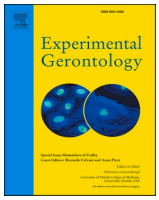
Experimental Gerontology 198 (2024) 112640

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero



Review article

Effects of physical exercise on Irisin and BDNF concentrations, and their relationship with cardiometabolic and mental health of individuals with Metabolic Syndrome: A Systematic Review

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ARTICLE INFO

Keywords:
Physical exercise
Metabolic syndrome
Irisin
Brain-derived neurotrophic factor
Mental health

ABSTRACT

Chronic Non-Communicable Diseases (NCDs), including cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes, are the leading global causes of mortality, accounting for 71 % of deaths annually. Metabolic Syndrome (MS), characterized by hypertension, obesity, insulin resistance, and dyslipidemia, is a significant risk factor for NCDs. Physical inactivity exacerbates these conditions, contributing to poor cardiovascular and mental health outcomes.

Objective: To analyze the effects of physical exercise on Irisin and Brain-Derived Neurotrophic Factor (BDNF) concentrations and their relationship with cardiometabolic and mental health of individuals with MS.

Methods: A systematic review was conducted of articles published between August 2023 and June 2024 in ScienceDirect, PubMed, and SciELO, following PRISMA guidelines. Inclusion criteria encompassed observational studies, clinical trials, and reviews with high methodological quality. The review focused on Irisin, BDNF, physical exercise, and MS.

Results: A total of 584 articles were identified, with 43 selected for detailed analysis. The review highlights that physical exercise significantly impacts Irisin and BDNF levels, which in turn influence metabolic and mental health. Irisin, a myokine secreted during exercise, promotes the conversion of white adipose tissue to brown adipose tissue, enhancing energy expenditure and metabolic health. Elevated Irisin levels are associated with improved cognitive function and mental well-being. BDNF, a neurotrophin, supports neuronal growth and cognitive function. Exercise-induced increases in BDNF levels are linked to enhanced neuroplasticity, reduced anxiety, and improved mood.

Conclusion: Understanding the role of Irisin and BDNF in response to physical exercise offers valuable insights for developing strategies to manage and prevent MS and its related mental health issues. Further research is needed to elucidate the molecular mechanisms involved.

1. Introduction

Chronic Non-Communicable Diseases (NCDs) include cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes (Sun et al., 2022). According to the World Health Organization (WHO), NCDs are the leading cause of death globally, accounting for 41 million deaths annually, which represents approximately 71 % of all deaths worldwide (World Health Organization (WHO), 2022). Epidemiological studies on NCDs indicate that the rise in these diseases is driven by factors such as aging process, urbanization, and exposure to modifiable risk factors. The WHO identifies cardiovascular diseases as the leading cause of death among NCDs (17.9 million annually), followed by cancer (9.0 million), respiratory diseases (3.9 million), and diabetes (1.6 million) (World Helath Organization, 2023), and according to the Pan American Health Organization (PAHO) in 2023, approximately 5.8 million people in Latin America died from NCDs (Pan American Health Organization, 2024), with 60 % cases directly linked to mental disorders (MS) (Budreviciute et al., 2020), since the insulin resistance, hyperglycemia, and imbalanced lipid levels, it is associated with vascular damage in the brain, affecting neuronal function and increase the risk of cognitive decline

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https://doi.org/10.1016/j.exger.2024.112640
Received 21 October 2024; Received in revised form 13 November 2024; Accepted 20 November 2024
Available online 24 November 2024

(González-Torres et al., 2023).

MS is a complex disorder characterized by a constellation of interrelated biochemical and physiological abnormalities, including oxidative stress, insulin resistance, dyslipidemia, inflammation, and abdominal obesity (Martemucci et al., 2023; Limon et al., 2020). These metabolic dysregulations not only affect physical health but also extend their influence to mental well-being, increasing the risk of depression, anxiety, and other mental disorders (Zhang et al., 2023). For example, the increase in pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) as a result of the chronic inflammatory response in MS contributes to insulin resistance and endothelial dysfunction while negatively affecting the brain, as these cytokines can cross the blood-brain barrier, altering neurotransmission and neuronal plasticity. Similarly, MS and its pathophysiological implications disrupt the hypothalamic-pituitary-adrenal axis through excessive cortisol release, which, at elevated and prolonged levels, can damage the hippocampus and other brain areas involved in mood regulation and anxiety (Werdermann et al., 2021). Another clearly related aspect between MS and mental disorders is the increase in visceral adiposity, which is associated with heightened release of free fatty acids and inflammatory adipokines, exacerbating systemic inflammation and oxidative stress, both linked to alterations in neuronal and synaptic function. Therefore, the biochemical, biological, and physiological processes of MS not only predispose individuals to cardiovascular diseases and type 2 diabetes but also have profound implications for mental health (MH) (Werdermann et al., 2021).

In this context, physical exercise plays a crucial role in the management, prevention, and control of MS. Regular physical activity reduces disturbances such as high blood pressure, hyperglycemia, excess visceral and muscle fat, and abnormal cholesterol or triglyceride levels (Budreviciute et al., 2020). These changes are associated with positive molecular responses, such as the activation of muscle hormones known as myokines and exerkines released during exercise (Chow et al., 2022). Myokines play a role in the communication between muscle tissue and other organs, influencing metabolic processes such as thermogenesis, biogenesis, energy clearance, and the regulation of metabolic waste (Bell et al., 1997). Consequently, regular exercise is associated with improvements in insulin sensitivity, glucose metabolism, and overall metabolic health, which are particularly relevant in the context of MS (Liang et al., 2021), Moreover, it promotes positive changes in the MS of individuals with MS due to the positive and negative regulation of protein and hormone synthesis involved in muscle and brain function (Zupkauskiene et al., 2022; Imayama et al., 2011).

Irisin, a myokine secreted primarily by skeletal muscle during physical exercise, has garnered scientific attention due to its potential positive impact on metabolic health, especially in patients with MS (Leustean et al., 2021). This protein is generated from the cleavage of the type III fibronectin precursor protein and has been shown to induce the transformation of white adipocytes into brown adipocytes, resulting in increased energy expenditure and improved lipid profiles (Leustean et al., 2021). Although extensively studied for its role in metabolism and obesity, emerging findings suggest that Irisin also exerts significant effects on cognitive functions and mental states of active individuals (Sousa et al., 2021a).

On the other hand, Brain-Derived Neurotrophic Factor (BDNF) is a neurotrophin essential for cognitive function and neuroplasticity. Synthesized in the brain, BDNF plays a crucial role in the survival, growth, and differentiation of neurons, as well as in memory formation and consolidation (Fernández-Rodríguez et al., 2022). Recently, BDNF has been discovered to have properties similar to those of myokines, influencing glucose homeostasis and insulin sensitivity, suggesting an interconnection between cognitive function and metabolic regulation (Liang et al., 2021; Alomari et al., 2020). This dual role of BDNF highlights the complexity of its functions and its potential for modulating various aspects of metabolic and brain health.

Recognizing that MS represents a significant global public health issue, with a high prevalence ranging from 44.9 % to 50.9 %, affecting 25 % of the world's population (Madan et al., 2023; Agarkov et al., 2023), and considering that individuals with MS have a higher likelihood of experiencing mental disorders such as depression and anxiety, with prevalence rates of 25.3 % for depression and 30.2 % for anxiety (Butnoriene et al., 2018), there is growing interest in understanding the role of physical exercise as an effective tool for addressing MS and its coexisting conditions. Therefore, the objective of this article is to provide an analysis of the known effects of physical exercise on Irisin and BDNF concentrations, as well as their relationship with cardiometabolic and MH of individuals with MS.

2. Methods

2.1. Document retrieval

A systematic review was conducted of scientific articles published in indexed journals in the ScienceDirect, PubMed, and SciELO databases between August 2023 and August 2024. This review followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, and the search terms used were: Exercise; Exercise Therapy; Brain-Derived Neurotrophic Factor; Irisin; Metabolic Syndrome; Mental Health. Publications related to Irisin, BDNF, physical exercise, and MS were considered.

2.2. Inclusion and exclusion criteria

Inclusion criteria were: observational studies, clinical trials, and reviews with a minimum methodological evaluation score of 18 on the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist for observational articles (Cuschieri, 2019), 8 on the PEDro scale for clinical trials (Paci et al., 2022), and 16 on the PRISMA checklist for reviews (Page et al., 2021). Additionally, articles that presented biomolecular responses related to Irisin, BDNF, physical exercise, and MS were selected. Exclusion criteria included: grey literature, studies involving individuals with cardiovascular diseases and MS who additionally received another therapeutic strategy, and articles that did not document results related to the proteins of interest for this review. Search limits were set to articles published in indexed journals in English, Spanish, and Portuguese.

2.3. Qualitative assessment of studies

The studies were evaluated methodologically on an individual basis and according to their type: 1) Observational studies were assessed using the STROBE statement, a checklist with 22 items that addresses all sections of the articles; 2) Randomized clinical trials were evaluated using the PEDro scale, a 10-point tool for assessing internal validity; and 3) Systematic reviews were appraised using the PRISMA checklist, which assesses the quality of the article based on 27 items (Table 1).

2.4. Data extraction

The search and selection of articles were performed by the principal investigator, while two external reviewers were responsible for selecting the articles based on the inclusion and exclusion criteria, as well as the minimum methodological evaluation scores (Table 1). In cases of disagreement, a third reviewer was consulted to review the relevant data of the article along with the methodological evaluation to discuss and make the final decision on inclusion or exclusion. Scientific articles that, after a complete reading, demonstrated publication bias, selective reporting, or presented low methodological quality or results that did not contribute to the objective of this review were discarded.

Table 1
Selected Articles.

Author	Year	DOI	Results	Article Type	Quality Assessment
Di Maio, et al. (30)	2024	10.1002/jcb.30565	Irisin influences the in vitro differentiation of human mesenchymal stromal cells, promoting a tendency toward beiging adipogenesis.	Clinical Trial	STROBE Statement 21/22
Park J, et al. (43)	2022	10.1016/j.bbr.2022.114008	Regular exercise following physical inactivity increased plasma irisin levels and enhanced the expression of the peroxisome proliferator-activated receptor gamma coactivator 1α.	Clinical Trial	STROBE Statement 22/22
Bastioli G, et al. (51)	2022	10.1523/jneurosci.2273-21.2022	Voluntary exercise for 30 days leads to increased dopamine release throughout the striatum and higher BDNF levels in the dorsal striatum (motor). The increase in dopamine release appears to require BDNF, as indicated by the lack of improvement in dopamine release in BDNF.	Clinical Trial	STROBE Statement 21/22
Islam M, et al. (40)	2021	10.1038/s42255-021-00438-z	Elevating circulating Irisin levels through peripheral administration of irisin via adeno-associated viral overexpression in the liver resulted in increased central irisin and was sufficient to improve both cognitive deficits and neuropathology in mouse models of Alzheimer's disease.	Clinical Trial	STROBE Statement 22/22
Ruiz-González D, et al. (44)	2021	10.1016/j.neubiorev.2021.05.025	BDNF levels increased significantly regardless of exercise type ($p < 0.001$, $p = 0.003$, and $p = 0.020$ for combined, aerobic, and resistance exercise, respectively), weekly exercise volume ($p < 0.001$ for ≥150 and < 150 min/week).	Clinical Trial	STROBE Statement 20/22
Szuhany k, et al. (54)	2020	10.1016/j.jpsychires.2020.02.003	Changes in BDNF before and after exercise had a moderate effect on the interaction between exercise and time that did not reach significance ($p = 0.13$, $d = 0.53$), with a similar moderate, non-significant effect on resting BDNF levels ($p = 0.20$, $d = 0.49$).	Clinical Trial	STROBE Statement 22/22
Rezola-Pardo C, et al. (55)	2020	10.1016/j.exger.2020.111024	Neither multicomponent exercise programs, dual-task exercises, nor walking programs caused changes in serum BDNF concentration in elderly adults living in care homes.	Clinical Trial	STROBE Statement 20/22
Antunes B, et al. (64)	2020	10.1080/17461391.2019.1611929	High-intensity exercise showed an inverse correlation between changes in BDNF and lactate ($r = -0.38$, $p = 0.044$). There was a significant correlation between BDNF and VO2max for moderate condition ($r = -0.57$, $p = 0.002$) and a trend for high-intensity condition ($r = -0.37$, $p = 0.050$) when assessing BDNF according to fitness level.	Clinical Trial	STROBE Statement 22/22
Huang L, et al. (36)	2018	10.3892/mmr.2018.9743	Irisin regulates the expression of BDNF and glucose metabolism in type 2 diabetic rats. The levels of mRNA and BDNF protein expression in primary cells after glucose exposure were significantly lower than in type 2 diabetic rats.	Clinical Trial	STROBE Statement 22/22
Li D, et al. (39)	2017	10.1016/j.metabol.2016.12.003	Exercise increases irisin concentrations, reducing neuronal injury induced by ischemia through the activation of Akt and ERK1/2 signaling pathways and contributes to the neuroprotective effect of physical exercise against cerebral ischemia.	Clinical Trial	STROBE Statement 22/22
Sleiman S, et al. (58)	2016	10.7554/eLife.15092	The metabolite β-hydroxybutyrate, which increases after prolonged exercise, induces BDNF promoter activities, particularly promoter I. Effects on BDNF expression in the hippocampus were observed after direct ventricular application of β-hydroxybutyrate.	Clinical Trial	STROBE Statement 21/22
Rizk FH, et al. (31)	2016	10.1139/cjpp-2015-0371	Irisin levels are significantly related to metabolic and liver functions in Egyptian patients with metabolic syndrome.	Clinical Trial	STROBE Statement 22/23
Huh JY, et al. (35)	2015	10.1210/jc.2014-2416	Exercise increases irisin levels in both individuals with metabolic syndrome and those without the condition. The magnitude of the increase was lower in patients with metabolic syndrome.	Clinical Trial	STROBE Statement 21/22
Bugge K, et al. (46)	2023	10.1097/wnn.0000000000000349	At the start of the study, the average serum BDNF level of individuals was 16.03 ng/ml (Val66Val = 15.89 ng/ml; Val66Met = 16.34 ng/ml); After exercise, the average serum BDNF level of individuals was 16.81 ng/ml (Val66Val = 16.14 ng/ml; Val66Met = 18.34 ng/ml).	Observational	PEDro Scale 9/10
Lourenco M, et al. (42)	2019	10.1038/s41591-018-0275-4	Peripheral overexpression of FNDC5/irisin prevents memory impairment, while peripheral or central blockade of FNDC5/irisin attenuates the neuroprotective actions of physical exercise on synaptic plasticity and memory.	Observational	PEDro Scale 9/10
Liu J, et al. (37)	2018	10.1038/s41598-018-33,229-w	Irisin suppresses migration and invasion of MIA PaCa-2 and Panc03.27 cells by inhibiting EMT. We demonstrated that irisin activates the AMPK-mTOR signaling pathway, which may play a critical role in inhibiting pancreatic cancer cell growth.	Observational	PEDro Scale 10/10
Nascimento C, et al. (50)	2015	10.3233/JAD-140576	Participants with BDNF-Met genotypes showed significant improvements in peripheral BDNF levels. The BDNF genotype seems to modulate the effects of physical exercise on BDNF secretion but does not affect cognition.	Observational	PEDro Scale 9/10
Hee K, et al. (34)	2013	10.1210/jc.2013-2373	Irisin was negatively associated with adiponectin ($r = -0.4$, $p < 0.001$) and positively with body mass index ($r = 0.22$, $p = 0.008$), blood pressure, fasting glucose ($r = 0.25$, $P = 0.002$), triglycerides ($r = 0.25$, $P = 0.003$), and the homeostasis model assessment for insulin resistance ($r = 0.33$, $P < 0.001$).	Observational	PEDro Scale 9/10
Sadier N, et al. (38)	2024	10.1016/j.lfs.2023.122393	The increase in Irisin concentration in rodents significantly reduced neuroinflammation, cytokine cascades, and neurodegeneration.	Review	PRISMA Statement 25/27
Liu S, et al. (29)	2022	10.3389/fendo.2022.962968	Irisin levels are highly associated with health status. Irisin levels are significantly lower in patients with obesity, osteoporosis/fractures, muscle atrophy, Alzheimer's disease, and cardiovascular diseases.	Review	PRISMA Statement 26/27

(*continued on next page*)

Table 1 (*continued*)

Author	Year	DOI	Results	Article Type	Quality Assessment
Azman K, et al. (45)	2022	10.3390/ijms23126827	Deficiencies in BDNF and TrkB signaling may play a role in the pathophysiology of Alzheimer's disease, Parkinson's disease, and Huntington's disease.	Review	PRISMA Statement 27/27
Shobeiri P, et al. (47)	2022	10.1371/journal.pone.0264557	Serum BDNF concentrations post-exercise were significantly higher than pre-intervention levels SMD: 0.33, 95 % CI: [0.04; 0.61], p = 0.02)	Review	PRISMA Statement 27/27
Alves H, et al. (28)	2022	10.3389/fendo.2022.879066	Exercise-induced irisin can counteract inflammatory modulation by reducing cytokine production. Elevated irisin levels, as seen in healthy individuals, may favor a better prognosis.	Review	PRISMA Statement 23/27
Qi J, et al. (33)	2022	10.1016/j.neuroscience.2022.07.018	Irisin showed neuroprotective effects and promoted neurogenesis in various experimental models. Irisin has great potential as a treatment for neurodegenerative diseases.	Review	PRISMA Statement 25/27
Jo D, et al. (27)	2021	10.7762/cnr.2021.10.4.292	Exercise increases the secretion of myokines such as irisin and myostatin in skeletal muscles. Irisin secreted during exercise could regulate energy expenditure through PGC-1α and improve BDNF production in the depressive brain	Review	PRISMA Statement 24/27
Jodeiri M, et al. (26)	2021	10.3389/fnagi.2021.649929	Irisin is a possible mediator of exercise-induced benefits for brain function. Irisin release induces BDNF expression in the hippocampus, leading to improvements in learning and memory, and protection against injuries.	Review	PRISMA Statement 27/27
Sousa R, et al. (41)	2021	10.3390/ijms22042199	Irisin is a myokine produced in response to exercise, which has been identified as a relevant mechanism explaining the benefits of exercise on cardiovascular and mental health in patients with Type 2 Diabetes	Review	PRISMA Statement 25/27
Murawska-Ciałowicz E, et al. (49)	2021	10.3390/ijerph18147553	BDNF is also secreted by contracting skeletal muscle, which likely exerts auto- and endocrine effects, supporting communication between skeletal muscle and other distant organs/tissues, such as the nervous system.	Review	PRISMA Statement 27/27
Ribeiro D, et al. (57)	2021	10.3390/ijms22168814	The positive regulation of BDNF seems relatively consistent, NT-4/5 appears to show contradictory and inconsistent conclusions.	Review	PRISMA Statement 27/27
Huang H, et al. (52)	2021	10.3233/RNN-201060	Acute and chronic physical exercises can improve cognitive impairment by increasing peripheral BDNF levels. Aerobic exercises and longer durations of exercise increased BDNF levels.	Review	PRISMA Statement 24/27
Lin C, et al. (48)	2020	10.1016/j.bj.2020.01.001	BDNF is relatively well-studied in major psychiatric disorders, but its protein levels alone may not fully explain the findings, requiring joint interpretation with the clinical condition of subjects.	Review	PRISMA Statement 25/27
Palasz E, et al. (60)	2020	10.3390/ijms21031170	Animal studies revealed that physical activity increases the expression of BDNF and tropomyosin receptor kinase B (TrkB), leading to inhibition of neurodegeneration through induction of transcription factors and expression of genes related to neuronal proliferation, survival, and inflammatory response.	Review	PRISMA Statement 25/27
Walsh E, et al. (65)	2020	10.1016/j.arr.2020.101044	Physical activity can elevate circulating BDNF levels, increasing neurotrophic, neuroprotective, and cognitively beneficial properties. Practical implementation of this knowledge is limited by the lack of clarity on context and dosage effects.	Review	PRISMA Statement 20/27
Arhire LI, et al. (32)	2019	10.3389/fendo.2019.00524	Irisin may improve energy regulation and metabolic homeostasis in metabolic syndrome, offering hope for new strategies in treating these disorders.	Review	PRISMA Statement 22/27
Liu P, et al. (56)	2018	10.3389/fnins.2018.00052	Exercise and BDNF are associated with increased neurogenesis. The specific biochemical mechanisms of exercise-mediated neurogenesis and BDNF remain unclear.	Review	PRISMA Statement 22/27
Walsh J, et al. (63)	2018	10.1139/apnm-2018-0192	The type, intensity, and duration of physical activity are factors determining BDNF elevations and the magnitude of the increase.	Review	PRISMA Statement 25/27
Kurebayashi Y, et al. (59)	2018	10.24869/psyd.2018.129	Physical exercise does not significantly increase BDNF in patients with major depressive disorder. However, increased BDNF has been shown to be beneficial in mental disorder patients.	Review	PRISMA Statement 22/27
Phillips C, et al. (74)	2017	10.1155/2017/7260130	Stress-induced depressive pathology contributes to altered BDNF levels and function in individuals with major depressive disorder, leading to changes in regional neuroplasticity.	Review	PRISMA Statement 20/27
Wrann C, et al. (35)	2013	10.1016/j.cmet.2013.09.008	Exercise can improve cognitive function and is associated with increased BDNF expression. Forced expression of FNDC5 in primary cortical neurons increases BDNF expression, while FNDC5 knockdown via RNAi reduces BDNF.	Review	PRISMA Statement 24/27
Coelho F, et al. (61)	2013	10.1016/j.archger.2012.06.003	Physical exercise, particularly moderate-intensity exercises, seems to be more effective in promoting increased peripheral BDNF levels in the elderly.	Review	PRISMA Statement 22/27
Erickson K, et al. (62)	2012	10.1177/1073858410397054	There is strong evidence that decreased BDNF is associated with age-related hippocampal dysfunction, memory impairment, and increased risk of depression, while increased BDNF through aerobic exercise appears to improve hippocampal atrophy, memory function, and reduce depression.	Review	PRISMA Statement 25/27
Autry AE, et al. (53)	2012	10.1124/pr.111.005108	Results show that BDNF is crucial for synaptic plasticity and neuronal function, and its dysfunction is associated with conditions such as depression, schizophrenia, and anxiety disorders.	Review	PRISMA Statement 24/27

Akt: Protein Kinase B (PKB), AMPK: AMP-Activated Protein Kinase, BDNF: Brain-Derived Neurotrophic Factor, BrdU: Bromodeoxyuridine, CVD: Cardiovascular Diseases, ERK1/2: Extracellular Signal-Regulated Kinases 1 and 2, EMT: Epithelial-Mesenchymal Transition, FNDC5: Fibronectin Type III Domain Containing 5, HT: Hypertension, Irisin:

A myokine that influences metabolic processes, MIA: Melanoma Inhibitory Activity, MIA PaCa-2: Human Pancreatic Cancer Cell Line, mRNA: messenger RNA, mTOR: mechanistic Target of Rapamycin, NT-4/5: Neurotrophin-4/5, PGC-1α: Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 Alpha, PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses, SARS-CoV2: Severe Acute Respiratory Syndrome Coronavirus 2, SMD: Standardized Mean Difference, STROBE: Strengthening the Reporting of Observational Studies in Epidemiology, TrkB: Tropomyosin Receptor Kinase B, Val66Me: Valine 66 Methionine, VO_2max: Maximum Oxygen Uptake.

2.5. Study risk of bias

We assessed the risk of bias across studies using a comprehensive and structured approach. We evaluated each study for potential sources of bias, including selection bias, performance bias, detection bias, and reporting bias. The assessment was conducted through a rigorous examination of study design, methodology, and adherence to protocols. We employed standardized tools and criteria, such as the Cochrane Risk of Bias. By systematically identifying and addressing these biases, we aimed to provide a reliable synthesis of the evidence and offer insights into the quality and credibility of the included studies.

3. Results

A total of 584 articles were identified in the consulted databases. During the title and abstract screening phase, 79 articles were selected, forming the initial matrix of articles. After a thorough review, 48 studies related to physical exercise, Irisin, BDNF, and MS and MH were identified, of which 43 were selected for further analysis (Fig. 1). The extracted information from the selected articles was organized into two systematic analysis lines: 1. Physical exercise, physical activity, and mental health through Irisin, and 2. Physical exercise, physical activity, and mental health mediated by BDNF.

3.1. Physical exercise, physical activity, and mental health through Irisin

Regular physical exercise is essential for the prevention and treatment of MS. Various studies have shown that exercise improves insulin sensitivity, reduces blood pressure, decreases abdominal fat, and improves lipid profiles –(Jodeiri Farshbaf and Alviña, 2021; Jo and Song, 2021). The mechanisms behind these benefits are multifaceted and involve the interaction of several molecular pathways that influence metabolism, mental health, and the overall well-being of individuals with this medical condition.

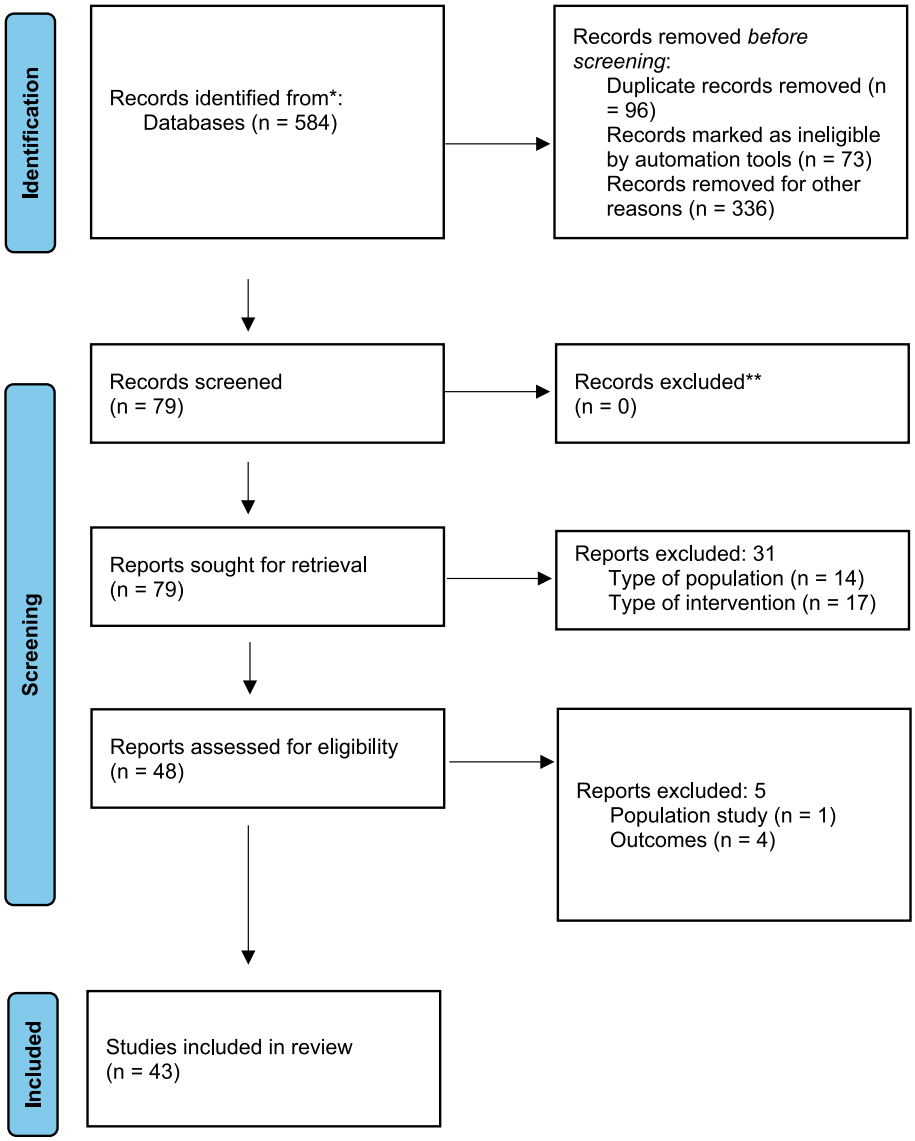

Fig. 1. PRISMA Flow Diagram of the Search Process.

3.1.1. Irisin and its effects

Animal and human studies have identified Irisin, a protein derived from the FNDC5 gene, as one of the main myokines released during physical activity. This myokine has gained attention for its potential role in mediating the positive effects of exercise on metabolic health and mental well-being (Jodeiri Farshbaf and Alviña, 2021; Alves et al., 2022). Irisin promotes the conversion of white adipose tissue (WAT) into brown adipose tissue (BAT) to generate calories and facilitate energy production or ATP through thermogenesis in a process known as "WAT browning" (10.3389/fendo.2022.962968, n.d.).

Irisin induces WAT browning by promoting the expression of specific brown fat genes, increasing thermogenesis and enhancing energy expenditure (Di Maio et al., 2024). Among the most relevant genes are nuclear receptors like PPARγ (Peroxisome Proliferator-Activated Receptor Gamma) and C/EBPβ (CCAAT/Enhancer Binding Protein Beta), which are transcription factors involved in regulating the differentiation of brown adipose cells. Additionally, Irisin activates the expression of UCP1 (Uncoupling Protein 1), an essential protein for thermogenesis in BAT that is found in the mitochondria of brown adipose cells and facilitates ATP production, contributing to increased energy expenditure and, consequently, greater calorie burning.

3.1.2. Irisin and mental health

Although the relationship between Irisin levels and MH in patients with MS is not fully understood, there is a growing trend to consider Irisin as an influential factor in the MH of individuals with MS. It has been established that those with MS, especially those with elevated liver enzymes, present significantly lower serum levels of Irisin, which correlate negatively with lipid metabolism parameters and positively with cognitive function mechanisms and self-perception (Rizk et al., 2016).

Archire et al., demonstrated that Irisin and its associated genes play a crucial role in the conversion of WAT to BAT, contributing to better management of blood glucose and lipid levels, as well as reducing systemic inflammation, improving cognitive function, and mental well-being in MS (Arhire et al., 2019).

Research conducted to date has shown a relationship between increased Irisin concentrations following physical exercise and improved cognitive function and greater mental well-being in MS (Qi et al., 2022; Hee Park et al., 2013). Huh et al., found that in individuals with MS, serum Irisin levels increased approximately 1.2 times after exercise, compared to a 1.4 times increase in healthy individuals, suggesting that physical exercise may be an effective intervention to enhance the synthesis and release of Irisin to improve both cardiovascular and mental health, regardless of age or physical condition (Huh et al., 2015).

Interest in understanding physical exercise as an effective intervention to increase Irisin levels and promote cardiovascular and MH has grown. Huang et al., suggest that Irisin may play a crucial role in regulating energy expenditure and brain homeostasis, indicating that regular physical activity not only improves overall physical condition but also promotes the benefits of Irisin on MH, even in MS (Huang et al., 2018). Gisaw et al. (Hee Park et al., 2013), establish that Irisin levels improve insulin sensitivity, increase energy expenditure, and reduce fat accumulation by activating the AMPK-mTOR signaling pathway, modulating inflammatory responses implicated in mental disorders such as depression, and enhancing cellular defense mechanisms against oxidative stress (Liu et al., 2018). Sadier et al., demonstrated that the exogenous administration of Irisin in mice (at levels similar to those achieved after physical exertion) reduces neuroinflammation, neurodegeneration, and oxidative stress, improving cognitive performance and social interaction capacity (Sadier et al., 2024). The authors suggest that Irisin could act as a bridge between physical exercise and brain health, offering neuroprotective benefits included in the maintenance of well-being or MH.

Studies in patients with neurological impairment have shown that physical exercise increases plasma Irisin concentrations through the *Protein Kinase B* (or Akt) and ERK1/2 pathways, indicating a possible connection between metabolism, cardio-cerebrovascular conditions, and Irisin (Li et al., 2017). It has been proposed that physical exercise, the levels of this myokine, and BDNF synthesis are interrelated, suggesting that Irisin positively influences BDNF levels (Islam et al., 2021; Sousa et al., 2021b), which is a relevant factor in synaptogenesis, neurogenesis, and synaptic plasticity, as essential neurobiological mechanisms for managing stress, depression, and anxiety (Sadier et al., 2024; Lourenco et al., 2019; Park et al., 2022).

3.2. Physical exercise, physical activity, and mental health mediated by BDNF

Currently, there is a growing body of scientific literature linking regular exercise with increased BDNF levels and its positive effects on mental health. BDNF, belonging to the neurotrophin family, is crucial for promoting neuronal growth, survival, and differentiation, directly linking its contractions to cognitive function and mental health (Fernández-Rodríguez et al., 2022).

3.2.1. BDNF and its effects

This myokine has been associated with several MH benefits, including increased endorphin synthesis, reduced cortisol activation related to stress, and consequently, improved stress management. Moreover, the increase in Irisin following physical exercise is related to an increase in BDNF synthesis, which in turn influences enhanced cognitive function, reduced cognitive decline due to aging, and better sleep patterns (Ruiz-González et al., 2021).

Exercise has consistently been linked to elevated BDNF levels, making it a protein directly associated with promoting growth, neuronal survival, and differentiation, and thus currently, its levels are linked to cognitive function and MH (Azman and Zakaria, 2022). BDNF is synthesized both in the brain and in peripheral muscle tissue, making it a myokine reactive to physical exertion (Bugge Kambestad et al., 2023; Shobeiri et al., 2022). Evidence has shown that exercise, particularly aerobic exercise, increases BDNF levels, promoting neuroplasticity, synaptic function, and modo (Shobeiri et al., 2022).

Lin et. Al., state that low BDNF levels contribute to hippocampal atrophy and impaired functioning, affecting mood regulation and stress response, so decreases in BDNF synthesis are strongly associated with poor stress response, anxiety, and depression (Lin and Huang, 2020). Conversely, regular exercise is associated with elevated BDNF levels, which is considered one of the mechanisms through which exercise exerts its antidepressant (Murawska-Ciałowicz et al., 2021), cognitive-enhancing (Azman and Zakaria, 2022) and neuroprotective effects against brain deterioration (Nascimento et al., 2015).

BDNF, as a neurotrophin, is crucial for neuron survival, growth, and differentiation. Beyond its role in neuroplasticity (Bastioli et al., 2022), BDNF has been implicated in the regulation of energy balance, glucose metabolism, and insulin sensitivity (Huang et al., 2018). Studies have shown that BDNF is produced not only in the brain but also in peripheral tissues (muscle), suggesting a broader role in systemic metabolic regulation (Huang et al., 2021). It is known that the release of growth factors and the activation of specific signaling pathways play a crucial role in regulating hormones related to stress management, anxiety, depression, and distress (Autry and Monteggia, 2012).

3.2.2. BDNF, exercise, and mental health

The elevation of BDNF levels during exercise has been correlated with better cognitive function, mood, and, more importantly, MH in patients with metabolic diseases. According to Azman K et al., physical exercise, regardless of load, intensity, volume, or mode, modifies BDNF concentrations and decreases depression (Szuhany and Otto, 2020). Meanwhile, Jodeiri F et. Al., establish that physical exercise reduces symptoms related to insomnia (irritation, intolerance, and

aggressiveness), and lowers the prevalence and incidence of anxiety and depressive disorders through the biological activation of neurophysiological mechanisms such as neuroplasticity and neuronal biogenesis, not only associated with increased BDNF but also with increased Irisin synthesis at the muscular level (Jodeiri Farshbaf and Alviña, 2021).

Despite the large number of publications supporting a positive relationship between physical exercise and BDNF, the molecular mechanisms of this relationship are not fully defined (Rezola-Pardo et al., 2020). Liu et al., conclude that although exercise significantly increases circulating BDNF levels, the mechanisms through which exercise influences BDNF production are not fully understood (Liu and Nusslock, 2018), a point also raised by Ribeiro D et al. (Ribeiro et al., 2021). On the contrary, Sleiman S, et al., assert that prolonged exercise increases BDNF concentrations as a result of increased hepatic synthesis of the energy metabolite Dβ-hydroxybutyrate (DBHB) (Sleiman et al., 2016), which, after traveling through the bloodstream, reaches the hippocampus, inhibiting histone deacetylases and stimulating BDNF and FNDC5 protein precursor of Irisin synthesis (Lin and Huang, 2020).

In contrast, Kurebayashi Y, et al., state that physical exercise does not significantly increase BDNF in patients with major depressive disorder, and while the increase in BDNF has been shown to be beneficial in patients with mental disorders, their study does not conclude this (Faculty of Nursing, Niigata University of Health and Welfare, Niigata, Japan, Kurebayashi Y, Otaki J, 2018). Conversely, authors such as Palasz E, et al. (Palasz et al., 2020), Coelho F, et al. (M, Gobbi S, Andreatto CAA, Corazza DI, Pedroso RV, Santos-Galduróz RF., 2013),Erickson K, et al. (Erickson et al., 2012), among others, determine not only that physical exercise increases BDNF synthesis but also that physical inactivity can lead to a decrease in this factor's concentration in the hippocampus, leading to earlier brain deterioration.

Palasz E et al., mention that the process by which BDNF increases following aerobic exercise is associated with the upregulation of tropomyosin receptor kinase B (TrkB), which leads to the inhibition of neurodegeneration through the induction of transcription factors and the expression of genes related to neuronal proliferation, survival, and inflammatory response (Palasz et al., 2020). Exercise increases BDNF concentrations in the brain, enhancing neurotrophic, neuroprotective, and cognitively beneficial properties (Walsh and Tschakovsky, 2018), However, the practical implementation of this knowledge is limited by the lack of clarity regarding the context and dosage effects (Antunes et al., 2020; Walsh et al., 2020).

BDNF may play a protective role against the development of MS (Shobeiri et al., 2022; Murawska-Ciałowicz et al., 2021; Liu and Nusslock, 2018), as it is involved in regulating appetite, energy expenditure, and insulin sensitivity. Low BDNF levels have been associated with obesity, insulin resistance, and other components of MS. Therefore, the ability of exercise to increase BDNF levels provides a potential neurotrophic mechanism through which physical activity can mitigate the risk and impact of MS.

4. Discussion

Irisin and brain-derived neurotrophic factor (BDNF) are integral to understanding how physical exercise interacts with risk factors of metabolic syndrome. Research suggests that irisin, a myokine released during physical activity, may modulate BDNF levels indirectly by enhancing metabolic processes that influence central nervous system (CNS) functionality and overall efficiency (Leger et al., 2024; Radikova et al., 2024). Specifically, irisin facilitates the transformation of white adipose tissue (WAT) into brown adipose tissue (BAT), which boosts metabolic performance in various tissues, including the brain. This transformation is linked to improved mental health outcomes, characterized by a decrease in anxiety and depression (Uysal et al., 2018). Furthermore, these metabolic benefits contribute to the reduction of chronic inflammation and oxidative stress, both of which are detrimental to brain health and cognitive function. As systemic inflammation subsides, the brain environment becomes more favorable for the synthesis and effectiveness of neurotrophic factors like BDNF, promoting cognitive abilities and enhancing resilience against mental health disorders (Leger et al., 2024; Skrzep-Poloczek et al., 2023).

The reviewed articles suggest that Irisin crosses the blood-brain barrier and exerts direct and efficient positive effects on the CNS, particularly in regions such as the hippocampus, which regulates emotions, behavior, and stress management through its influence on hormonal regulation (Sousa et al., 2021a; Jodeiri Farshbaf and Alviña, 2021; Islam et al., 2021). This interaction positions Irisin as a myokine favorable to metabolic health, brain plasticity, and mental well-being in individuals with risk factors such as MS. Consequently, Irisin is projected as an exercise-induced myokine or protein released by muscle tissue with a dual function (metabolic and hormonal regulator).

On the other hand, the production of BDNF in response to physical exercise is another essential component of mental and cardiovascular well-being in individuals with MS. BDNF supports the growth and differentiation of new neurons and synapses (Kurdi and Flora, 2019), which are vital for maintaining and optimizing cognitive functions and mental well-being. Exercise-induced increases in BDNF concentrations are associated with enhanced neurogenesis, synaptogenesis, and plasticity in the hippocampus, neurobiological changes essential for counteracting the effects of stress, anxiety, and depression (Dadkhah et al., 2023).

Publications suggest that neurotrophins and growth factors induced by exercise, such as BDNF (among others), positively and significantly contribute to brain health throughout life (Zühtü, 2023). Thus, the relationship between exercise and BDNF involves intrinsic biological mechanisms ranging from neuronal biogenesis, optimization of cerebral blood flow, and activation of myokines in the brain and other peripheral tissues, constituting positive effects of exercise on overall health in individuals with and without MS (Cefis et al., 2023).

Although the interaction between Irisin and BDNF highlights a sophisticated biological response to physical exercise that promotes metabolic and mental health, the underlying biological and physiological mechanisms are not yet fully understood. However, the clinical physical and mental changes resulting from exercise are well-documented and studied (Phillips, 2017). The relationship between Irisin and BDNF in MS underscores the importance of regular physical exercise or activity not only for cardiometabolic health but also for improving metabolic syndrome.

5. Conclusion

Despite the current global interest in MS and prevention and management strategies, there is still limited understanding of the implications of neurotrophic factors on mental well-being, the molecular mechanisms of action of Irisin and BDNF, and the known effects of physical exercise on depression and anxiety. Currently, the effects of exercise on Irisin and BDNF concentrations, and how these relate to cardiovascular and MH in individuals with MS, are not well understood.

The link between exercise, BDNF, Irisin, and MS offers promising pathways for preventive and therapeutic interventions in patients with metabolic diseases. Understanding the molecular and cellular mechanisms involved in the interaction between exercise-induced Irisin and BDNF could lead to the development of targeted strategies for individuals with symptoms such as depression and anxiety associated with MS. Thus, knowledge about the behavior of these proteins could represent a holistic approach to addressing both neurological and metabolic aspects of cardiovascular and MH in individuals with MS.

Abbreviations

ATP	Adenosine Triphosphate
BDNF	Brain-Derived Neurotrophic Factor
BAT	Brown Adipose Tissue

CNS	Central Nervous System
DBHB	Dβ-hydroxybutyrate
HDL	High-Density Lipoproteins
IL-6	Interleukin-6
LDL	Low-Density Lipoproteins
MH	Mental Health
MS	Metabolic Syndrome
NCDs	Non-Communicable Diseases
PAHO	Pan American Health Organization
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TNF-α	Tumor Necrosis Factor-alpha
TrkB	Tropomyosin Receptor Kinase B
UCP1	Uncoupling Protein 1
WAT	White Adipose Tissue
WHO	World Health Organization

CRediT authorship contribution statement

Wilder Villamil-Parra: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Luisa Moscoso-Loaiza:** Writing – review & editing, Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis, Data curation.

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

In the process of developing this article, the researchers employed the artificial intelligence tool ChatGPT 3.0, created by OpenAI (San Francisco, California, USA, 2020), to improve the writing and clarity of the text, especially in the introduction. This step was taken to enhance the English language usage, as the authors are non-native English speakers. The author then reviewed and modified the content generated, taking full responsibility for its final publication.

Funding

No funding was received for this research.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Luisa Moscoso-Loaiza reports article publishing charges was provided by National University of Colombia. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

There are no acknowledgments for this study. All participants in the research are listed as authors of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2024.112640.

Data availability

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

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