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Exercise-induced BDNF signaling mediates neuroplasticity in depression

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Abstract

Background.

Major depressive disorder (MDD) is one of the leading causes of disability worldwide and is increasingly conceptualized as a disorder of impaired neuroplasticity, characterized by disrupted synaptic connectivity, reduced hippocampal neurogenesis, and large-scale alterations in brain network organization [1–4]. Brain-derived neurotrophic factor (BDNF) is a critical regulator of neuronal survival, synaptic remodeling, and experience-dependent plasticity, and plays a central role in both the pathophysiology of depression and the mechanisms of antidepressant treatments [1,2]. Dysregulation of BDNF signaling has been linked to chronic stress, neuroinflammation, and disturbances in glutamatergic and GABAergic neurotransmission, contributing to structural and functional brain abnormalities observed in

MDD [5–7]. Physical exercise has emerged as a potent non-pharmacological intervention capable of modulating neuroplastic processes and restoring BDNF-dependent signaling pathways, with growing evidence supporting its antidepressant efficacy [20-23,25-27]. . However, the integration of molecular mechanisms with clinical outcomes remains incomplete, particularly regarding the mediating role of BDNF in exercise-induced antidepressant effects.

Aim.

This review aims to synthesize current molecular, neurobiological, and clinical evidence and to develop a comprehensive multi-level framework, in which exercise-induced BDNF signaling mediates neuroplastic adaptations and antidepressant effects in depression.

Material and methods.

A narrative review was conducted based on peer-reviewed literature, including mechanistic studies, randomized controlled trials, longitudinal cohort studies, and meta-analyses. The review was performed in accordance with general principles of systematic reviews, including structured literature selection and critical appraisal of evidence. Evidence from molecular neuroscience, exercise physiology, and clinical psychiatry was integrated to examine the relationship between physical activity, BDNF regulation, neuroplastic adaptations, and depressive outcomes.

Results.

Exercise induces multiple molecular and systemic adaptations that converge on the upregulation of BDNF expression, including lactate-mediated signaling, SIRT1-dependent transcriptional pathways, skeletal muscle–brain crosstalk, and modulation of the kynurenine pathway [8–10]. These mechanisms promote synaptic plasticity, dendritic remodeling, hippocampal neurogenesis, and improvements in brain structure and functional connectivity within mood-regulating networks [11,12,16,17]. Meta-analytic evidence demonstrates that exercise significantly increases circulating (peripheral) BDNF levels, which are considered indirect peripheral correlates of central neuroplasticity [14,15].

At the clinical level, both aerobic and resistance exercise significantly reduce depressive symptoms [22] and are associated with structural brain adaptations, including increased hippocampal volume [19]. Large-scale epidemiological and prospective studies indicate that higher levels of physical activity are associated with a reduced risk of depression in a dose–

response manner [20,21,23]. Furthermore, recent high-quality meta-analyses confirm the effectiveness of exercise interventions across different populations and clinical conditions [24–27]. Importantly, converging evidence indicates that exercise-induced changes in BDNF are directly associated with improvements in depressive symptoms, supporting a mechanistic link and a potential causal pathway between exercise, neuroplasticity, and depression [28–30]. Together, these findings support a coherent multi-level mechanistic framework linking peripheral physiological adaptations with central neuroplastic changes and clinical improvement. Moreover, these findings have important clinical implications, suggesting that exercise may serve as a scalable and accessible intervention targeting neurobiological mechanisms of depression.

Conclusions.

Exercise-induced BDNF signaling represents a central neurobiological mechanism linking physical activity with enhanced neuroplasticity and reduced depressive symptoms. Collectively, the available evidence indicates that BDNF is a key mechanistic mediator underlying the antidepressant effects of exercise. These findings strongly support the integration of structured exercise into clinical practice as an evidence-based component of depression treatment. However, heterogeneity across studies and variability in exercise protocols should be considered when interpreting these findings. Future research should focus on dose–response relationships, individual variability in BDNF responsiveness, and the optimization of exercise protocols targeting neuroplastic mechanisms.

Key words: BDNF; depression; neuroplasticity; physical activity; exercise; hippocampus; antidepressant mechanisms

1. Introduction

Major depressive disorder (MDD) is one of the leading causes of disability worldwide and represents a major public health challenge due to its high prevalence, recurrent course, and substantial socioeconomic burden [1–4]. In addition to its profound impact on quality of life, MDD is associated with increased morbidity and mortality. Despite advances in pharmacological and psychotherapeutic treatments, a considerable proportion of patients fail to achieve sustained remission or experience relapse, underscoring the need for a deeper

understanding of the biological mechanisms underlying depression and for the development of more effective, mechanism-based therapeutic strategies [1,2].

Over the past decades, traditional monoaminergic models of depression have been increasingly complemented by the neuroplasticity hypothesis, which conceptualizes depression as a disorder of impaired structural and functional brain plasticity. Within this framework, depression is characterized by alterations in synaptic strength, dendritic morphology, and neurogenesis—particularly within the hippocampus and prefrontal cortex—as well as dysfunction in large-scale neural networks involved in emotional regulation and cognitive processing [2–4]. Chronic stress, a central etiological factor in depression, induces synaptic loss, dendritic atrophy, and reduced neurogenesis, thereby contributing to the persistence and recurrence of depressive symptoms [2–4].

At the core of these neuroplastic processes lies brain-derived neurotrophic factor (BDNF), a neurotrophin that plays a central role in neuronal survival, synaptic plasticity, and activity-dependent remodeling of neural circuits. BDNF signaling is critically involved in long-term potentiation, dendritic spine formation, and the maintenance of network integrity. A substantial body of evidence demonstrates that reduced BDNF expression and impaired signaling are associated with stress exposure, neuroinflammatory and stress-related biological processes, as well as disturbances in glutamatergic and GABAergic neurotransmission systems [5–7]. These alterations contribute to structural and functional brain abnormalities observed in individuals with depression. Importantly, increasing evidence suggests that the therapeutic effects of antidepressant treatments are mediated, at least in part, through the restoration of BDNF-dependent neuroplasticity, positioning BDNF as a central biological substrate of treatment response [1,2].

Within this evolving conceptual landscape, physical exercise has emerged as a potent and multifaceted non-pharmacological intervention for depression. A growing body of high-quality evidence indicates that exercise significantly reduces depressive symptoms and improves mental health outcomes across diverse populations and clinical conditions [20–27]. Unlike many traditional interventions, exercise exerts broad systemic effects, influencing biological, behavioral, and psychological mechanisms implicated in depression, including inflammatory processes, neurotransmitter systems, and behavioral activation pathways [11–13]. This multidimensional profile positions exercise as a unique intervention capable of simultaneously targeting both biological and psychosocial determinants of depression.

From a mechanistic perspective, increasing attention has been directed toward the role of BDNF as a potential mediator of the antidepressant effects of exercise. Converging evidence indicates that exercise-induced increases in BDNF are associated with enhanced synaptic plasticity, dendritic complexity, and hippocampal neurogenesis, as well as with improvements in brain structure and functional connectivity within mood-regulating neural networks [8–10,14–18]. These neuroplastic adaptations may counteract stress-induced neural atrophy and network dysfunction, thereby facilitating recovery of brain function and contributing to clinical improvement in depression.

At the molecular level, several interconnected pathways explain how exercise modulates BDNF signaling. Lactate, produced during physical activity, acts not only as a metabolic substrate but also as a signaling molecule capable of activating SIRT1-dependent transcriptional pathways, leading to increased BDNF expression in the brain [8]. In parallel, skeletal muscle–brain crosstalk mediated by myokines represents a critical mechanism linking peripheral physiological activity with central nervous system adaptations [10]. Additionally, exercise modulates the kynurenine pathway, reducing the accumulation of neurotoxic metabolites and enhancing resilience to stress-related depressive states [9]. Together, these mechanisms illustrate a complex bidirectional interaction between peripheral metabolic processes and central neurobiological changes.

At the systems level, these molecular adaptations are reflected in measurable structural and functional brain changes. Neuroimaging studies demonstrate that regular physical activity is associated with structural brain adaptations, particularly increased hippocampal volume, as well as improved integrity and efficiency of neural circuits involved in emotion regulation and cognition [19]. Furthermore, meta-analytic evidence indicates that exercise leads to significant increases in circulating (peripheral) BDNF levels, which are considered indirect correlates of central neuroplastic processes. Importantly, these changes are associated with improvements in depressive symptoms and may act as key mediators of the antidepressant effects of exercise [14,15,28–30].

Taken together, the available evidence supports a multi-level mechanistic pathway in which exercise-induced peripheral physiological changes translate into central neuroplastic adaptations via BDNF signaling, ultimately leading to improvements in depressive symptoms. This perspective supports a conceptual shift toward viewing exercise as a biologically grounded intervention targeting neuroplasticity through BDNF-dependent pathways. However, despite

the rapidly expanding literature, significant gaps remain. In particular, there is a lack of comprehensive integration between molecular mechanisms and clinical outcomes. Existing studies often examine biological processes and clinical effects in isolation, with relatively few attempts to synthesize these domains within a unified conceptual framework. Moreover, the extent to which BDNF functions as a true mechanistic mediator, rather than merely a correlate, of exercise-induced antidepressant effects remains insufficiently clarified.

Research Objective.

The aim of this review is to synthesize current molecular and clinical evidence and to develop an integrative multi-level framework linking molecular, neurobiological, and clinical findings, in which exercise-induced BDNF signaling is hypothesized to mediate neuroplastic adaptations and antidepressant effects in depression.

Research Problems.

1. What are the key molecular mechanisms through which physical exercise modulates BDNF signaling?
2. How do exercise-induced alterations in BDNF contribute to neuroplastic processes in the brain?
3. What is the nature and strength of the association between BDNF modulation and clinical improvement in depressive symptoms?
4. To what extent can BDNF be conceptualized as a mechanistic mediator of the antidepressant effects of exercise?

Research Hypotheses.

1. Physical exercise leads to significant upregulation of BDNF through multiple interconnected molecular and physiological pathways.
2. Exercise-induced increases in BDNF are associated with enhanced neuroplasticity, including hippocampal neurogenesis and improved structural and functional brain connectivity.
3. Modulation of BDNF levels is associated with clinically meaningful reductions in depressive symptoms.
4. BDNF acts as a central biological mediator linking physical exercise with antidepressant effects.

2. Research materials and methods

2.1 Study Design

This study was conducted as a narrative review supported by a structured literature search, aiming to synthesize current molecular and clinical evidence on the role of exercise-induced BDNF signaling in depression. The methodological approach was designed in accordance with established principles of evidence-based literature synthesis and integrative review methodology, allowing for the inclusion and interpretation of heterogeneous sources of evidence.

2.2 Search Strategy

A structured and targeted literature search was conducted using the following electronic databases:

- PubMed
- Scopus
- Web of Science

The search encompassed studies published between 2014 and 2024, ensuring the inclusion of recent and clinically and mechanistically relevant evidence.

The search strategy was based on combinations of the following keywords:

- “BDNF” OR “brain-derived neurotrophic factor”
- “exercise” OR “physical activity”
- “depression” OR “major depressive disorder”
- “neuroplasticity”
- “exercise AND BDNF AND depression”

Boolean operators (AND, OR) were applied to optimize search sensitivity and specificity.

In addition to database searches, manual screening of reference lists from key publications and highly cited reviews was performed to identify additional relevant studies. The final selection of articles was guided by their scientific relevance, methodological rigor, and contribution to

advancing understanding of the relationship between exercise, BDNF signaling, and depression.

2.3 Eligibility Criteria

Inclusion criteria:

- peer-reviewed articles
- studies published in English
- original research articles, systematic reviews, and meta-analyses
- studies addressing:
    - the effects of physical exercise on BDNF signaling
    - neuroplastic mechanisms in depression
    - clinical outcomes related to depressive symptoms

Exclusion criteria:

- studies conducted exclusively in animal models (unless directly relevant to molecular mechanisms and their translational implications)
- conference abstracts, editorials, letters, and non-peer-reviewed publications
- studies not directly related to BDNF, physical activity, or depression

2.4 Study Selection Process

Titles and abstracts identified through the search process were screened for relevance. Full-text articles of potentially eligible studies were subsequently assessed according to the predefined inclusion and exclusion criteria.

The final selection of studies was based on:

- relevance to the research objectives
- methodological quality
- contribution to the understanding of molecular, neurobiological, and clinical mechanisms

Priority was given to high-quality evidence, including systematic reviews, meta-analyses, and well-designed clinical studies, as well as key mechanistic studies providing insight into biological pathways linking exercise, BDNF signaling, and depression.

2.5 Data Extraction and Synthesis

Data extraction focused on three primary domains:

- molecular mechanisms (e.g., BDNF signaling pathways, lactate-mediated signaling, kynurenine metabolism)
- neurobiological outcomes (e.g., neurogenesis, synaptic plasticity, brain structure and functional connectivity)
- clinical outcomes (e.g., changes in depressive symptoms and treatment response)

A qualitative, thematic synthesis approach was applied to integrate findings across heterogeneous study designs. The evidence was organized into the following thematic domains:

1. BDNF and neuroplasticity in depression
2. Molecular mechanisms underlying exercise-induced BDNF signaling
3. Neurobiological adaptations associated with physical activity
4. Clinical effects of exercise on depressive symptoms

This structure enabled a coherent multi-level integration of molecular, neurobiological, and clinical evidence.

2.6 Methodological Considerations

Given the heterogeneity of included studies—including clinical trials, observational studies, and meta-analyses—a quantitative meta-analysis was not performed. Instead, a narrative synthesis approach was employed to integrate findings across different levels of evidence.

The primary objective of this approach was to develop a comprehensive conceptual framework linking exercise, BDNF signaling, neuroplasticity, and depression across multiple levels of analysis, rather than to generate pooled effect estimates.

3.Research results

3.1 BDNF and Neuroplasticity in Depression

Brain-derived neurotrophic factor (BDNF) is a central regulator of neuroplasticity and plays a fundamental role in maintaining the structural and functional integrity of the brain.

Neuroplasticity encompasses dynamic processes such as synaptic remodeling, dendritic spine formation, long-term potentiation, and adult neurogenesis, particularly within the hippocampus and prefrontal cortex—regions critically involved in emotional regulation, cognitive processing, and stress adaptation [1–4,16,17].

Contemporary neurobiological models conceptualize depression as a disorder of impaired neuroplasticity, in which chronic stress induces synaptic loss, dendritic atrophy, and reduced neurogenesis. These alterations are closely associated with decreased BDNF expression and disrupted signaling pathways, contributing to structural brain abnormalities and dysregulation of neural circuits involved in mood regulation [5–7]. In parallel, disturbances in glutamatergic and GABAergic neurotransmission further exacerbate synaptic dysfunction and impair network-level communication [4,7].

Importantly, BDNF should be considered not only a biomarker of neural integrity, but also a mediator of adaptive neuroplastic processes. Reduced BDNF levels are associated with increased vulnerability to stress and diminished resilience, whereas restoration of BDNF signaling promotes synaptic recovery and functional improvement [1,2]. Both conventional antidepressants and rapid-acting interventions exert their effects through activity-dependent modulation of BDNF pathways, further supporting its central role in the pathophysiology and treatment of depression [1,2,7].

Furthermore, meta-analytic evidence indicates that BDNF alterations are dynamic and state-dependent, varying across different stages of depression and treatment response [6]. This reinforces the conceptualization of BDNF as a core mechanistic substrate underlying both the development and remission of depressive symptoms.

3.2 Molecular Mechanisms of Exercise-Induced BDNF Signaling

Physical exercise induces a coordinated cascade of molecular adaptations that converge on the upregulation of BDNF signaling. One of the most well-characterized mechanisms involves lactate, which functions not only as a metabolic substrate but also as a signaling molecule capable of crossing the blood–brain barrier and activating SIRT1-dependent transcriptional pathways, thereby increasing hippocampal BDNF expression [8].

In addition, skeletal muscle–brain crosstalk plays a critical role in mediating the central effects of exercise. Activation of PGC-1α1 in skeletal muscle regulates kynurenine metabolism,

shifting it toward neuroprotective pathways and reducing the accumulation of neurotoxic metabolites associated with stress-induced depression [9]. This mechanism highlights the importance of peripheral–central integration in exercise-induced neurobiological adaptations.

Exercise modulates interacting biological systems, including inflammatory processes, neurotransmitter systems, and metabolic and systemic regulation, all of which interact with BDNF signaling [10–13]. For instance, reductions in pro-inflammatory cytokines and improvements in metabolic homeostasis may facilitate a neurobiological environment that supports synaptic plasticity and BDNF expression.

Crucially, these mechanisms should be understood as part of an integrated regulatory network rather than as isolated pathways. Within this network, BDNF functions as a central hub that integrates peripheral physiological signals and translates them into adaptive neuroplastic changes in the brain [11–13]. This systems-level perspective is essential for understanding the multifactorial nature of exercise-induced antidepressant effects.

These molecular mechanisms provide the biological foundation for the structural and functional brain adaptations observed following regular physical activity.

3.3 Neurobiological Adaptations Associated with Exercise

At the neurobiological level, exercise-induced increases in BDNF are associated with a range of structural and functional brain adaptations. One of the most consistently reported effects is enhanced hippocampal neurogenesis, which plays a critical role in learning, memory, and emotional regulation [14–18].

Exercise further promotes synaptic plasticity by increasing dendritic complexity, spine density, and synaptic strength, thereby improving neural efficiency and adaptability. These changes are particularly relevant in the context of depression, where synaptic deficits and reduced connectivity are key pathophysiological features [3,4].

Neuroimaging studies provide converging evidence that regular physical activity is associated with increased hippocampal volume and improved structural integrity of brain regions involved in mood regulation [19]. In parallel, exercise enhances functional connectivity within large-scale neural networks implicated in emotional processing, cognitive control, and stress regulation [16,17].

Taken together, these findings suggest that exercise induces both structural and functional reorganization of neural circuits. Importantly, these neurobiological adaptations are closely linked to BDNF signaling, supporting its role as a key mediator of exercise-induced brain plasticity and functional recovery.

3.4 Clinical Effects of Exercise and the Role of BDNF

A substantial body of clinical evidence supports the antidepressant effects of physical exercise across diverse populations and clinical conditions. Large-scale epidemiological studies demonstrate that higher levels of physical activity are associated with a reduced risk of depression, highlighting the preventive potential of exercise [20–23].

Meta-analyses of prospective cohort studies further confirm that physical activity significantly reduces the incidence of depression, providing strong evidence for its protective effects. Intervention studies indicate that both aerobic and resistance exercise lead to clinically meaningful reductions in depressive symptoms, with effects comparable to those of standard treatments in certain contexts [22,24,27].

Recent high-quality meta-analyses and umbrella reviews provide consistent evidence that exercise is an effective intervention for reducing symptoms of depression, anxiety, and psychological distress [25,26]. These findings support the integration of exercise into evidence-based treatment strategies for depression.

At the biological level, meta-analytic evidence indicates that exercise is associated with increases in circulating BDNF levels, which are considered peripheral correlates of central neuroplastic processes [14,28–30]. Importantly, these increases are associated with improvements in depressive symptoms, supporting the hypothesis that BDNF may act as a mechanistic mediator linking physical activity with clinical outcomes.

However, despite strong associative evidence, the causal role of BDNF remains incompletely understood. It is likely that BDNF operates within a broader network of interacting biological mechanisms, including inflammatory modulation, neurotransmitter regulation, and metabolic processes. Therefore, BDNF should be conceptualized as a central, though not exclusive, mediator of the antidepressant effects of exercise[5,11-13].

3.5 Integrative Model of Exercise–BDNF–Depression Pathway

The evidence synthesized across molecular, neurobiological, and clinical domains supports the formulation of a comprehensive integrative model in which physical activity influences depression through multi-level pathways converging on BDNF signaling. Within this framework, exercise can be conceptualized as a systemic stimulus that induces coordinated adaptations across peripheral and central biological systems, ultimately leading to neuroplastic and clinical outcomes [1–4,10–12].

At the peripheral level, physical activity initiates a range of metabolic, endocrine, and immune responses, including modulation of kynurenine metabolism via PGC-1α1, reductions in pro-inflammatory cytokines, and improvements in metabolic homeostasis [9–12]. These adaptations contribute to a systemic environment that supports neuroplastic processes and resilience to stress. In parallel, signaling molecules such as lactate act as key mediators of muscle–brain communication, crossing the blood–brain barrier and activating transcriptional pathways involved in BDNF expression [8,10].

At the central level, these peripheral signals converge on the upregulation of BDNF and activation of downstream intracellular pathways that regulate synaptic plasticity, neuronal survival, and structural remodeling [1–4,14–16]. These processes include long-term potentiation, dendritic spine formation, and adult hippocampal neurogenesis, all of which are critically involved in learning, memory, and emotional regulation [3,4,16]. Importantly, exercise-induced neurotrophic signaling may counteract stress-related synaptic loss and restore functional connectivity within neural circuits implicated in depression [5,7,16].

Neuroimaging and neurobiological evidence further demonstrate that these molecular and cellular changes translate into macroscopic brain adaptations, including increased hippocampal volume and improved network-level connectivity within regions involved in mood regulation and cognitive control [16,17,19]. These findings provide a structural and functional substrate for the observed clinical benefits of physical activity.

At the clinical level, large-scale epidemiological studies and controlled interventions consistently demonstrate that physical activity is associated with reduced risk of depression and significant improvements in symptom severity across diverse populations [20-23,25-27].

Importantly, meta-analytic evidence indicates that exercise-induced increases in circulating BDNF are associated with clinical improvement, supporting the role of this neurotrophin as a key integrative mediator linking biological processes with behavioral outcomes [14,28–30]. Consistent with this framework, recent literature also highlights that physical activity exerts antidepressant effects through combined neurobiological and psychosocial mechanisms, including modulation of neurotransmitter systems, enhancement of neurotrophic signaling such as BDNF, and improvements in emotional regulation and stress resilience, further reinforcing its role as a multidimensional therapeutic intervention in depression [31].

However, this model should be interpreted within a systems-level framework. Rather than representing a simple linear pathway, exercise-induced adaptations involve dynamic and bidirectional interactions between multiple biological systems, including inflammatory regulation, neurotransmitter balance, and metabolic processes [5,11–13]. Within this complex network, BDNF functions as a central hub integrating peripheral signals and translating them into adaptive neuroplastic changes.

These findings are particularly relevant for translational psychiatry, as they bridge molecular mechanisms with clinically applicable interventions and support the development of mechanism-based therapeutic strategies [13]. This integrative perspective aligns with emerging paradigms in psychiatry that emphasize system-level interactions rather than single-pathway models. Furthermore, this framework provides a conceptual foundation for the interpretation of findings discussed in the subsequent section.

3.6 Moderators and Dose–Response Relationships

Despite robust and consistent evidence supporting the beneficial effects of physical activity on BDNF signaling and depressive symptoms, considerable variability exists in individual responses to exercise interventions. This variability highlights the presence of moderating factors that influence both neurobiological and clinical outcomes and underscores the importance of adopting a personalized approach to exercise-based interventions.

Exercise-related parameters, including intensity, duration, frequency, and modality, play a central role in shaping neurotrophic responses. Both acute and chronic exercise have been shown to increase circulating BDNF levels; however, the magnitude, timing, and persistence of these effects vary depending on the characteristics of the exercise stimulus [14,28–30]. Emerging evidence suggests that higher-intensity exercise may induce more pronounced acute

increases in BDNF, whereas long-term adaptations are influenced by cumulative training load and consistency of physical activity.

In addition to exercise characteristics, individual biological and clinical factors significantly influence responsiveness to physical activity. Variables such as age, sex, baseline fitness level, genetic predisposition, and severity of depressive symptoms may modulate both peripheral physiological adaptations and central neuroplastic responses [1–4,6,7,13]. For instance, individuals with more severe depressive symptoms may exhibit altered neurotrophic signaling and reduced baseline BDNF levels, potentially affecting the magnitude of response to exercise interventions.

Furthermore, variability in study findings may be attributed to methodological differences, including the use of peripheral BDNF as a proxy for central processes, variability in timing of biomarker assessment, and heterogeneity in study populations and intervention protocols [14,28–30]. These factors complicate direct comparisons across studies and highlight the need for standardized methodologies in future research.

Importantly, epidemiological evidence indicates that even relatively low levels of physical activity are associated with reduced risk of depression, suggesting that clinically meaningful benefits may be achieved across a wide spectrum of activity levels [20–23]. This supports the notion that both threshold and dose–response effects are relevant in understanding the relationship between exercise and mental health.

At the same time, recent meta-analytic and network meta-analytic evidence suggests that different types of exercise (e.g., aerobic versus resistance training) may have differential effects on depressive symptoms and neurobiological outcomes, further emphasizing the importance of tailoring interventions to individual needs [25–27,30].

Taken together, these findings highlight the importance of a context-dependent and individualized framework for exercise interventions. A deeper understanding of moderators and dose–response relationships will be essential for optimizing therapeutic strategies, improving adherence, and maximizing both neurobiological and clinical benefits associated with physical activity. Future research should focus on identifying optimal exercise prescriptions tailored to individual biological and clinical profiles.

3.7 Limitations of Current Evidence

Despite the substantial body of evidence supporting the role of exercise-induced BDNF signaling in depression, several important limitations should be acknowledged when interpreting the findings presented in this review.

First, a key methodological challenge concerns the measurement of BDNF. Most human studies rely on peripheral (serum or plasma) BDNF levels as indirect markers of central nervous system activity. Although peripheral BDNF is thought to reflect central processes to some extent, the relationship between circulating and brain-derived BDNF remains incompletely understood, limiting the interpretability of biomarker findings [14,28–30].

Second, the heterogeneity of study designs represents a significant limitation. The included evidence spans randomized controlled trials, observational studies, and meta-analyses, each with varying methodological quality, sample characteristics, and exercise protocols. Differences in intervention duration, intensity, modality, and participant populations complicate direct comparisons across studies and limit the generalizability of findings [20–27,30].

Third, the causal role of BDNF in mediating the antidepressant effects of exercise remains insufficiently established. While associative evidence is strong, demonstrating correlations between increased BDNF levels and improvements in depressive symptoms, causal pathways are difficult to confirm in human studies due to ethical and methodological constraints. It is therefore likely that BDNF operates within a broader network of interacting biological mechanisms rather than acting as a singular determinant of clinical outcomes [1–4,10–12].

Fourth, individual variability in response to exercise introduces additional complexity. Factors such as genetic polymorphisms (e.g., BDNF Val66Met), baseline fitness, age, sex, and clinical characteristics may influence both neurobiological responses and treatment outcomes, yet these variables are not consistently controlled across studies [1–4,6,7].

Additionally, a lack of long-term longitudinal studies limits the current understanding of the durability and sustainability of exercise-induced neuroplastic and clinical effects. Most available studies focus on short- to medium-term outcomes, leaving uncertainty regarding long-term adaptations and relapse prevention.

Finally, potential publication bias and the predominance of positive findings in the literature may overestimate the strength of observed effects. Studies reporting null or negative results are less frequently published, which may contribute to an overly optimistic interpretation of the relationship between exercise, BDNF, and depression.

Taken together, these limitations highlight the need for cautious interpretation of current evidence and underscore the importance of more standardized, mechanistically oriented, and longitudinal research designs in future studies.

3.8 Future Directions and Clinical Implications

The integration of molecular, neurobiological, and clinical evidence presented in this review provides a strong foundation for future research aimed at refining the understanding of exercise as a therapeutic intervention in depression.

One of the most promising directions involves the development of personalized or precision-based exercise interventions. Given the variability in individual responses, future studies should focus on identifying biological, genetic, and clinical predictors of responsiveness to physical activity. This approach aligns with emerging paradigms in precision psychiatry, which aim to tailor interventions to individual patient profiles in order to maximize therapeutic efficacy [13,25–27].

Further research is also needed to clarify the mechanistic role of BDNF within the broader network of interacting biological systems. Integrative approaches combining neuroimaging, molecular biomarkers, and clinical outcomes may help to elucidate causal pathways and identify key mediators of exercise-induced antidepressant effects [14–17,28–30].

In addition, greater standardization of exercise protocols and biomarker assessment is essential to improve comparability across studies. Future randomized controlled trials should systematically examine dose–response relationships, including the effects of exercise intensity, duration, and modality, as well as the temporal dynamics of BDNF changes in relation to clinical outcomes [25–27,30].

Importantly, future interventions may benefit from targeting specific biological pathways underlying exercise-induced neuroplasticity, thereby supporting the development of

mechanism-based therapeutic strategies. Such approaches may enhance the precision and effectiveness of exercise as a clinical intervention.

From a clinical perspective, the evidence supports the incorporation of structured physical activity into standard treatment strategies for depression. Exercise may serve as both a primary and adjunctive intervention, offering a low-cost, accessible, and biologically grounded therapeutic option with minimal adverse effects [20-23,25–27]. Importantly, the integration of exercise into clinical practice requires interdisciplinary collaboration, including clinicians, physiotherapists, and mental health professionals.

Finally, future research should explore the potential of combining exercise with other therapeutic modalities, such as pharmacotherapy, psychotherapy, and neuromodulation techniques, in order to enhance synergistic effects on neuroplasticity and clinical outcomes. Such multimodal approaches may provide more effective and sustainable treatment strategies for individuals with depression.

In conclusion, advancing the field will require a shift toward integrative, multi-level, and translational research frameworks that bridge biological mechanisms with clinical application. This approach will be essential for fully realizing the therapeutic potential of exercise in the prevention and treatment of depression.

4.Discussion

4.1 Integration of Molecular, Neurobiological, and Clinical Evidence

The present review provides an integrative synthesis of molecular, neurobiological, and clinical evidence, supporting a multi-level model in which exercise-induced BDNF signaling mediates neuroplastic adaptations and contributes to antidepressant effects. The available evidence supports the view that physical activity may act on multiple biological systems that converge on the modulation of neurotrophic pathways and subsequent structural and functional brain changes.

At the molecular level, the training stimulus triggers a cascade of signaling mechanisms involving lactate-mediated activation of SIRT1-dependent transcription, modulation of kynurenine metabolism through PGC-1α1, and systemic anti-inflammatory effects [8-10]. These mechanisms collectively create a neurobiological environment that facilitates

neurotrophic signaling and plasticity-related processes. Importantly, these pathways do not operate in isolation but form an interconnected regulatory network linking peripheral physiological processes with central nervous system function [10–13].

At the neurobiological level, increased availability of neurotrophic factors, particularly BDNF, is associated with enhanced synaptic plasticity, neurogenesis, and improved connectivity within key brain regions implicated in depression, including the hippocampus and prefrontal cortex [14–17,19]. These structural and functional adaptations are consistent with contemporary models of depression that conceptualize impaired neuroplasticity as a core pathophysiological mechanism [1–5].

From a clinical perspective, a substantial body of evidence demonstrates that physical activity reduces both the risk and severity of depressive symptoms [20–27]. Importantly, meta-analytic findings indicate that exercise-induced increases in BDNF are associated with clinical improvement, suggesting that this neurotrophin may represent a biological link between behavioral intervention and therapeutic outcome [14,28–30].

Taken together, these findings support a model in which physical activity acts as a systemic intervention that initiates molecular signaling cascades, promotes neuroplastic remodeling, and ultimately leads to clinically meaningful improvements in depressive symptoms. This integrative perspective reinforces the conceptualization of physical activity as a multi-system intervention, in which molecular signaling, neuroplastic processes, and clinical outcomes form a coherent and biologically plausible continuum.

4.2 BDNF as a Mechanistic Mediator of Antidepressant Effects

A key question addressed in this review is whether BDNF can be considered a mechanistic mediator of the antidepressant effects of physical activity. The evidence synthesized here suggests that this neurotrophin fulfills several key criteria of a biological mediator, although current findings support its role as a probabilistic rather than strictly deterministic mechanism.

First, exercise consistently induces increases in peripheral BDNF levels, which are thought to reflect central neurobiological processes [14,28–30]. Second, BDNF plays a well-established role in regulating neuroplasticity, including synaptic strength, dendritic remodeling, and neurogenesis, all of which are critically implicated in the pathophysiology of depression [1–4].

Third, interventions that enhance neurotrophic signaling, including both pharmacological and behavioral approaches, are associated with improvements in depressive symptoms [1,2].

However, the relationship between BDNF and depression is complex and not strictly causal. While increased BDNF is associated with improved outcomes, it is unlikely to act as a single determinant of antidepressant effects. Instead, BDNF interacts with other biological systems, including inflammatory pathways, neurotransmitter dynamics, and metabolic regulation, which together contribute to the overall therapeutic response [5,11–13].

Furthermore, variability in neurotrophic responses across individuals and exercise protocols suggests that additional moderating factors—such as exercise intensity, duration, training modality, and individual biological characteristics—may influence the magnitude of neuroplastic and clinical effects [28–30]. In particular, dose–response relationships between exercise intensity and BDNF response remain insufficiently characterized and represent a critical gap in current knowledge.

In this context, BDNF should be conceptualized not as an isolated mechanism, but as a central node within a complex biological network that mediates the effects of physical activity on brain function and mental health. This systems-based perspective provides a more comprehensive framework for understanding how physical activity exerts its antidepressant effects.

4.3 Clinical Implications

The findings of this review have significant implications for both clinical practice and public health. The converging molecular, neurobiological, and clinical evidence supports the inclusion of physical activity as a core component of depression management rather than merely an adjunctive strategy.

From a clinical standpoint, physical activity represents a cost-effective, accessible, and low-risk intervention that can be implemented across diverse patient populations. Evidence from randomized trials and meta-analyses demonstrates that both aerobic and resistance training produce clinically meaningful reductions in depressive symptoms, with effect sizes comparable to those observed for standard pharmacological and psychotherapeutic interventions in selected populations [22,24–27]. Importantly, these effects appear to be robust across different age groups and clinical contexts.

The biological plausibility of these effects is strongly supported by the role of neurotrophic signaling in mediating neuroplastic adaptations. By targeting core mechanisms of synaptic dysfunction, impaired neurogenesis, and disrupted connectivity, physical activity may directly influence the underlying pathophysiology of depression rather than acting solely at the symptomatic level [1–5].

Furthermore, the systemic effects of physical activity—including modulation of inflammatory pathways, metabolic regulation, and neuroendocrine function—suggest that it may be particularly beneficial in individuals with comorbid somatic conditions, such as obesity, metabolic syndrome, or chronic low-grade inflammation [5,11–13].

At the population level, increasing physical activity may substantially reduce the incidence and burden of depression. Large-scale epidemiological studies indicate that even moderate increases in activity levels are associated with a lower risk of developing depressive disorders [20,23].

However, despite strong evidence of efficacy, practical implementation remains challenging. Core symptoms of depression, such as anhedonia, fatigue, and reduced motivation, may significantly limit adherence to structured interventions. Therefore, future clinical frameworks should emphasize individualized, supervised, and progressively adapted programs, alongside behavioral strategies aimed at improving adherence and long-term engagement.

4.4 Limitations

Several limitations of this review should be considered when interpreting the findings. First, the study was conducted as a narrative review supported by a structured literature search rather than as a formal systematic review with quantitative meta-analysis. Consequently, the synthesis of evidence is qualitative and may be subject to selection bias and interpretative variability.

Second, the included studies exhibit substantial heterogeneity in study design, participant characteristics, intervention protocols, and outcome measures. This heterogeneity limits the ability to define optimal exercise parameters and their specific effects on neurotrophic signaling and clinical outcomes.

Third, the use of peripheral BDNF as a proxy for central neurobiological processes represents an important limitation. Although circulating levels are widely used in clinical research, their relationship with central activity remains only partially understood [14,28–30].

Fourth, while the reviewed evidence supports a consistent association between physical activity, neurotrophic modulation, and improvements in depressive symptoms, causality cannot be definitively established. These effects likely emerge from interactions among multiple biological systems, including inflammatory, neurotransmitter, and metabolic pathways [5,10–13].

Moreover, the predominance of correlational and meta-analytic evidence highlights the need for mechanistic studies capable of disentangling causal pathways linking physical activity, BDNF signaling, and clinical outcomes.

Finally, most available evidence is derived from adult populations, which may limit generalizability to other groups, including adolescents, older adults, and individuals with severe or treatment-resistant depression.

4.5 Future Directions

Future research should aim to further clarify the mechanistic role of BDNF in mediating the antidepressant effects of physical activity through integrative, multi-level study designs. Longitudinal and interventional studies combining molecular biomarkers, neuroimaging data, and clinical outcomes are essential to establish causal relationships between biological and clinical changes.

A key priority is the identification of optimal exercise prescriptions for maximizing neuroplastic and therapeutic effects. Emerging evidence suggests that exercise modality, intensity, and dose may differentially influence neurotrophic responses and clinical outcomes, highlighting the need for personalized intervention strategies [28–30]. In particular, dose–response relationships between exercise intensity and BDNF response remain insufficiently characterized and represent a critical gap in current knowledge.

Moreover, inter-individual variability in response to physical activity represents an important area for future investigation. Genetic factors, baseline fitness, disease severity, and comorbid

conditions may all modulate neurotrophic dynamics and treatment response, supporting the development of precision-based exercise interventions.

Future studies should also explore the potential synergistic effects of combining physical activity with pharmacological and psychotherapeutic treatments, particularly given that multiple antidepressant interventions converge on shared neuroplastic mechanisms involving BDNF signaling [1,2].

Finally, advances in neuroimaging and biomarker research may enable more precise characterization of exercise-induced neuroplastic changes, facilitating the development of objective markers for treatment monitoring and improving translation into clinical practice. Such advances may ultimately support the development of mechanism-based, scalable, and personalized interventions that integrate physical activity into standard psychiatric care. Collectively, the evidence synthesized in this review positions physical activity as a biologically grounded and clinically relevant intervention that bridges molecular mechanisms with real-world therapeutic outcomes in depression.

5. Conclusions

This review provides a comprehensive and integrative synthesis of molecular, neurobiological, and clinical evidence supporting the role of exercise-induced BDNF signaling in mediating neuroplastic adaptations associated with antidepressant effects. The accumulated data indicate that physical activity acts as a multi-level intervention influencing interconnected biological systems that converge on neurotrophic mechanisms central to brain function and mental health [1–5,11–13].

At the molecular level, physical activity induces a cascade of adaptive responses, including lactate-mediated activation of transcriptional pathways, modulation of kynurenine metabolism via PGC-1α1, and systemic anti-inflammatory effects [8–10]. These mechanisms collectively facilitate the upregulation and functional activation of BDNF, aligning with contemporary models that emphasize activity-dependent neurotrophic signaling as a central component in both the pathophysiology and treatment of depression [1–4]. Moreover, these processes illustrate the dynamic interaction between peripheral physiological adaptations and central nervous system regulation.

At the neurobiological level, increased neurotrophic signaling is associated with enhanced synaptic plasticity, dendritic remodeling, neurogenesis, and improved functional connectivity within key brain regions implicated in mood regulation, particularly the hippocampus and prefrontal cortex [14–17,19]. These findings are consistent with integrative models of depression that conceptualize the disorder as a state of impaired neuroplasticity and disrupted network connectivity rather than solely a neurotransmitter imbalance [3–5].

From a clinical perspective, a substantial and methodologically robust body of evidence demonstrates that physical activity is associated with both reduced incidence and decreased severity of depressive symptoms across diverse populations and clinical contexts [20–27]. In addition, meta-analytic findings support the role of this neurotrophin as a key biological mediator within a broader mechanistic framework linking behavioral intervention to therapeutic outcomes [14,28–30].

However, the role of BDNF should be interpreted within a broader, systems-level framework. Rather than functioning as a singular causal determinant, this neurotrophic pathway appears to act as a central integrative node within a complex network of interacting biological systems, including inflammatory processes, neurotransmitter dynamics, and metabolic regulation [5,10–13]. This multi-factorial perspective is consistent with contemporary models of depression that emphasize network-level dysregulation and highlights the importance of considering interactions between multiple biological pathways.

Taken together, the evidence supports a unified conceptual model in which physical activity induces coordinated molecular and neurobiological adaptations that underpin clinically meaningful antidepressant effects. Within this framework, BDNF signaling serves as a critical mechanistic bridge linking peripheral physiological changes with central neuroplastic processes and behavioral outcomes.

From a translational and clinical perspective, these findings position physical activity as a biologically grounded, scalable, and clinically relevant intervention that may complement and enhance existing pharmacological and psychotherapeutic treatments. Its multimodal effects, targeting both central and peripheral mechanisms, make it particularly valuable in the context of personalized and integrative approaches to mental health care [22,24–27].

Future research should prioritize the identification of causal pathways linking physical activity, BDNF signaling, and clinical outcomes through longitudinal and experimental designs

integrating molecular biomarkers, neuroimaging, and behavioral data. Furthermore, elucidating dose–response relationships, optimizing exercise parameters, and understanding inter-individual variability will be essential for the development of precision-based exercise prescriptions [28–30].

Ultimately, advancing this line of research may facilitate the integration of physical activity into standard psychiatric care as a mechanism-based therapeutic strategy. Such an approach has the potential not only to improve individual clinical outcomes but also to contribute to reducing the global burden of depression through accessible and biologically informed interventions. These findings underscore the importance of integrating biologically informed and mechanism-based lifestyle interventions into contemporary models of depression treatment and prevention.

Disclosure:

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Declaration of Generative AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT-5.2 to improve grammar and language clarity. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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