relevance to healthy aging, neuroprotection, and the prevention of neurodegenerative diseases in older adults. Through this analysys the author aimed to review evidence on the effects of different exercise modalities — with emphasis on aging populations — on the PGC-1α–FNDC5–irisin–BDNF signaling pathway, and to examine implications for cognitive health and neuroplastic adaptations across the lifespan. A structured, reproducible search of PubMed, Scopus, Web of Science, and Google Scholar was conducted for studies published between January 1995 and September 2025, using Boolean combinations of 'irisin', 'BDNF', 'exercise', 'aging', 'neuroplasticity', and 'cognitive function'. Human and animal studies exploring the irisin–BDNF axis in the context of aging, physical activity, or immobilization were eligible. Data were extracted and synthesized qualitatively. Consistent with the narrative design, no formal risk-of-bias instrument or PRISMA systematic-review reporting framework was applied, and the review was not prospectively registered. Twenty-four studies met inclusion criteria. Resistance and High-Intensity Interval Training (HIIT) consistently increased circulating irisin and hippocampal BDNF levels. Aging-related declines in both biomarkers were attenuated by chronic resistance training, particularly in older adults. Immobilization suppressed the irisin–BDNF pathway. Epigenetic modifications at BDNF promoters represent a plausible mechanism for sustained neuroplastic adaptations. The PGC-1α–FNDC5–irisin–BDNF axis may constitute a key molecular link between skeletal muscle activity and brain health in aging populations. Resistance training and HIIT offer the most consistent evidence for attenuating age-related neurotrophic decline, although HIIT-specific data in older adults remain limited and warrant cautious interpretation. Causal conclusions remain premature given the predominantly associative and preclinical evidence base. Well-powered, longitudinal prospective trials in older adults with standardized biomarker protocols are needed.

Key words: irisin; BDNF; exercise; aging; neuroplasticity; FNDC5; PGC-1α; hippocampus; cognitive decline; resistance training.

Regular exercise exerts profound protective effects on both metabolic and neurological health throughout the lifespan. These benefits become particularly significant in the context of aging, where progressive declines in neurotrophic factor expression, synaptic plasticity, and hippocampal neurogenesis contribute to cognitive deterioration and increased risk of neurodegenerative disease.[1,2,3] Understanding the molecular mechanisms that link skeletal muscle activity to brain health is therefore central to geroscience.

Two myokines have emerged as principal mediators of the exercise–brain axis: irisin and Brain-Derived Neurotrophic Factor (BDNF). Irisin is derived from the proteolytic cleavage of Fibronectin Domain-Containing Protein 5 (FNDC5), itself upregulated by the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) during exercise.[4] Preclinical evidence suggests that circulating irisin may cross the blood-brain barrier and stimulate hippocampal BDNF expression, thereby linking peripheral muscle contraction to central neuroplastic adaptations.[5] BDNF, the most abundantly expressed neurotrophin in the brain, plays critical roles in neuronal survival, synaptic potentiation, hippocampal neurogenesis, and cognitive function across the aging continuum.[6,7] Mechanistically, BDNF binds the tropomyosin receptor kinase B (TrkB) receptor to activate downstream MAPK/ERK, PI3K/Akt, and PLCγ signaling cascades that support neuronal survival, dendritic arborization, and long-term potentiation.[8,9] Clinically, reduced circulating and hippocampal BDNF has been implicated in age-related cognitive decline, late-life depression, and neurodegenerative diseases such as Alzheimer's disease, underscoring its relevance as both a candidate biomarker and a potential therapeutic target in aging populations.[2,10]

Aging is associated with progressive reductions in circulating irisin and hippocampal BDNF levels, paralleling declines in muscle mass, physical activity, and cognitive performance.[11] This convergence suggests that the PGC-1α–FNDC5–irisin–BDNF pathway may represent a modifiable molecular target

for exercise-based interventions aimed at preserving cognitive health in older adults. Despite a growing body of literature, no prior review has comprehensively synthesized this axis with explicit attention to aging populations, exercise modality, and translational implications. In particular, existing reviews have not systematically contrasted resistance training, HIIT, and aerobic training specifically within aging cohorts, nor addressed the practical feasibility and safety considerations that determine which modalities are appropriate for older adults — gaps this review aims to address.

The present narrative review aims to evaluate the effects of exercise modalities — with emphasis on resistance training and HIIT in aging contexts — on the irisin–BDNF signaling pathway, and to identify implications for the prevention of age-related cognitive decline and neurodegenerative diseases.

Materials and Methods

Study design

This is a narrative review; a structured and reproducible search and selection process was nonetheless used to identify relevant literature, and the selection flow is summarized for transparency (Figure 1).

Search strategy

PubMed, Scopus, Web of Science, and Google Scholar were searched for studies published between January 1995 and September 2025. Boolean operators (AND, OR) were applied to combine: 'irisin', 'BDNF', 'exercise', 'resistance training', 'aging', 'older adults', 'FNDC5', 'PGC-1α', 'neuroplasticity', 'cognitive function', 'immobilization'. Full database-specific search strings are available as supplementary material.

Inclusion and exclusion criteria

Studies eligible for inclusion comprised experimental or clinical research linking exercise or physical inactivity to irisin or BDNF expression in human or animal subjects. Studies focusing specifically on older adult or aging populations were prioritized. In vitro-only studies, pharmacological interventions without exercise comparison, and studies with incomplete datasets were excluded.

Data extraction and quality appraisal

Data extraction employed standardized templates and was performed by the primary reviewer, with all decisions validated by a second independent reviewer; disagreements were resolved by consensus.Given the narrative design of this review, no formal risk-of-bias instrument was applied; instead, each included study was qualitatively appraised for design (randomized, observational, or animal-based), sample size, and potential sources of bias, and these considerations are flagged where they affect interpretation of the findings (see also Section 4.6, Limitations). Due to substantial heterogeneity in study designs (RCTs, observational studies, animal experiments), quantitative meta-analysis was not undertaken; findings were synthesized narratively, and the overall certainty of evidence is considered low to moderate.

Results

The initial search identified 661 records. After duplicate removal (n=153) and title/abstract screening (n=298 excluded), 161 full-texts were assessed for eligibility, of which 24 studies met inclusion criteria (Figure 1). Tables 1–3 summarize study characteristics, epigenetic and signaling findings, immobilization effects, and resistance training data with specific relevance to aging populations.

Exercise intensity, epigenetic regulation, and the irisin–BDNF axis

High-intensity exercise consistently produced the greatest increases in FNDC5/irisin and hippocampal BDNF levels across included studies, supporting the role of exercise intensity in neuroplastic adaptations (Table 1).[5,12,13] Epigenetic mechanisms — including decreased DNA methylation at BDNF promoters and increased histone acetylation — were identified as plausible molecular substrates for sustained, long-term neuroplastic effects of exercise; these epigenetic findings derive primarily from rodent aerobic and voluntary-wheel-running models rather than from resistance training or HIIT paradigms.[4,14] These epigenetic modifications may be especially relevant in aging populations, in whom baseline BDNF methylation is elevated and neuroplasticity is reduced. (Figure 2).

Immobilization and age-related suppression of the pathway

Physical inactivity and immobilization were consistently associated with suppression of the irisin–BDNF pathway (Table 2).[15,16,17] Sedentary older adults exhibited significantly lower circulating irisin and BDNF

levels, paralleling impairments in metabolic health (increased insulin resistance, reduced thermogenesis) and cognitive performance. Reduced BDNF was further associated with diminished hippocampal LTP and heightened risk of cognitive decline. These findings underscore the bidirectional relationship between physical activity and neurotrophic signaling across the aging process. (Figure 3).

Resistance training and healthy aging

Resistance training demonstrated the most consistent and clinically relevant effects on the irisin–BDNF axis in aging populations (Table 3).[18,19,20] Progressive resistance training programs attenuated age-related declines in plasma and hippocampal irisin and BDNF levels in both animal and human studies. Twelve-week resistance training interventions increased total BDNF levels in elderly individuals. Strength training also upregulated follistatin and downregulated myostatin, suggesting synergistic anabolic and neuroprotective effects. HIIT produced greater acute irisin responses than moderate-intensity continuous training in late middle-aged and older adults, with more pronounced effects reported in younger individuals and those with type 2 diabetes mellitus;[13] evidence on the safety and tolerability of HIIT in frail or multimorbid older adults remains limited (see Section 4.3). (Figure 4).

Dıscussıon

This narrative review synthesizes evidence that the irisin–BDNF axis is a central molecular mediator of exercise-induced neuroplastic and metabolic benefits, with particular relevance to the biology of aging. Resistance training and HIIT consistently upregulated both biomarkers, while aging and physical inactivity were associated with their suppression — a pattern consistent with the geroscience hypothesis that sedentary behavior accelerates neurobiological aging.

Mechanistic ınsights: the ırisin–BDNF axis in aging

Age-related declines in PGC-1α expression in skeletal muscle reduce FNDC5 transcription and consequently attenuate irisin secretion.[4,5,21] Concurrently, reduced irisin availability may diminish the central stimulus for hippocampal BDNF synthesis, contributing to impaired neurogenesis, reduced synaptic plasticity, and cognitive decline characteristic of normal aging and neurodegenerative conditions. It should be emphasized that direct evidence of irisin crossing the blood-brain barrier and

stimulating hippocampal BDNF derives principally from animal and in vitro models rather than from human studies;[5,22,23] this mechanistic link, while plausible, has not been directly confirmed in humans and is discussed further in Section 4.5. Importantly, resistance training was shown to partially reverse these age-related changes across multiple tissue compartments, including cardiac, hepatic, and plasma, suggesting systemic benefits extending beyond the muscle–brain axis.

Resistance training as a therapeutic strategy

Among the exercise modalities examined, resistance training was associated with some of the most consistent and clinically meaningful effects reported in aging populations,[18,19,24,25,20] although this conclusion is tempered by the heterogeneity, generally modest sample sizes, and mixed methodological quality of the underlying studies. Progressive resistance training programs not only increased circulating irisin but also attenuated age-related declines in BDNF, follistatin, and associated neurotrophic markers. The co-upregulation of follistatin alongside suppression of myostatin suggests that resistance exercise may simultaneously support anabolic muscle preservation and neuroprotection — a dual benefit of high clinical relevance in older adults at risk of sarcopenia and cognitive decline. These findings align with accumulating evidence supporting resistance exercise as a primary non-pharmacological intervention for healthy aging.

Suitability and safety of HIIT in older adults

Although HIIT produced the largest acute increases in circulating irisin and BDNF among the modalities examined,[13] its applicability to unselected older populations should not be assumed. Most of the supporting evidence derives from relatively fit, community-dwelling older adults without significant cardiovascular, orthopedic, or cognitive comorbidities; data in frail, multimorbid, or very old individuals are lacking. High-intensity protocols carry greater cardiovascular and musculoskeletal risk than moderate-intensity continuous training and typically require medical clearance, supervised progression, and individualized intensity prescription (e.g., via heart-rate reserve or rating of perceived exertion). HIIT may therefore be appropriate as a supervised, individually tailored option for relatively healthy, motivated older adults, whereas resistance training and moderate-intensity aerobic exercise remain more broadly applicable first-line modalities for the general aging population.

Epigenetic mechanisms and longevity

Exercise-induced epigenetic modifications at BDNF promoters — particularly decreased CpG methylation and increased histone acetylation — represent a mechanistically plausible explanation for sustained neuroplastic adaptations beyond the exercise period itself. In the context of aging, where epigenetic drift increasingly silences neurotrophic gene expression, these exercise-induced epigenetic modifications may counteract age-related transcriptional decline. Early-life exercise programming of epigenetic landscapes may extend protective effects into later life, highlighting the importance of lifelong physical activity.

Translational challenges: from animal models to human studies

A substantial portion of the mechanistic evidence linking irisin to hippocampal BDNF signaling — including the proposed crossing of irisin across the blood–brain barrier — derives from rodent models using genetic overexpression, recombinant irisin administration, or forced exercise paradigms that do not fully replicate voluntary exercise behavior or irisin kinetics in humans.[5,22,23] Species differences in FNDC5 cleavage efficiency, candidate irisin receptors, and blood–brain barrier permeability remain incompletely characterized, and circulating irisin immunoassays used in human studies have shown limited cross-platform reliability. Findings from preclinical models should therefore be regarded as hypothesis-generating rather than as direct evidence of an analogous mechanism in aging humans, and claims of a causal irisin-to-BDNF pathway in humans should be interpreted with corresponding caution until confirmed by adequately powered, biomarker-validated human trials.

Limitations and future directions

Several limitations constrain the conclusions of this review: i) substantial heterogeneity in study design, population characteristics, and biomarker measurement methodologies precluded meta-analysis; ii) most mechanistic findings derive from animal models, and human translational data remain heterogeneous and largely associative; iii) irisin measurement via commercial ELISA kits lacks standardization, complicating cross-study comparisons; iv) circulating and hippocampal BDNF were not consistently distinguished across studies; v) this review was not prospectively registered; vi) as a narrative review,

no formal risk-of-bias or quality-appraisal instrument was applied to individual studies, and the inclusion of a structured literature-selection diagram (Figure 1) should not be interpreted as indicating systematic-review methodology. Future research should prioritize standardized exercise protocols, validated biomarker assay platforms, adequately powered prospective human trials specifically in older adult cohorts, and formal GRADE evidence grading.

Conclusions

This narrative review synthesizes evidence suggesting that the PGC-1α–FNDC5–irisin–BDNF pathway represents a plausible molecular interface between physical activity and brain health in aging populations. Resistance training and HIIT are the exercise modalities most consistently associated with upregulation of this pathway, with resistance training demonstrating particular efficacy in attenuating age-related neurotrophic decline. Conversely, physical inactivity accelerates the suppression of this axis, with adverse consequences for metabolic and cognitive aging. Epigenetic regulation of BDNF expression emerges as a plausible mechanism for sustained neuroplastic adaptations. Causal conclusions remain premature given the predominantly associative and preclinical evidence base. Well-powered, longitudinal prospective trials in older adults, incorporating standardized exercise protocols and validated biomarker platforms, are essential to establish the clinical utility of exercise-based interventions targeting the irisin–BDNF axis for healthy aging.

List of Abbreviations

AD, Alzheimer's Disease
BDNF, Brain-Derived Neurotrophic Factor
CpG, Cytosine–Phosphate–Guanine
CSF, Cerebrospinal Fluid
DNA, Deoxyribonucleic Acid
ECS, Electroconvulsive Seizure
ELISA, Enzyme-Linked Immunosorbent Assay
ERK, Extracellular Signal-Regulated Kinase
FNDC5, Fibronectin Type III Domain-Containing Protein 5
GRADE, Grading of Recommendations Assessment, Development and Evaluation

GSK3, Glycogen Synthase Kinase 3
HIIT, High-Intensity Interval Training
HIV/AIDS, Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
LTP, Long-Term Potentiation
MAPK, Mitogen-Activated Protein Kinase
MICT, Moderate-Intensity Continuous Training
mTOR, Mechanistic Target of Rapamycin
PGC-1α, Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1 Alpha
PI3K, Phosphoinositide 3-Kinase
PLCγ, Phospholipase C Gamma
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT, Randomized Controlled Trial
SMD, Standardized Mean Difference
T2DM, Type 2 Diabetes Mellitus
TrkB, Tropomyosin Receptor Kinase B
UCP1, Uncoupling Protein 1

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Conflicts of interest

The author certifies that there is no conflict of interest with any financial organization regarding the material discussed in this manuscript.

Ethics approval and consent to particpate

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Not applicable.

Data availability

Data extraction sheets, excluded study list with reasons, and full database-specific search strings are available as supplementary material upon reasonable request to the corresponding author.

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Declaration of Generative AI and AI-assisted technologies in the writing process

Artificial intelligence has been used only in grammar editing and visualization.

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Table 1. Exercise, Irisin–BDNF Signaling, and Aging: Epigenetic and Mechanistic Evidence

Author (Year)	**Focus**	**Key Findings**	**Implications for Aging**
Leger (2024)	Exercise intensity & FNDC5/Irisin–BDNF, late middle-aged/older adults	High-intensity exercise ↑ FNDC5/Irisin & hippocampal BDNF; dose-response confirmed in older subjects.	Supports high-intensity exercise prescription for cognitive benefits in aging populations.
Tsai et al. (2021)	HIIT vs MICT, BDNF & irisin, late middle-aged & older adults (≥55 yrs)	HIIT produced greater acute ↑ in BDNF & irisin than MICT; improvements in neurocognitive performance.	HIIT may be superior to moderate exercise for neurotrophic responses in older adults.
Farshbaf (2021)	Skeletal muscle-brain axis, neuropsychiatric disorders & aging	Exercise enhances brain function and mental health via irisin-mediated pathways across aging.	Therapeutic role of exercise for age-related neuropsychiatric disorders via irisin.
Xu (2024)	T2DM mice, hippocampal neurogenesis & aging model	Exercise ↓ neuroinflammation, ↑ hippocampal neurogenesis & memory via irisin signaling.	Highlights exercise for T2DM-related cognitive impairment — highly prevalent in older adults.

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Chen (2017)	Epigenetic regulation of BDNF, aging brains	Exercise alters epigenetic marks at BDNF promoters; ↓ methylation, ↑ acetylation.	Epigenetic basis for sustained BDNF effects — particularly relevant as epigenetic drift increases with age.
Raus (2021)	Early-life exercise & histone modifications, lifespan perspective	Early-life exercise alters histone modifications → long-term ↑ BDNF expression across lifespan.	Early exercise programming may buffer aging-related BDNF decline.
Dicarlo (2023)	Irisin, neurotrophins & neuroinflammation in aging brain	Irisin modulates neurotrophin/cytokine expression in hippocampus & prefrontal cortex.	Irisin as anti-neuroinflammatory mediator — relevant to age-related neurodegeneration.
Kazeminasab (2022)	Acute vs chronic exercise, aerobic vs anaerobic, irisin release	Acute exercise ↑ irisin more than chronic; aerobic > anaerobic for irisin release.	Exercise modality & intensity must be optimized for aging-specific neurotrophic protocols.
Kim et al. (2015)	Resistance training, irisin, aging mice & older humans	Resistance training ↑ irisin concomitant with improved muscle function in aging mice and humans.	Resistance exercise restores age-related irisin decline in both animal and human models.
Liu (2020)	Irisin, ischemic stroke, neuroprotection in aging	Exercise-induced irisin alleviates ischemic brain injury via neuroprotection.	Supports exercise as adjunct therapy for stroke — leading

			cause of disability in older adults.
Ceylan (2024)	Sex, obesity, cognitive impairment & exercise in aging	Age, sex & obesity influence irisin/BDNF dynamics; personalized protocols needed.	Age- and sex-specific exercise programs critical for maximizing neurotrophic effects in older adults.
Lourenco et al. (2019)	FNDC5/irisin, Alzheimer's disease models, synaptic plasticity	FNDC5/irisin levels ↓ in AD hippocampi & cerebrospinal fluid (CSF); boosting irisin rescues synaptic plasticity & memory.	Irisin as therapeutic target for Alzheimer's disease — the most common dementia in older adults.

Table 2. Physical Inactivity, Aging, and Suppression of the Irisin–BDNF Pathway

Author (Year)	**Focus**	**Key Findings**	**Implications for Aging**
Vaynman (2004)	Exercise-induced memory & cognition; BDNF post-immobilization (animal)	Exercise ↑ BDNF → improved memory; BDNF critical mediator; immobilization reverses gains.	BDNF as therapeutic target for post-immobilization cognitive deficits in older/hospitalized adults.
Patterson (1996)	BDNF knockout mice, hippocampal synaptic plasticity & LTP	Recombinant BDNF rescues synaptic transmission & hippocampal LTP deficits in knockout mice.	BDNF replacement strategies relevant for age-related cognitive disorders & neurodegeneration.

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Moreno-Navarrete (2013)	Diabetic & sedentary humans, irisin levels	Irisin ↓ in sedentary & diabetic individuals; loss of beige/brown fat characteristics.	Physical inactivity in older adults compounds irisin decline, worsening metabolic & brain health.
Peng & Wu (2022)	FNDC5/irisin, elderly dementia & cognitive impairment (review)	Irisin ↓ in aging; exercise-induced irisin may protect against neuroinflammation & dementia progression.	Irisin as potential biomarker and therapeutic target for dementia prevention in older adults.
Guo et al. (2023)	Irisin, age-associated sarcopenia & metabolic dysfunction	FNDC5/irisin ↓ with aging in skeletal muscle & serum; irisin treatment attenuates sarcopenia.	Sarcopenia and irisin decline are interlinked aging processes; exercise may simultaneously address both.
Zhang et al. (2025)	Irisin, apelin & sarcopenia in community-dwelling older adults	Sarcopenia associated with significantly lower irisin levels (73.75 vs 131.15 ng/mL, $p<0.05$).	Circulating irisin may serve as a clinically accessible biomarker for sarcopenia risk in older adults.
Martinowich (2003)	Epigenetic regulation of BDNF gene (CpG methylation)	↑ BDNF synthesis correlates with ↓ CpG methylation; sedentary aging ↑ methylation → silenced BDNF.	Epigenetic drift with aging silences BDNF expression; exercise-induced demethylation may reverse this.
Nibuya (1995)	Electroconvulsive seizure & antidepressants, neuronal survival	ECS & antidepressants ↑ BDNF & trkB mRNA → neuroprotection;	Combined exercise & pharmacological strategies maximize

		physical inactivity opposes this.	neurotrophic benefits in aging.

Table 3. Resistance Training, HIIT, and the Irisin–BDNF Axis in Aging Populations

Author (Year)	**Population / Design**	**Key Findings**	**Implications for Healthy Aging**
Cosio & Crespo-Posadas (2021)	Systematic review & meta-analysis; older adults, progressive resistance training	Resistance training ↑ circulating irisin, especially with progressive, demanding protocols in older adults.	Progressive resistance training is the most supported modality to enhance irisin in aging populations.
Belviranli & Okudan (2018)	Aging mice & older humans; resistance training, cardiac/hepatic/plasma BDNF & irisin	Resistance training mitigates aging-induced ↓ in BDNF & irisin across multiple tissue compartments.	Systemic reversal of age-related neurotrophin decline via resistance training — supports clinical application.
Eidukaite et al. (2023)	Elderly individuals (≥60 yrs), 12-week resistance training pilot RCT	12-week resistance training ↑ total BDNF levels in elderly subjects; feasible and well-tolerated.	Short-term resistance training sufficient for neurotrophic benefit in elderly — low barrier to implementation.
Afshar et al. (2025)	Active middle-aged women, 12-week strength training RCT	Strength training ↑ irisin, BDNF, follistatin; ↓	Dual anabolic/neuroprotective effects of strength

		myostatin → simultaneous anabolic & neuroprotective effects.	training relevant for sarcopenia-cognitive decline comorbidity.
Kim et al. (2015)	Aging mice & older humans; resistance training & irisin expression	Resistance training ↑ irisin expression concomitant with improved muscle function in both aging mice and humans.	Confirms translational relevance: resistance exercise restores irisin in aging humans and animal models.
Trombeta et al. (2021)	Adults with HIV/AIDS; combined physical training & BDNF	↑ BDNF levels linked with ↓ risk of cognitive disorders; resistance training may reduce dementia risk.	Resistance training as non-pharmacological intervention for dementia prevention across aging populations.
Cheng et al. (2025)	Older adults (≥55 yrs); systematic review & network meta-analysis; aerobic exercise & BDNF	Aerobic exercise (walking, running, cycling) ↑ BDNF in older adults; resistance training showed largest SMD (0.76).	Resistance training outperforms aerobic modalities for BDNF elevation in older adults — guides exercise prescription.
Tsai et al. (2021)	Late middle-aged & older adults (≥55 yrs); HIIT vs MICT, BDNF & irisin	HIIT > MICT for acute ↑ in both BDNF and irisin; improved	HIIT is a time-efficient strategy for maximizing neurotrophic responses in aging populations.

		neurocognitive performance in older subjects.	

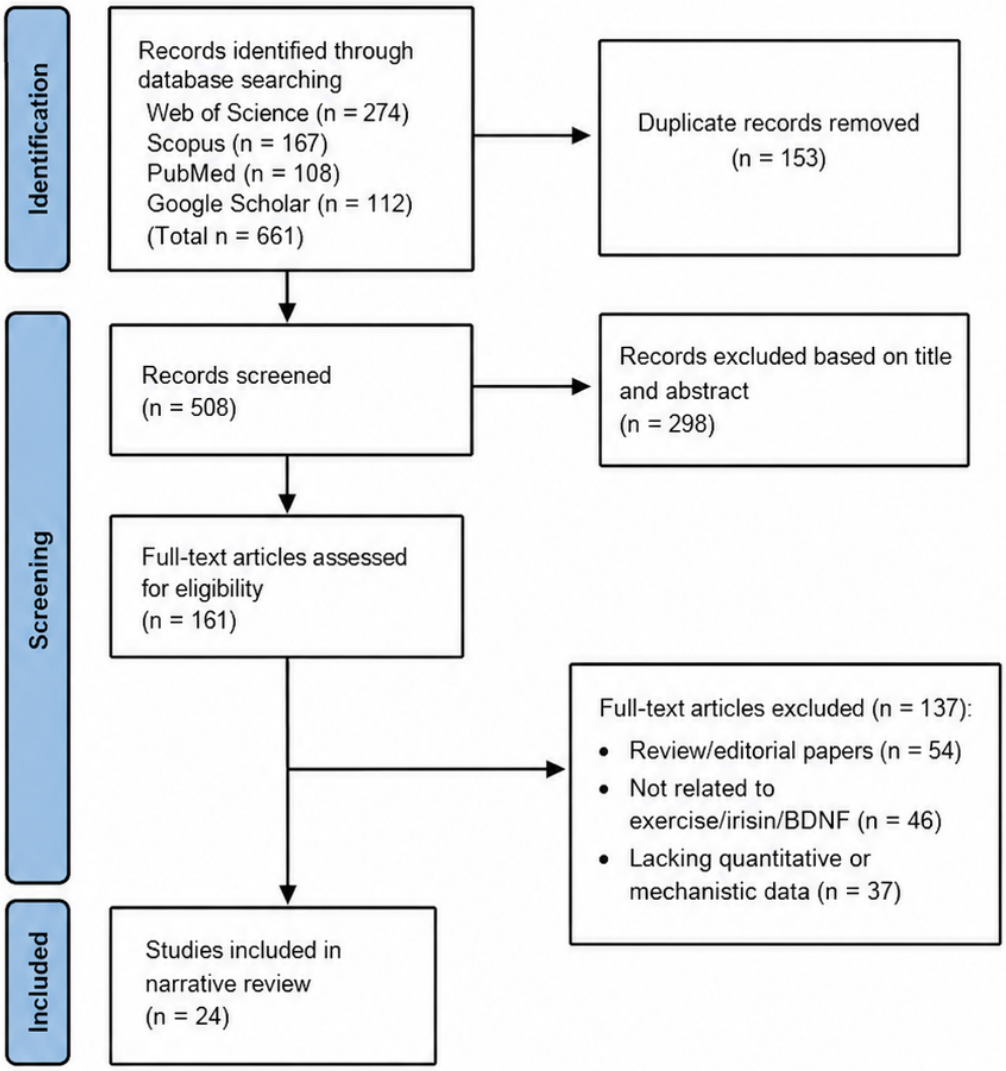

Figure 1. Study selection flow diagram illustrating the process of identifying, screening, and including studies in this narrative review.

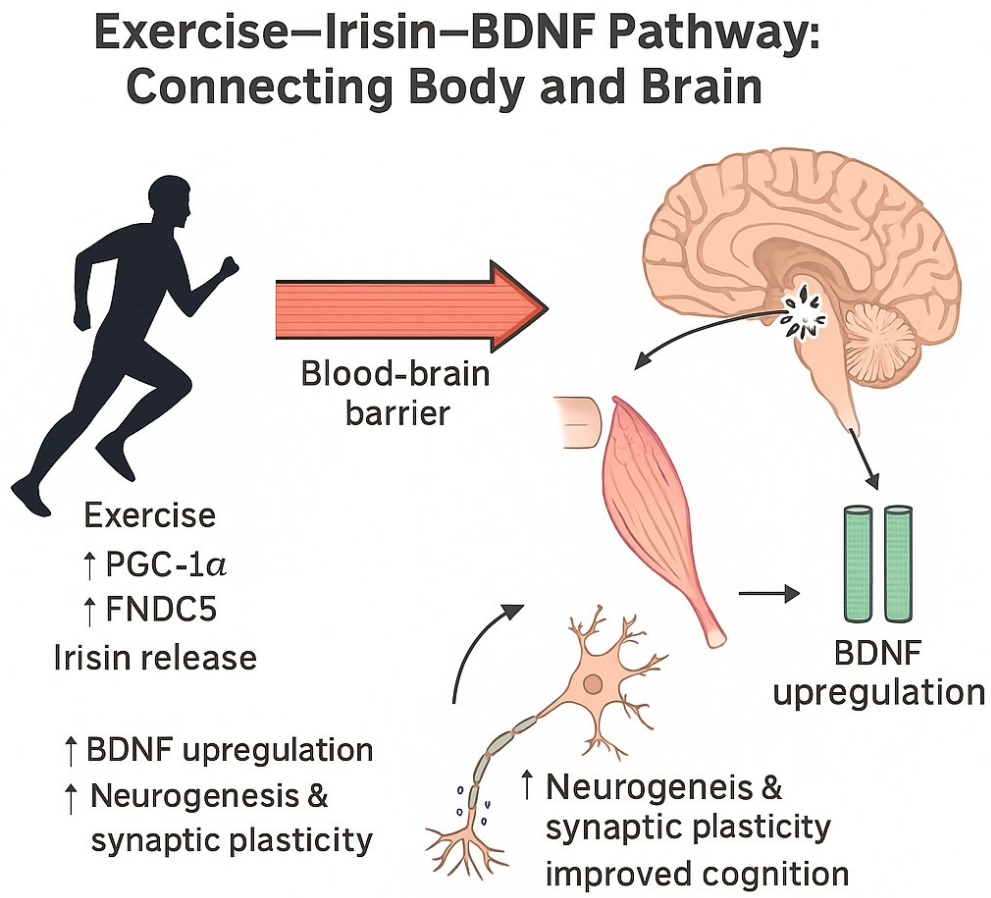

Figure 2. Exercise-Irisin-BDNF Pathway: Connecting Body and Brain. Exercise upregulates PGC-1α and FNDC5 in skeletal muscle, triggering irisin release. Irisin crosses the blood-brain barrier and stimulates hippocampal BDNF upregulation, leading to increased neurogenesis, synaptic plasticity, and improved cognition.

Exercise-induced irisin–BDNF signaling in aging

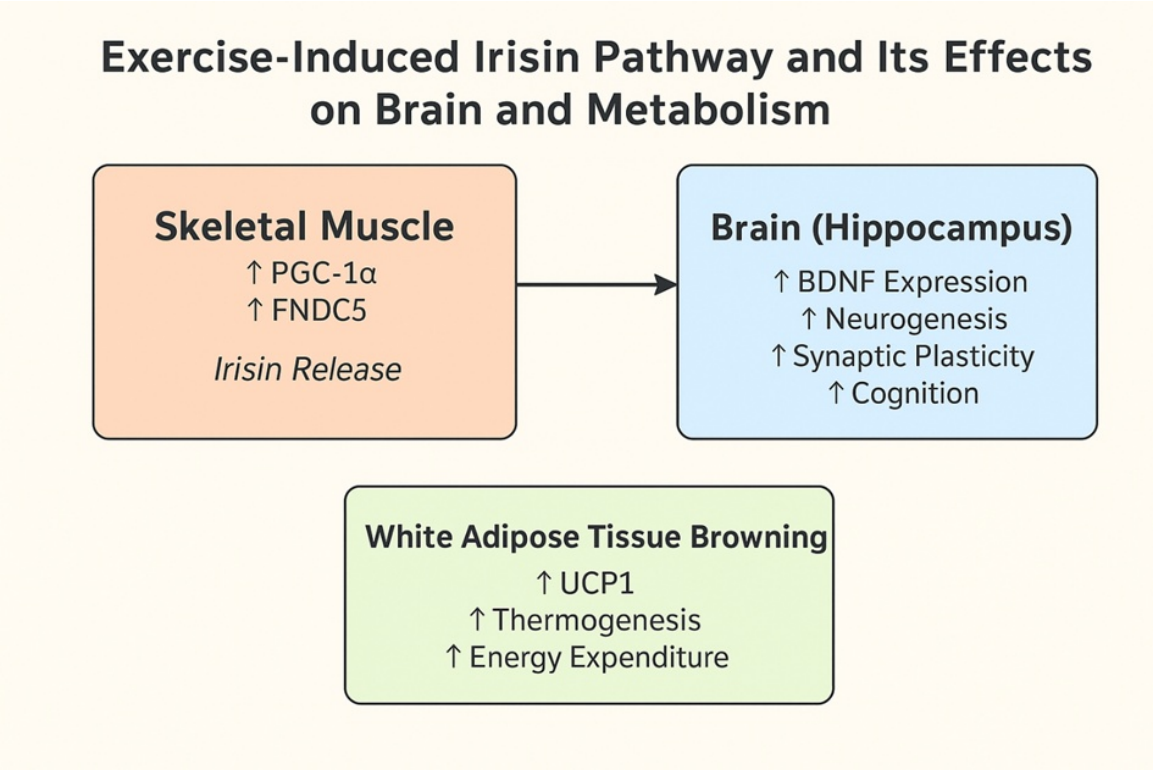

Figure 3. Exercise-Induced Irisin Pathway and Its Effects on Brain and Metabolism. Skeletal muscle-derived irisin (via PGC-1α/FNDC5) acts on hippocampal neurons to enhance BDNF expression, neurogenesis, synaptic plasticity, and cognition. Concurrently, irisin promotes white adipose tissue browning, increasing UCP1, thermogenesis, and energy expenditure.

Exercise-induced irisin–BDNF signaling in aging

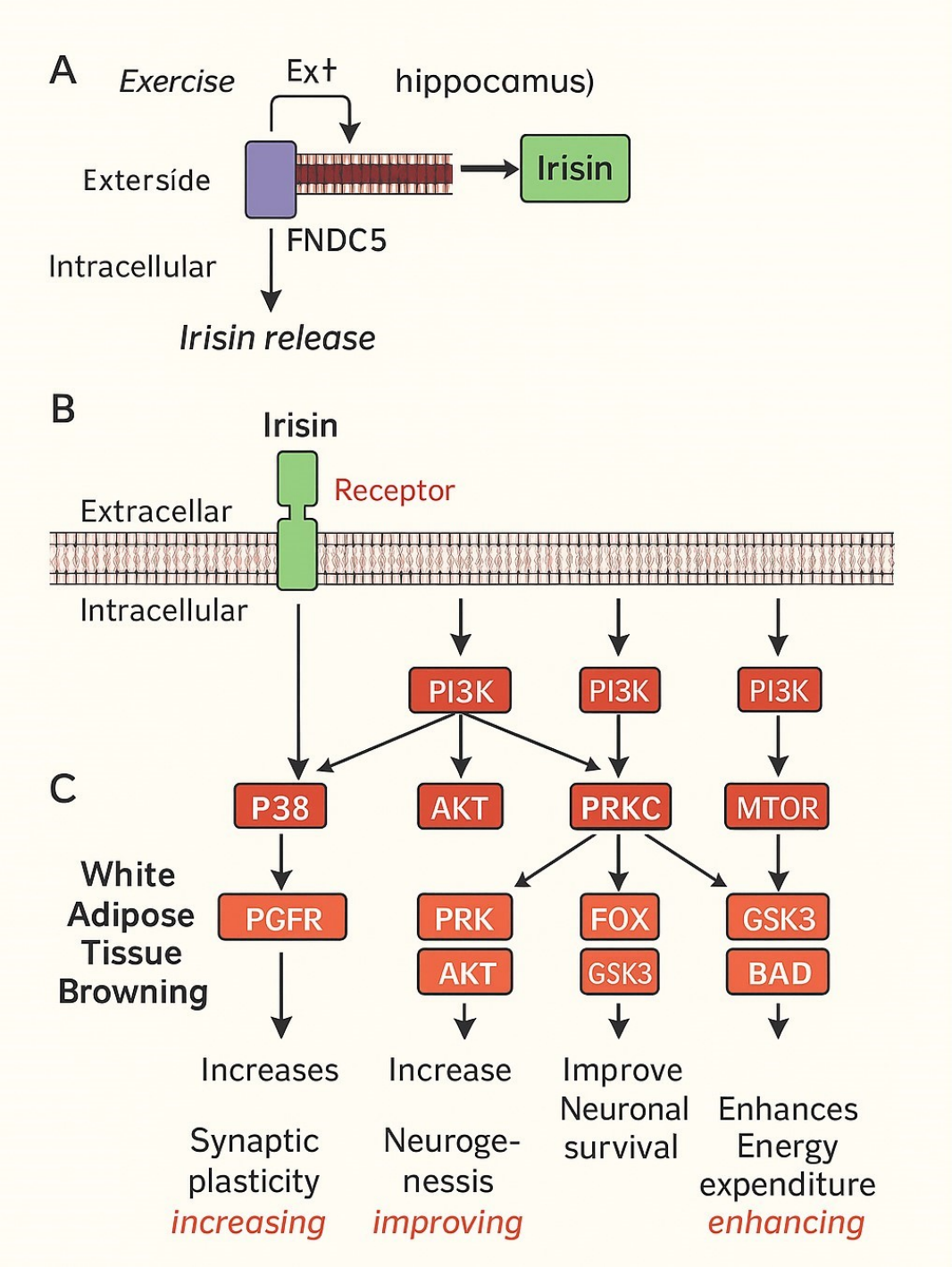

Figure 4. Molecular Signaling Cascades Mediating Irisin Effects on Brain and Metabolism. (A) Exercise-induced FNDC5 cleavage releases irisin. (B-C) Irisin activates membrane receptors triggering downstream pathways including PI3K/AKT (neurogenesis), p38/PGFR (synaptic plasticity), PRKC/FOX/GSK3 (neuronal survival), and mTOR/GSK3/BAD (energy expenditure).