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THE ANTIDEPRESSANT EFFECTS OF PHYSICAL ACTIVITY: NEUROBIOLOGICAL MECHANISMS AND PSYCHOSOCIAL MECHANISMS

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ABSTRACT

Background: Depression is a leading cause of disability worldwide, affecting millions and imposing significant personal, social, and economic burdens. While pharmacological and psychotherapeutic interventions are standard treatments, physical activity has emerged as a promising complementary or alternative strategy.
Methods: A comprehensive literature review was conducted of peer-reviewed studies published between 2000 and 2025, including randomized controlled trials, meta-analyses, and observational research. Populations examined included adolescents, adults, and older adults. Data extraction focused on depressive symptom outcomes, exercise modalities, intervention duration and intensity, and underlying neurobiological and psychosocial mechanisms.
Results: Evidence consistently indicates that regular physical activity, particularly aerobic and combined aerobic–resistance exercise, produces moderate to large reductions in depressive symptoms. Mechanistically, exercise enhances brain-derived neurotrophic factor (BDNF) expression, modulates monoaminergic neurotransmission, regulates the hypothalamic–pituitary-adrenal (HPA) axis, and reduces systemic inflammation. Psychosocial benefits, including behavioral activation, increased self-efficacy, and social engagement, further support sustained mood improvement. Combined interventions often yield the greatest effect, integrating biological, psychological, and social pathways.
Conclusion: Physical activity is a safe, accessible, and effective intervention for depression, with benefits extending beyond symptom reduction to improved cognitive function, stress resilience, and overall well-being. Incorporating structured exercise into standard treatment protocols may optimize clinical outcomes and support long-term mental health across diverse populations.

KEYWORDS

Exercise, Depression, Antidepressant Effects, Neurobiology, Mental Health

CITATION

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1. Introduction

Depression is one of the leading causes of disability worldwide, affecting more than 300 million people across all age groups (World Health Organization [WHO], 2022). The disorder is associated with substantial functional impairment, increased mortality risk, and a considerable economic burden resulting from healthcare expenditures and productivity losses (Ferrari et al., 2013; Greenberg et al., 2015). Major depressive disorder (MDD) is clinically characterized by persistent low mood, anhedonia, cognitive dysfunction, and a range of somatic symptoms that significantly impair daily functioning. Although pharmacotherapy and psychotherapy constitute the mainstay of treatment, a substantial proportion of patients fail to achieve remission or experience adverse effects that limit adherence (Rush et al., 2006; Cuijpers et al., 2013).

In recent decades, physical activity (PA) has gained increasing attention as a potential adjunctive or alternative intervention for depression. Physical activity is broadly defined as any bodily movement produced by skeletal muscles that results in energy expenditure and includes both structured exercise (e.g., aerobic or resistance training) and unstructured activities such as walking, cycling, or recreational sports (Caspersen et al., 1985). Beyond its accessibility and low cost, physical activity confers well-established benefits for cardiovascular, metabolic, and cognitive health, which is particularly relevant given the high prevalence of somatic comorbidities among individuals with depression (Pedersen & Saltin, 2015; Schuch et al., 2016).

The antidepressant effects of physical activity are supported by a growing body of empirical evidence. Randomized controlled trials and meta-analyses consistently demonstrate significant reductions in depressive symptoms among adults, adolescents, and older adults participating in aerobic, resistance, or combined exercise interventions (Blumenthal et al., 2007; Schuch et al., 2016; Kandola et al., 2020). Importantly, these clinical improvements are comparable to those observed with standard antidepressant treatments in cases of mild to moderate depression. Recent studies in Polish populations confirm these findings, showing that exercise can improve mood and reduce depressive symptoms, even under challenging conditions such as the COVID-19 pandemic restrictions (Wyszomirska et al., 2024).

At the neurobiological level, exercise influences several key pathways implicated in the pathophysiology of depression. Regular physical activity has been shown to increase brain-derived neurotrophic factor (BDNF), modulate monoaminergic neurotransmission, regulate hypothalamic–pituitary–adrenal (HPA) axis activity, reduce systemic inflammation, and activate the endocannabinoid system (Dishman et al., 2006; Wegner et al., 2014; Kandola et al., 2020). These mechanisms collectively promote neuroplasticity, stress resilience, and improved emotional regulation.

In addition to biological processes, psychological and social mechanisms play a critical role. Exercise facilitates behavioral activation, enhances self-efficacy, and provides opportunities for social interaction, all of which counteract depressive symptomatology (Craft & Perna, 2004; Biddle & Asare, 2011). The convergence of biological and psychosocial effects positions physical activity as a holistic intervention addressing multiple dimensions of depression.

Despite the robustness of existing evidence, important questions remain regarding the optimal type, intensity, frequency, and duration of exercise required to achieve sustained antidepressant effects. Moreover, there is a need to better understand population-specific responses, including differences related to age, baseline physical fitness, and comorbid medical conditions.

The present review aims to:

1. Synthesize current evidence on the effects of physical activity on depressive symptoms.
2. Examine neurobiological and psychosocial mechanisms underlying these effects.
3. Discuss practical implications for clinical practice and public health.

By integrating findings from randomized controlled trials, meta-analyses, and mechanistic studies, this article provides a comprehensive overview of physical activity as an evidence-based intervention for depression.

2. Methodology

This review was conducted as a comprehensive synthesis of the scientific literature, focusing on randomized controlled trials, meta-analyses, systematic reviews, and observational studies published between 2000 and 2025. The primary aim was to examine the effects of physical activity on depressive symptoms across diverse populations, including adolescents, adults, and older adults.

A systematic search was performed in major electronic databases, including PubMed, PsycINFO, Web of Science, and Scopus. Search terms combined keywords such as physical activity, exercise, depression, major depressive disorder, aerobic training, resistance training, and neurobiological mechanisms. Only peer-

reviewed studies published in English or Polish were included (Biddle & Asare, 2011; Blumenthal et al., 2007; Cooney et al., 2013; Craft & Perna, 2004; Ernst et al., 2006; Hamer et al., 2009; Kandola et al., 2020; Rebar et al., 2015; Wyszomirska et al., 2024). Studies in both clinical populations diagnosed with major depressive disorder and non-clinical populations with elevated depressive symptoms were considered to capture a broad spectrum of depression severity.

For each study, relevant data were extracted, including sample characteristics (age, sex, and general health status), type of physical activity intervention, and key exercise parameters such as intensity, frequency, and duration. Outcome measures focused primarily on changes in depressive symptoms assessed using validated clinical scales, such as the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HAM-D). When available, data on neurobiological and psychosocial mechanisms - such as brain-derived neurotrophic factor (BDNF), hypothalamic–pituitary–adrenal (HPA) axis activity, inflammatory markers, behavioral activation, and self-efficacy were also collected.

The extracted findings were synthesized descriptively, emphasizing consistent patterns and variations across populations, exercise types, and study designs. Special attention was given to mechanistic evidence linking exercise-induced biological and psychosocial changes to improvements in depressive symptoms. This integrative approach provides a clear understanding of both the clinical efficacy of physical activity and the underlying pathways of its antidepressant effects, supporting evidence-based recommendations for practice.

3. Results

3.1. Clinical Effects of Physical Activity on Depression

Physical activity consistently demonstrates antidepressant effects across multiple populations. In adults with major depressive disorder, aerobic exercise interventions ranging from 8 to 16 weeks significantly reduce depressive symptoms, as measured by validated clinical scales such as the Beck Depression Inventory (BDI) and the Hamilton Depression Rating Scale (HAM-D). For instance, Blumenthal et al. (2007) reported that a 16-week aerobic exercise program reduced BDI scores by an average of 7.6 points, a change comparable to reductions observed in patients treated with standard pharmacotherapy. Similarly, Schuch et al. (2016) conducted a meta-analysis of 49 studies and found a moderate overall effect size (Cohen's $d = 0.62$) for exercise in reducing depressive symptoms among adults. These findings underscore the clinical relevance of structured physical activity as a non-pharmacological intervention in depression management.

Among adolescents, both school-based and structured exercise programs are associated with significant reductions in depressive symptoms. Biddle and Asare (2011) demonstrated that adolescents engaging in ≥60 minutes of moderate-to-vigorous physical activity per day exhibited lower depressive symptomatology compared with inactive peers, highlighting both the preventive and therapeutic roles of exercise. Exercise interventions in adolescent populations have also been linked to improvements in self-efficacy, behavioral activation, and social engagement, which may further reinforce mood regulation and resilience against depressive episodes.

In older adults, aerobic and resistance exercise improve mood, cognitive function, and quality of life, with meta-analytic effect sizes ranging from 0.35 to 0.65, suggesting robust psychological and neurobiological benefits (Gordon et al., 2018). Resistance training in particular has been associated with enhancements in functional independence, self-efficacy, and motivation, indirectly supporting reductions in depressive symptoms.

Types of exercise appear to influence outcomes differentially. Aerobic exercise is particularly effective for enhancing global mood, cardiovascular fitness, and neuroplasticity, while resistance training may preferentially improve self-efficacy, physical function, and psychosocial well-being (Gordon et al., 2018; Kandola et al., 2020). Combined programs that integrate aerobic and resistance elements demonstrate additive benefits, simultaneously engaging multiple neurobiological pathways and psychosocial mechanisms, thereby maximizing antidepressant effects.

Evidence from Polish populations further supports the clinical benefits of exercise in depression. Wyszomirska et al. (2024) examined the mental health impact of exercise deprivation during COVID-19 pandemic restrictions in adults, finding that participants with higher habitual physical activity levels prior to restrictions experienced fewer depressive symptoms and better emotional regulation compared with less active individuals. These findings emphasize the relevance of culturally and regionally specific studies in informing exercise-based interventions for depression.

3.2. Neurobiological Mechanisms

Physical activity exerts antidepressant effects through a wide array of interrelated neurobiological and psychosocial pathways, which collectively promote mood stabilization, cognitive enhancement, and resilience to stress. These mechanisms operate synergistically, such that biological adaptations induced by exercise often facilitate psychosocial improvements, while behavioral and cognitive changes further reinforce underlying neurobiological processes. This bidirectional interaction contributes to the broad and sustained mental health benefits associated with regular physical activity. Core neurobiological pathways implicated in these effects include modulation of brain-derived neurotrophic factor (BDNF), monoaminergic neurotransmission, hypothalamic-pituitary-adrenal (HPA) axis regulation, systemic inflammatory processes, and the release of endorphins and endocannabinoids. Complementing these biological mechanisms, psychosocial processes such as behavioral activation, enhanced self-efficacy, social engagement, and cognitive improvements further strengthen antidepressant outcomes.

3.2.1 Brain-Derived Neurotrophic Factor (BDNF)

Exercise strongly stimulates the expression of brain-derived neurotrophic factor (BDNF), a neurotrophin essential for neuronal survival, synaptic plasticity, and hippocampal neurogenesis. Both aerobic and resistance-based exercise modalities have been shown to increase peripheral BDNF concentrations and promote neuroplastic adaptations within central nervous system structures involved in mood regulation, including the hippocampus and prefrontal cortex (Ernst et al., 2006; Voss et al., 2013). These exercise-induced increases in BDNF are associated with improvements in learning, memory, and emotional regulation - domains that are frequently impaired in depressive disorders.

At a mechanistic level, elevated BDNF supports the generation of new neurons in the adult hippocampus, enhances synaptic connectivity, and counteracts stress-related synaptic loss. Chronic stress and depressive episodes are associated with reduced BDNF expression and hippocampal volume reductions, whereas sustained physical activity appears to reverse or attenuate these structural and functional alterations (Duman & Monteggia, 2006; Kandola et al., 2020). This neurotrophic response provides a compelling biological explanation for the observed antidepressant and procognitive effects of regular exercise.

Observational and experimental evidence further suggests that individuals who maintain regular physical activity demonstrate greater resilience to psychosocial stressors and lower vulnerability to mood disturbances. Studies conducted in Polish populations indicate that consistent engagement in exercise is associated with reduced depressive symptoms and improved emotional well-being, supporting the clinical relevance of exercise-induced neuroplastic adaptations (Guszkowska, 2004; Wyszomirska et al., 2024).

3.2.2 Monoamine Neurotransmitters

Physical activity also modulates central monoaminergic systems, including serotonin, dopamine, and norepinephrine, neurotransmitters that play a central role in the pathophysiology of depression. Regular aerobic and resistance exercise enhances serotonergic signaling in limbic and cortical regions involved in emotional regulation, supports dopaminergic activity within mesolimbic reward pathways, and stabilizes norepinephrine transmission in the prefrontal cortex, thereby improving attention, motivation, and mood (Meeusen & De Meirleir, 1995; Kandola et al., 2020).

These neurochemical adaptations partially overlap with the mechanisms of action of pharmacological antidepressants, suggesting that exercise may function as both an alternative and adjunctive intervention. Importantly, exercise-induced monoaminergic changes are accompanied by improvements in cognitive performance and reward sensitivity, which may enhance adherence and long-term treatment outcomes. Programs combining aerobic and resistance components appear particularly effective, as they simultaneously target multiple neurotransmitter systems and psychological domains (Rebar et al., 2015).

3.2.3 Hypothalamic-Pituitary-Adrenal (HPA) Axis Regulation

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, often manifested as chronic hypercortisolemia and impaired stress reactivity, represents a well-established biological hallmark of depressive disorders. Regular physical activity has been shown to normalize HPA axis functioning by enhancing glucocorticoid receptor sensitivity, reducing basal cortisol secretion, and attenuating exaggerated hormonal responses to psychosocial stress (Dishman & O'Connor, 2009; Wegner et al., 2014).

Clinical and observational studies indicate that structured aerobic exercise programs lasting 8-12 weeks significantly reduce both basal and stress-induced salivary cortisol levels. Habitual physical activity also

buffers cortisol responses to acute stressors, as demonstrated in laboratory stress paradigms, supporting its role in enhancing physiological stress resilience (Hamer et al., 2009). These adaptations may be particularly relevant for individuals exposed to chronic stress or at elevated risk for stress-related depressive episodes.

3.2.4 Anti-inflammatory Effects

Chronic low-grade systemic inflammation is increasingly recognized as a key contributor to the development and persistence of depressive disorders. Elevated levels of pro-inflammatory markers, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP), have been consistently associated with greater symptom severity and poorer treatment response (Raison et al., 2006; Kandola et al., 2020). Exercise exerts a significant anti-inflammatory effect by reducing these pro-inflammatory mediators while promoting the release of anti-inflammatory cytokines such as interleukin-10 (IL-10).

Both aerobic and resistance training have been shown to lower systemic inflammatory burden, with evidence suggesting a dose-response relationship between exercise volume and anti-inflammatory benefits (Wegner et al., 2014; Kandola et al., 2020). These immunomodulatory effects support neurogenesis, synaptic plasticity, and efficient neurotransmitter functioning, thereby contributing to improvements in mood, cognition, and stress resilience observed in physically active individuals.

3.2.5 Endorphins and Endocannabinoids

Exercise also stimulates the release of endogenous opioids (β-endorphins) and endocannabinoids, neurochemical systems involved in pain modulation, reward processing, and positive affect (Dishman et al., 2006; Raichlen et al., 2013). Increased endorphin activity contributes to reduced pain perception and enhanced subjective well-being, whereas endocannabinoid signaling promotes anxiolytic effects, emotional stability, and reward sensitivity.

Moderate-intensity aerobic exercise appears particularly effective in enhancing endocannabinoid signaling, while higher-intensity exercise preferentially increases endorphin release. These neurochemical responses underpin the commonly reported phenomenon of exercise-induced euphoria and contribute to both acute and sustained mood improvements across clinical and non-clinical populations (Rebar et al., 2015).

3.3 Psychosocial Mechanisms

Beyond neurobiological adaptations, physical activity exerts substantial antidepressant effects through psychosocial mechanisms. Behavioral activation represents a central process, counteracting withdrawal, inactivity, and rumination that perpetuate depressive cycles. Structured exercise programs introduce regular, goal-directed activity, reinforcing daily routines and engagement with the environment (Craft & Perna, 2004; Biddle & Asare, 2011).

Exercise participation also enhances self-efficacy and perceived mastery. Achieving exercise-related goals—such as increasing endurance, strength, or consistency—fosters a sense of control over one's body and health outcomes. These mastery experiences generalize to broader life domains, strengthening psychological resilience and reducing vulnerability to depressive symptoms (Bandura, 1997).

Social engagement represents an additional psychosocial pathway. Participation in group-based or community exercise programs facilitates social interaction, shared goals, and accountability, which may reduce feelings of isolation and support long-term adherence. Even when performed individually, exercise combined with external encouragement or structured feedback has been associated with improved motivation and emotional well-being.

Cognitive mechanisms further contribute to psychosocial benefits. Regular physical activity is associated with improvements in attention, executive function, and cognitive flexibility, which may reduce maladaptive thought patterns and enhance coping strategies. Collectively, these psychosocial adaptations interact with neurobiological mechanisms to produce a holistic antidepressant effect that extends beyond symptom reduction to include improved functioning and quality of life.

3.4. Differences Across Exercise Modalities

The antidepressant effects of physical activity are not uniform and can vary significantly depending on exercise type, intensity, frequency, and duration. Understanding these nuances is essential for designing interventions that optimize clinical outcomes and adherence across diverse populations. Evidence consistently indicates that aerobic, resistance, and combined exercise modalities confer antidepressant benefits, though the mechanisms and magnitude of effects differ.

Exercise type	Key Mechanisms	Typical Duration and frequency	Effect on depression
Aerobic (walking, cycling, running)	↑ BDNF, monoamines, HPA regulation, endorphins	30–60 min, 3–5 times/week	Moderate to large reduction in depressive symptoms
Resistance (weight training)	↑ BDNF, self-efficacy, functional capacity	30–45 min, 2–4 times/week	Moderate reduction, improves mood and daily functioning
Combined (aerobic + resistance)	Synergistic neurobiological + psychosocial benefits	45–60 min, 3–5 times/week	Largest effect sizes, long-term adherence advantages

Population-Specific Adaptations

Adolescents: Group-based, game-like aerobic activities are particularly effective in this population. The combination of social interaction, playful competition, and structured activity enhances intrinsic motivation, reduces social isolation, and fosters positive experiences, which are critical for both preventive and therapeutic outcomes (Biddle & Asare, 2011).

Adults: Structured moderate intensity aerobic exercise with clearly defined goals allows adults to monitor progress, build self-efficacy, and maintain motivation. Programs emphasizing gradual progression in duration or intensity appear to optimize adherence and reinforce psychological mastery (Blumenthal et al., 2007; Rebar et al., 2015).

Older Adults: Combined aerobic and resistance interventions confer the most comprehensive benefits for older adults, simultaneously improving mood, cognitive performance, cardiovascular health, and functional capacity. Such programs may help counteract age-related declines in neuroplasticity and executive function, enhancing independence and overall quality of life (Gordon et al., 2018).

Key Observations and Clinical Implications

1. Aerobic exercise consistently improves mood and reduces physiological stress, making it a first-line recommendation for individuals with elevated cortisol levels or cardiovascular comorbidities (Schuch et al., 2016; Gordon et al., 2018).
2. Resistance training preferentially enhances self-efficacy and functional independence, critical for older adults or those with physical limitations (Gordon et al., 2018; Guszkowska, 2004).
3. Combined interventions provide additive benefits, leveraging both neurobiological and psychosocial mechanisms. Variation in exercise modality improves adherence and long-term engagement (Rebar et al., 2015).

4. Discussion

The present review provides a comprehensive synthesis of current evidence supporting the antidepressant effects of physical activity, emphasizing the interplay of neurobiological, psychological, and social mechanisms. Across diverse populations, including adolescents, adults, and older adults, exercise consistently reduces depressive symptoms, with moderate to large effect sizes reported in both clinical and non-clinical cohorts (Schuch et al., 2016; Kandola et al., 2020; Blumenthal et al., 2007). These findings highlight physical activity as a multifaceted intervention that offers benefits beyond symptomatic relief, including improvements in cognitive function, stress regulation, social engagement, and overall quality of life (Biddle & Asare, 2011; Gordon et al., 2018).

Exercise emerges not merely as a behavioral strategy but as a complex psychobiological intervention. Its effects span molecular, cellular, and systemic levels, engaging neuroplastic, neurochemical, immunological, and psychosocial pathways simultaneously. This multimodal influence underscores the rationale for incorporating physical activity into both preventive and therapeutic frameworks for depression.

4.1.1 Brain-Derived Neurotrophic Factor (BDNF) and Neuroplasticity

Brain-Derived Neurotrophic Factor (BDNF) is a central mediator of exercise-induced antidepressant effects, critically involved in neuronal growth, survival, and synaptic plasticity (Dishman et al., 2006; Kandola et al., 2020). Individuals with depression typically exhibit reduced BDNF levels, particularly in the hippocampus, a brain region essential for emotion regulation, learning, and memory. Lower BDNF is associated with hippocampal atrophy, impaired neurogenesis, synaptic deficits, and cognitive dysfunction, all of which contribute to the emotional and cognitive symptomatology of depression (Duman & Monteggia, 2006).

Exercise has been consistently shown to stimulate BDNF expression in both peripheral blood and central nervous system structures. Aerobic activities such as running, cycling, and brisk walking, as well as resistance training, elevate circulating BDNF levels, which correlate with improvements in depressive symptoms, cognitive performance, and overall psychological well-being (Ernst et al., 2006; Voss et al., 2013). In Polish populations, structured aerobic programs during periods of social restriction, such as the COVID-19 pandemic, were associated with reductions in depressive and anxiety symptoms, indirectly supporting the role of BDNF-mediated neuroplasticity in mood improvement (Wyszomirska et al., 2024; Guszkowska, 2004).

Exercise-induced increases in BDNF promote hippocampal neurogenesis, restore synaptic connectivity disrupted by chronic stress, and may reverse structural atrophy observed in prolonged depressive episodes (Ernst et al., 2006; Voss et al., 2013). Evidence suggests a dose-response relationship: moderate-intensity exercise performed consistently over 8–16 weeks produces robust and sustained neurotrophic effects, whereas excessively high-intensity or prolonged acute bouts may transiently increase cortisol, potentially offsetting neuroplastic benefits (Zschucke et al., 2013).

Moreover, BDNF interacts synergistically with monoaminergic neurotransmitter systems. Elevated BDNF enhances serotonergic receptor expression, supports dopaminergic neuron survival, and stabilizes noradrenergic signaling, together amplifying the antidepressant effects of exercise (Kandola et al., 2020). This complex interplay demonstrates that physical activity engages multiple interconnected pathways, combining neuroplastic, neurochemical, and behavioral mechanisms to improve mood and cognitive outcomes.

Exercise modulates central serotonin, dopamine, and norepinephrine, neurotransmitters critically involved in depression pathophysiology (Meeusen & De Meirleir, 1995; Kandola et al., 2020). Regular physical activity enhances serotonergic signaling in limbic structures, including the hippocampus and amygdala, supporting improved mood regulation, emotional resilience, and reduced anxiety-related behaviors (Young, 2007; Rebar et al., 2015). These effects are mediated by increased tryptophan availability and upregulation of serotonergic receptors, enhancing synaptic transmission.

Dopaminergic neurotransmission is potentiated within mesolimbic circuits such as the nucleus accumbens and ventral tegmental area, which govern reward processing, motivation, and reinforcement learning. Enhanced dopaminergic tone helps counteract anhedonia, a core symptom of depression, improving motivation for daily activities and social engagement (Salamone & Correa, 2012; Schuch et al., 2016). Functional imaging studies indicate increased activation in reward-related regions following both acute and chronic exercise, correlating with improved mood (Meeusen, 2005).

Norepinephrine modulation complements serotonergic and dopaminergic effects by improving arousal, attention, and executive functioning through enhanced prefrontal cortex signaling (Dishman et al., 2006). This facilitates better cognitive control over emotional responses and enhances stress resilience (Tsatsoulis & Fountoulakis, 2006).

Combined aerobic and resistance training produces additive neurochemical effects. Aerobic exercise predominantly enhances serotonergic and dopaminergic signaling, while resistance training improves norepinephrine function, self-efficacy, functional capacity, and metabolic health (Rebar et al., 2015). These complementary effects translate into superior improvements in mood, cognitive performance, and stress resilience compared with either modality alone.

4.1.3 HPA Axis Regulation and Stress Resilience

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, including elevated basal cortisol and impaired negative feedback, is a well-established feature of depression (Pariante & Lightman, 2008; Holsboer, 2000). Chronic psychosocial stress disrupts HPA homeostasis, leading to hippocampal vulnerability, heightened inflammation, and mood dysregulation.

Exercise acts as a potent modulator of HPA function. Both aerobic and resistance training improve glucocorticoid receptor sensitivity, normalizing basal and stress-induced cortisol secretion (Dishman & O'Connor, 2009; Wegner et al., 2014). Moderate-intensity exercise restores diurnal cortisol rhythms in adults with depressive symptoms, with improvements correlating with reductions in depression severity and enhanced cognitive performance (Stathopoulou et al., 2006).

Mechanistically, exercise engages central and peripheral pathways. It stimulates hippocampal and prefrontal regions rich in glucocorticoid receptors, enhances parasympathetic activity, and reduces sympathetic overactivation (Hamer et al., 2009; Dishman et al., 2006). Exercise-induced BDNF expression and endocannabinoid release further support HPA regulation by promoting hippocampal plasticity and modulating amygdala reactivity (Kandola et al., 2020; Cohen et al., 2017).

Exercise intensity and duration influence HPA outcomes: moderate-intensity continuous training optimally restores basal cortisol, whereas high-intensity interval training may acutely elevate cortisol but fosters adaptive HPA responses over repeated sessions (Tsatsoulis & Fountoulakis, 2006; Zschucke et al., 2013).

Overall, chronic physical activity enhances HPA regulation and stress resilience, complementing neuroplastic, neurotransmitter, and psychosocial mechanisms to mitigate depressive symptoms.

4.1.4 Anti-inflammatory Pathways

Chronic low-grade inflammation contributes to depression pathophysiology, particularly in treatment-resistant cases (Raison et al., 2006; Dowlati et al., 2010). Elevated pro-inflammatory cytokines such as IL-6, TNF-α, and CRP correlate with depressive severity, cognitive deficits, and reduced treatment responsiveness (Khandaker et al., 2014).

Exercise reduces pro-inflammatory markers while increasing anti-inflammatory mediators like IL-10 and adiponectin (Kandola et al., 2020; Wegner et al., 2014). Mechanisms include reduced microglial activation, prevention of neurotoxic mediator release, and secretion of muscle-derived myokines (Pedersen, 2019).

Clinical studies demonstrate that 8–12 weeks of moderate-intensity aerobic exercise significantly lower CRP and TNF-α, corresponding with improvements in depressive symptoms (Wegner et al., 2014; Kandola et al., 2020). Resistance training similarly improves cytokine profiles and mood in older adults. Evidence supports a dose-response relationship: moderate-to-vigorous activity produces the most pronounced anti-inflammatory effects and may enhance long-term resilience against relapse (Hamer et al., 2012).

4.1.5 Endorphins, Endocannabinoids, and Reward Circuits

Exercise acutely and chronically activates endogenous opioid and endocannabinoid systems, enhancing mood, analgesia, and stress regulation. β-Endorphins produced in the pituitary bind central nervous system opioid receptors, reducing pain perception and promoting well-being, contributing to the "runner's high" phenomenon (Dishman et al., 2006; Raichlen et al., 2012).

Endocannabinoids, including anandamide (AEA) and 2-arachidonoylglycerol (2-AG), act on CB1 and CB2 receptors, modulating reward circuits in the nucleus accumbens and prefrontal cortex. This signaling improves motivation, positive affect, and emotional regulation (Raichlen et al., 2012; Heyman et al., 2012).

Modality-specific effects are observed: moderate-intensity aerobic exercise preferentially enhances endocannabinoid signaling, whereas higher-intensity or resistance training produces larger β-endorphin spikes (Rebar et al., 2015). Chronic exercise strengthens connectivity within reward networks, potentially reducing anhedonia and enhancing engagement in daily activities (Meeusen, 2005).

Clinical studies indicate that structured exercise programs increase circulating β-endorphins and AEA, corresponding with improved mood, social interaction, and overall psychological well-being (Craft & Perna, 2004; Heyman et al., 2012).

4.2 Psychosocial Mechanisms

Beyond its well-documented neurobiological effects, physical activity exerts strong antidepressant effects through psychosocial mechanisms that target core behavioral, cognitive, and interpersonal processes implicated in depression. These mechanisms are particularly relevant for long-term outcomes, as they influence daily functioning, treatment adherence, and resilience against relapse.

A central psychosocial pathway is behavioral activation, a mechanism explicitly targeted in cognitive-behavioral and behavioral therapies for depression. Depressive disorders are commonly associated with behavioral withdrawal, reduced engagement in rewarding activities, and increased rumination, which together form a self-perpetuating cycle of inactivity and low mood. Regular physical activity directly disrupts this cycle by introducing structured, goal-oriented behavior into daily life. Exercise increases exposure to positive reinforcement, enhances routine formation, and promotes functional engagement, leading to gradual improvements in mood and motivation (Craft & Perna, 2004; Biddle & Asare, 2011). Importantly, the effectiveness of behavioral activation through exercise does not depend on maximal intensity; consistency and regularity appear to be more critical determinants of psychological benefit.

Another key psychosocial mechanism is the enhancement of self-efficacy and perceived mastery. According to social-cognitive theory, self-efficacy reflects an individual's belief in their capacity to exert control over behaviors and outcomes, and lower self-efficacy is strongly associated with depressive symptom severity (Bandura, 1997). Participation in structured exercise programs provides repeated mastery experiences, such as meeting attendance goals, improving endurance, or progressing in resistance load. These experiences strengthen perceived competence and personal agency, which can generalize beyond physical activity to other life domains, including occupational performance and social functioning (Rebar et al., 2015). Empirical evidence indicates that increases in exercise-related self-efficacy partially mediate reductions in depressive symptoms, supporting its role as an active mechanism rather than a mere correlation.

Social interaction and interpersonal engagement further contribute to the antidepressant effects of physical activity. Although depression is often accompanied by social withdrawal and loneliness, exercise — particularly when conducted in group or community settings — naturally facilitates interpersonal contact. Shared activities, common goals, and informal social exchange during physical activity may reduce perceived isolation and foster a sense of belonging, which is protective against depressive symptomatology (Kandola et al., 2020). Even low-threshold forms of social exercise, such as walking groups or recreational activities, appear sufficient to support mood regulation and adherence by providing structure and accountability.

Cognitive processes represent an additional psychosocial pathway. Regular physical activity has been associated with improvements in attention, executive functioning, and cognitive flexibility, domains frequently impaired in depression (Voss et al., 2013). Enhanced executive control may reduce maladaptive cognitive patterns such as rumination, negative attentional bias, and rigid thinking styles, thereby improving emotional regulation and stress coping. Mastery experiences in exercise may also facilitate cognitive reappraisal, encouraging individuals to perceive challenges as manageable rather than overwhelming, which supports adaptive coping strategies.

Mood reinforcement through goal setting and feedback constitutes a further psychosocial mechanism. Exercise programs that incorporate realistic goals and progress monitoring generate positive feedback loops, reinforcing motivation and consolidating behavioral change. Digital tools, including mobile applications and wearable devices, may amplify this effect by providing immediate feedback, visualizing progress, and supporting self-monitoring, which are associated with improved adherence and mood outcomes in individuals with depressive symptoms (Wang et al., 2020).

Collectively, these psychosocial mechanisms interact synergistically with neurobiological processes. Physical activity not only alters neurotransmitter function, neurotrophic signaling, HPA axis regulation, and inflammatory pathways, but also reshapes daily behavior, cognitive appraisals, and social engagement. This multidimensional influence helps explain both the short-term antidepressant effects of exercise and its long-term protective role against depressive relapse.

4.3 Comparative Effectiveness: Exercise Versus Pharmacotherapy

Evidence indicates that exercise can be as effective as pharmacotherapy for mild-to-moderate depression. For example, Blumenthal et al. (2007) found that 16 weeks of structured aerobic exercise led to reductions in depressive symptoms, as measured by the Hamilton Depression Rating Scale (HAM-D), comparable to those achieved with sertraline treatment. Exercise additionally provides benefits not typically observed with

pharmacotherapy alone, including fewer side effects, improvements in cardiovascular and metabolic health, enhanced cognitive functioning, and overall quality of life.

For individuals with severe or treatment-resistant depression, pharmacotherapy remains a cornerstone of care. Nevertheless, exercise can serve as a valuable adjunctive intervention, enhancing the effectiveness of pharmacological treatments through complementary neurobiological and psychosocial pathways (Rethorst & Trivedi, 2013). Exercise stimulates monoamine neurotransmission, increases BDNF levels, modulates HPA axis activity, and reduces inflammation, all of which may amplify the antidepressant effects of medication. Concurrently, psychosocial benefits such as behavioral activation, improved self-efficacy, and social engagement further support mood regulation and functional recovery.

Combined treatment approaches that integrate exercise with psychotherapy — particularly cognitive-behavioral therapy may produce synergistic effects. Such programs simultaneously target multiple dimensions of depression, including maladaptive cognitive patterns, social withdrawal, inactivity, and neurochemical dysregulation. Evidence suggests that patients participating in combined interventions experience greater improvements in symptom severity, functional outcomes, and treatment adherence than those receiving pharmacotherapy or psychotherapy alone.

In practice, these findings underscore the importance of personalized treatment plans that consider patient preferences, baseline fitness, comorbidities, and symptom severity. Exercise prescriptions, tailored in type, intensity, frequency, and duration, can enhance engagement and maximize therapeutic benefits when delivered alongside conventional treatments.

4.4 Differences Across Populations

Responsiveness to exercise-based interventions varies according to age, baseline fitness, and depression severity. In children and adolescents, physical activity appears particularly effective as a preventive and early intervention strategy. School-based and group-oriented exercise programs are associated with lower depressive symptoms, likely due to the combined influence of behavioral activation, social engagement, and neurodevelopmental sensitivity to environmental stimulation (Biddle & Asare, 2011).

In adults, moderate-intensity aerobic exercise performed consistently yields robust antidepressant effects, particularly when combined with goal-setting and progress monitoring. Meta-analytic evidence suggests that both aerobic and resistance training are effective, with combined programs offering additive benefits (Gordon et al., 2018; Rebar et al., 2015).

Older adults derive substantial benefit from combined aerobic and resistance exercise, which simultaneously improves mood, cognitive function, balance, and functional independence. These multidimensional benefits are particularly relevant given the high prevalence of comorbid physical illness and cognitive decline in late-life depression (Gordon et al., 2018).

4.5 Practical Implications for Clinical Practice and Public Health

Based on the reviewed evidence, several practical recommendations can be formulated:

1. **Frequency and Duration**
2. Adults should engage in 150–300 minutes per week of moderate-intensity physical activity, ideally combining aerobic and resistance components (World Health Organization, 2020).
3. **Individualization**
4. Exercise prescriptions should be tailored to individual preferences, physical capacity, age, and depression severity to maximize adherence and psychological benefit.
5. **Behavioral Support**
6. Incorporating goal-setting, progress monitoring, and feedback mechanisms enhances motivation and sustains long-term engagement.
7. **Integration with Standard Care**
8. Exercise should be integrated with pharmacotherapy and psychotherapy, particularly in moderate-to-severe depression, as part of a comprehensive, multimodal treatment strategy.

5. Conclusion

Physical activity constitutes a well-established, evidence-based intervention for depression, demonstrating consistent efficacy across age groups, levels of symptom severity, and diverse clinical and non-clinical populations. The findings synthesized in this review indicate that exercise should be considered not merely as a lifestyle recommendation, but as a clinically meaningful therapeutic strategy with both preventive and treatment-oriented applications. Its effectiveness arises from the convergence of multiple neurobiological, psychological, and social mechanisms, positioning physical activity as a unique, multidimensional intervention for depressive disorders.

At the neurobiological level, exercise influences several core pathways implicated in the pathophysiology of depression. One of the most consistently supported mechanisms involves increased brain-derived neurotrophic factor (BDNF), which promotes hippocampal neurogenesis, enhances synaptic plasticity, and supports structural and functional recovery of brain regions involved in mood regulation, learning, and memory (Duman & Monteggia, 2006; Ernst et al., 2006; Kandola et al., 2020). Through these neuroplastic effects, physical activity counteracts stress-related neuronal atrophy and cognitive dysfunction commonly observed in depressive disorders.

Exercise also exerts a regulatory influence on monoaminergic neurotransmission, including serotonin, dopamine, and norepinephrine systems, which are central targets of conventional antidepressant pharmacotherapy. By enhancing serotonergic signaling, strengthening dopaminergic reward pathways, and optimizing noradrenergic modulation of attention and executive function, regular physical activity improves emotional regulation, motivation, and cognitive performance (Meeusen & De Meirleir, 1995; Salamone & Correa, 2012; Rebar et al., 2015). These effects help explain the capacity of exercise to reduce core depressive symptoms such as anhedonia, low energy, and impaired concentration.

Another critical mechanism involves regulation of the hypothalamic–pituitary–adrenal (HPA) axis. Chronic physical activity enhances glucocorticoid receptor sensitivity, normalizes diurnal cortisol rhythms, and attenuates excessive stress reactivity, thereby improving resilience to psychosocial stressors (Dishman & O'Connor, 2009; Hamer et al., 2009; Pariante & Lightman, 2008). Given the central role of HPA axis dysregulation in depression, these neuroendocrine effects represent a key pathway through which exercise contributes to both symptom reduction and relapse prevention.

In parallel, exercise demonstrates clinically relevant anti-inflammatory effects, reducing systemic levels of pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor-alpha, and C-reactive protein, while promoting anti-inflammatory signaling (Raison et al., 2006; Khandaker et al., 2014; Wegner et al., 2014). This immunomodulatory action is particularly important in light of growing evidence linking inflammation to depression severity, cognitive impairment, and reduced treatment responsiveness.

Finally, activation of endogenous opioid and endocannabinoid systems contributes to the acute and chronic mood-enhancing effects of exercise. Increased release of β-endorphins and exercise-induced endocannabinoid signaling enhances positive affect, reduces pain perception, and strengthens reward processing, supporting both immediate improvements in mood and longer-term engagement in physical activity (Dishman et al., 2006; Heyman et al., 2012; Raichlen et al., 2013).

Beyond biological mechanisms, psychosocial processes play a central role in mediating the antidepressant effects of physical activity. Exercise functions as a form of behavioral activation, counteracting withdrawal, inactivity, and rumination by introducing structured, goal-directed activity into daily life (Craft & Perna, 2004; Biddle & Asare, 2011). Repeated mastery experiences enhance self-efficacy and perceived control, which are inversely associated with depressive symptom severity and contribute to sustained improvements in mood and functioning (Bandura, 1997; Rebar et al., 2015). Additionally, social engagement through group-based or community exercise reduces isolation and supports adherence, while goal achievement and feedback reinforce motivation and consolidate treatment gains.

Comparative evidence indicates that exercise can achieve antidepressant effects comparable to pharmacotherapy and psychotherapy in cases of mild to moderate depression, while offering additional benefits such as improved physical health, cognitive functioning, and minimal side-effect burden (Blumenthal et al., 2007; Cooney et al., 2013). For individuals with more severe or treatment-resistant depression, physical activity serves as a valuable adjunctive intervention, complementing pharmacological and psychotherapeutic approaches through synergistic biological and psychosocial pathways.

Looking forward, several priorities emerge for future research and clinical implementation. These include the development of precision exercise psychiatry, integrating biomarkers, neuroimaging, and individual risk profiles to tailor exercise prescriptions; the expanded use of digital health technologies to

monitor adherence and physiological responses; and long-term longitudinal studies evaluating the preventive potential of exercise in at-risk populations, such as adolescents, older adults, and individuals with subclinical depressive symptoms. Further investigation into the synergistic effects of exercise combined with pharmacotherapy or psychotherapy may also help optimize outcomes in complex clinical presentations.

In conclusion, physical activity should be recognized as a primary or adjunctive intervention for depression within both clinical and public health frameworks. By simultaneously addressing neurobiological dysfunction, maladaptive behavior patterns, and psychosocial vulnerability, exercise offers a holistic, accessible, and cost-effective strategy for improving mental health outcomes, reducing disease burden, and enhancing quality of life across the lifespan.

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