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Physical activity as an adjunctive intervention in the treatment of depression: a review of neurobiological, immunological, and gut-brain axis mechanisms

Arkadiusz Psiuk
District Hospital in Zawiercie, Miodowa 14, 42-400 Zawiercie, Poland
arkadiuszpsiuk@gmail.com
https://orcid.org/0009-0007-1948-1165

Joanna Szymocha
District Hospital in Zawiercie, Miodowa 14, 42-400 Zawiercie, Poland
joanaa.szymocha@gmail.com
https://orcid.org/0009-0005-8310-0406

Igor Smędowski
Independent Researcher
igor.smedowski@gmail.com
https://orcid.org/0009-0003-3910-8035

Jarosław Tsukerman
Municipal Hospital in Żory, ul.Dąbrowskiego 20, 44-240 Żory, Poland
yarko.pppppppppp@gmail.com

https://orcid.org/0009-0006-5061-5574

Aleksandra Wojas
Municipal Hospital in Żory, ul.Dąbrowskiego 20, 44-240 Żory, Poland
ola.wojas@gmail.com
https://orcid.org/0009-0007-4546-0288

Corresponding Author
Igor Smędowski E-mail: igor.smedowski@gmail.com

Abstract

Background: Major depressive disorder (MDD) poses a significant global burden. Since a large proportion of patients do not achieve full remission with standard pharmacotherapy alone, there is a pressing need for pleiotropic adjunctive interventions.
Aim: To synthesize current evidence on the pleiotropic neurobiological, immunological, and gut-brain axis mechanisms that drive the antidepressant effects of physical activity.
Material and methods: A narrative review of the medical literature was conducted using PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar databases, covering the years 2003–2026. Ultimately, 33 research papers were included, with a particular focus on network meta-analyses and evidence-based medicine (EBM) clinical guidelines.
Results: Structured physical exercise modulates the reactivity of the hypothalamic-pituitary-adrenal (HPA) axis to psychosocial stress and strongly stimulates neurogenesis in the atrophic hippocampus through the release of brain-derived neurotrophic factor (BDNF). Furthermore, recent studies highlight the critical role of contracting skeletal muscles as a detoxifying organ that converts neurotoxic kynurenine into kynurenic acid. Similarly, aerobic training strengthens the epithelial barrier and optimizes the gut microbiome, thereby suppressing systemic neuroinflammation.
Conclusions: Physical activity appears to be a highly effective, multidirectional therapeutic intervention. Beyond alleviating core depressive symptoms with an efficacy comparable to

standard psychopharmacotherapy, it is the only method that radically reduces premature cardiovascular mortality in this patient population.

Keywords: depression; physical activity; BDNF; HPA axis; neurobiology; kynurenine pathway; microbiome.

1. Introduction

Major Depressive Disorder (MDD) is currently one of the leading causes of disability, imposing a substantial health and economic burden globally. Despite the widespread use of monoamine reuptake inhibitors, a significant percentage of patients fail to achieve full clinical remission, often struggling with delayed therapeutic onset and numerous adverse drug effects. These limitations drive the need to explore and optimize safe, non-pharmacological, and pleiotropic adjunctive interventions [1].

Historically, interest in the relationship between physical activity and mental health has evolved from simple behavioral observations to advanced neurobiological studies. By the early 2000s, researchers started identifying the biological correlates of exercise-induced mood improvements. Initial efforts focused on the subjective "runner's high" and the involvement of endogenous opioid and endocannabinoid systems [2, 3]. Around the same time, the classic monoamine hypothesis was broadened to account for how regular exercise increases the bioavailability and turnover of essential neurotransmitters, such as serotonin, norepinephrine, and dopamine. This laid the groundwork for our modern understanding of exercise biology in psychiatry [4].

As neuroscience progressed, it became evident that a chronic lack of physical activity (a sedentary lifestyle) severely compromises the integrity of the central nervous system, reducing the neuroplastic potential of neurons and making them more susceptible to oxidative damage [5]. It was also shown that exercise interventions in individuals with affective deficits trigger a rapid, measurable improvement in the neuroendocrine stress response, seen as the stabilization of cortisol and other stress hormones [6].

Today, the treatment paradigm for psychiatric disorders is shifting significantly, moving physical activity from the realm of general "lifestyle advice" to a fully fledged therapeutic intervention. This is reflected by the inclusion of structured exercise programs in the official guidelines of major scientific organizations, including the European Psychiatric Association (EPA), as well as in rigorous evidence-based medicine (EBM) recommendations [7, 8].

However, the latest literature indicates that the antidepressant effects of exercise are far more complex than the classic neurochemical pathways suggest. These mechanisms also involve immune signaling cascades and bidirectional communication within the gut-brain axis [9, 10, 11].

The objective of this paper is to critically synthesize current evidence on the biological mechanisms responsible for the therapeutic effects of physical exercise in depression. This review details five core pillars: optimization of the HPA axis, stimulation of neurotrophic factors (including BDNF), regulation of the monoaminergic system, the novel mechanism of kynurenine detoxification in skeletal muscles, and the impact on the intestinal barrier and microbiome.

2. Materials and Methods

2.1. Study design

The present study was designed as a structured narrative review. Its primary objective was to collate and synthesize current scientific evidence regarding the biological mechanisms that underlie the antidepressant properties of physical activity. Instead of focusing solely on clinical outcomes, the review was framed to bridge the gap between clinical efficacy and the exact neurobiological, immunological, and metabolic pathways induced by exercise.

2.2. Literature search strategy

A comprehensive literature search was conducted across four major electronic databases: PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar. The search strategy captured relevant literature available up to May 2026. To accurately identify appropriate publications, a combination of Medical Subject Headings (MeSH) and free-text terms was linked using standard Boolean operators (AND, OR). The primary search string utilized the following keywords: *depression, major depressive disorder, physical activity,*

exercise, brain-derived neurotrophic factor, BDNF, HPA axis, cortisol, kynurenine pathway, gut-brain axis, and *microbiota*.

2.3. Inclusion and exclusion criteria

To ensure a high standard of evidence consistent with Evidence-Based Medicine (EBM) principles, the review prioritized network meta-analyses, systematic reviews, original randomized controlled trials, and recognized clinical guidelines. Articles were considered eligible for inclusion if they met the following criteria: (1) publication in peer-reviewed scientific journals in English or Polish; (2) focus on adult cohorts diagnosed with mild to moderate depressive episodes; and (3) direct investigation of neuroendocrine, immunological, or microbiome-mediated responses to physical exercise. Furthermore, foundational mechanistic studies elucidating specific biochemical routes (such as the kynurenine metabolism) were included, provided their findings demonstrated clear clinical translatability. Non-peer-reviewed preprints, opinion pieces, and studies lacking sufficient methodological rigor were excluded from the analysis.

2.4. Data synthesis

Following the initial screening of titles and abstracts, potentially relevant manuscripts underwent a thorough full-text evaluation. Ultimately, 33 publications spanning the years 2003 to 2026 were deemed suitable for inclusion in the final analysis. The source selection followed a hierarchical approach, deliberately favoring recent high-impact meta-analyses while also capturing contemporary discourse within specialized sports and health journals. The extracted data were critically appraised and subsequently categorized into thematic blocks. These sections were structured to align with the principal pathophysiological domains of depression, allowing for a logical progression from central nervous system adaptations to systemic and gut-level changes.

3. Literature Review

3.1. Modulation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis and Neuroendocrine Adaptation to Stress

The hypothalamic-pituitary-adrenal (HPA) axis serves as the primary system integrating the body’s response to stressors, and its dysregulation is widely regarded as a fundamental,

evolutionarily grounded pillar of major depressive disorder (MDD) pathophysiology. Under physiological conditions, cortisol secretion is tightly regulated by a negative feedback loop, where glucocorticoid receptors (GR) in the hippocampus and hypothalamus inhibit the further release of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH). In the context of depression, chronic psychosocial stress often leads to what is known as allostatic load. This results in GR resistance (characterized by down-regulation and reduced ligand affinity), causing a failure of the feedback mechanism and subsequent persistent hypercortisolemia. Prolonged exposure of the central nervous system to high glucocorticoid concentrations is profoundly neurotoxic, triggering a cascade of atrophic changes in limbic structures, particularly the hippocampus. Clinically, these changes correlate with the severity of anhedonia and cognitive deficits [12, 13].

Physical activity introduces a unique modulatory mechanism here. Biologically, a single bout of moderate-to-high intensity exercise acts as an acute physiological stressor that temporarily activates the HPA axis. However, regular training may induce adaptations consistent with the 'cross-stressor adaptation hypothesis'. According to this paradigm, repetitive exposure of the neuroendocrine system to controlled, exercise-induced surges of cortisol and catecholamines promotes physiological habituation. Consequently, a conditioned organism manages energy resource distribution more efficiently, leading to sensitized GR receptors and the restoration of negative feedback integrity [14, 15].

Clinically, this adaptation manifests as a measurable reduction in HPA axis reactivity to non-exercise-related stressors. Depressed patients undergoing regular exercise programs exhibit a dampened cortisol response to daily psychological stressors and a significantly faster return to baseline hormone levels once the stressor subsides. Optimizing this neuroendocrine pathway is vital not only for mitigating core depressive symptoms but also for reducing comorbid somatic anxiety and restoring the circadian rhythm architecture often disrupted by chronic hypercortisolemia [13, 14].

3.2. Neuroplasticity, Neurogenesis, and the Role of BDNF

The neurotrophic hypothesis of depression has emerged as a leading paradigm in understanding affective disorders. Neuroimaging and post-mortem structural analyses consistently demonstrate that patients with chronic depression exhibit measurable atrophy in key limbic structures, specifically the dentate gyrus of the hippocampus and the prefrontal cortex. This phenomenon is linked to a significant decline in both central and peripheral

concentrations of brain-derived neurotrophic factor (BDNF), a pivotal protein for neuronal survival, dendritic spine development, and long-term potentiation (LTP). Physical exercise—particularly aerobic training—is widely recognized as a potent non-pharmacological stimulator of BDNF gene expression, capable of reversing stress-induced neurodegeneration and restoring neuronal plasticity [16, 17].

The molecular pathways through which peripheral muscle work induces central neurogenesis are remarkably sophisticated. A breakthrough discovery in recent years identified a metabolic pathway involving endogenous ketone bodies. Prolonged exercise, by depleting glycogen reserves, enhances lipolysis and stimulates the hepatic production of β-hydroxybutyrate (β-HB). This molecule readily crosses the blood-brain barrier (BBB), where it serves not only as a highly efficient alternative fuel for neuronal mitochondria but also as an endogenous inhibitor of histone deacetylases (HDAC). The physiological inhibition of HDAC enzymes by β-HB relaxes chromatin structure, which may facilitate transcriptional upregulation of the BDNF gene promoter in hippocampal cells [18].

The efficacy of neurotrophic stimulation is also strictly dependent on exercise kinetics, such as duration and intensity, following a clear dose-response relationship. Recent systematic reviews suggest that while most forms of regular activity promote neuroplasticity, the most robust and sustained BDNF release occurs after moderate-to-high intensity aerobic interventions and structured high-intensity interval training (HIIT) protocols. The resulting de novo neurogenesis translates clinically into a gradual restoration of hippocampal volume. The integrity of this structure facilitates improved cognitive flexibility, enhances memory consolidation, and provides the biological substrate for sustained symptomatic remission, making exercise interventions functionally isomorphic to neurotrophic-profile pharmacotherapy [17, 19].

3.3. The Monoaminergic System and Mood Regulation

Despite the shift toward more complex models in modern neuroscience, the classic monoamine hypothesis remains a cornerstone for explaining the pathophysiology of MDD. It posits that core depressive symptoms arise from a deficit in the synaptic bioavailability of serotonin (5-HT), norepinephrine (NE), and dopamine (DA) within limbic and prefrontal structures. Current evidence in the neurobiology of exercise suggests that regular physical activity is functionally isomorphic to the mechanisms of SSRIs and SNRIs. Through complex neuromodulatory pathways, exercise not only stimulates the de novo release of these

neurotransmitters but also optimizes their turnover rate and induces favorable adaptations in postsynaptic receptor density and sensitivity [20, 21].

Dopaminergic dysfunction, which manifests clinically as anhedonia—the loss of pleasure and motivation—plays a particularly critical role in depression. Physical activity exerts a strong stimulatory effect on the mesolimbic pathway, specifically the projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc), the brain's primary reward center. Molecular studies show that chronic endurance training promotes the up-regulation of dopamine D2 receptors (DRD2) in the striatum. This mechanism sensitizes the mesolimbic system to endogenous stimuli, effectively reversing motivational deficits and restoring psychomotor drive [20, 22].

Simultaneously, exercise directly modulates serotonergic and noradrenergic pathways. Increased muscular activity raises the demand for branched-chain amino acids (BCAA), which compete with tryptophan (the precursor to serotonin) for the same transporter across the BBB. A decline in plasma BCAA levels during exercise relatively increases the transport of free tryptophan into the CNS, enhancing 5-HT biosynthesis in the raphe nuclei. Furthermore, the activation of the locus coeruleus in the brainstem during exercise leads to increased norepinephrine release. The synergy between these two systems improves cognitive alertness, regulates the sleep-wake cycle, and reduces the somatic tension and free-floating anxiety that often accompany depressive episodes [21].

Expanding beyond the monoaminergic paradigm, exercise also impacts endogenous opioid and endocannabinoid systems, responsible for the acute post-workout mood elevation often called the "runner’s high". Moderate-to-high intensity exertion stimulates the pituitary gland to release β-endorphins, which activate mu-opioid receptors to produce analgesic and euphoric effects. Equally significant is the release of anandamide (AEA), a lipophilic endocannabinoid that easily penetrates the BBB to activate CB1 receptors. The interaction between the endocannabinoid and dopaminergic systems not only provides immediate anxiolytic effects but also plays a key role in positive reinforcement, drastically increasing the likelihood that a psychiatric patient will maintain adherence to a prescribed training regimen [20, 22].

3.4. The Immuno-Inflammatory Hypothesis and the Kynurenine Pathway

Biological psychiatry is increasingly moving away from an exclusive focus on monoamines, shifting toward an immuno-inflammatory hypothesis that views depression as

rooted in chronic, systemic low-grade inflammation. Clinical data consistently show that patients with MDD exhibit elevated levels of peripheral inflammatory markers, including high-sensitivity C-reactive protein (hs-CRP) and pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These circulating mediators can cross the BBB, initiating neuroinflammation in the CNS. This process directly impairs synaptic plasticity, inhibits hippocampal neurogenesis, and promotes excitotoxicity within sensitive limbic structures [23, 24].

In this framework, exercise interventions of sufficient volume may exert a meaningful immunomodulatory effect. While exercise triggers a transient pro-inflammatory response immediately after a session (linked to myokines and muscle fiber micro-damage), chronic training permanently lowers baseline systemic inflammation and restores physiological immune balance. A critical, newly defined mechanism linking inflammation, depression, and exercise is the kynurenine pathway of tryptophan metabolism. Under homeostatic conditions, tryptophan is the primary precursor for serotonin synthesis. However, chronic psychosocial stress, glucocorticoid surges, and elevated pro-inflammatory cytokines stimulate the enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). The activation of these enzymes shifts tryptophan metabolism away from serotonin and toward the production of kynurenine (KYN). KYN, a highly lipophilic molecule, easily diffuses across the BBB, where activated microglia metabolize it into, among other substances, quinolinic acid (QUIN). QUIN acts as a potent and destructive NMDA receptor agonist, triggering a massive influx of calcium into neurons, which leads to oxidative stress, astrocyte dysfunction, and apoptosis—strongly correlating with MDD severity [25].

A breakthrough in translational medicine and exercise neurobiology revealed that contracting skeletal muscles function as an endogenous detoxifying organ, clearing KYN from the bloodstream. Regular endurance and resistance training, by altering cellular energy status and activating the AMPK kinase pathway, stimulate the over-expression of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α1) in muscle tissue. Increased PGC-1α1 levels enhance the transcription of kynurenine aminotransferases (KATs). These enzymes convert peripheral kynurenine into kynurenic acid (KYNA) within the muscle [25].

Unlike kynurenine, the resulting KYNA is a large, polar metabolite that is entirely unable to cross the blood-brain barrier. Consequently, exercising muscles actively "filter" KYN from the plasma, neutralizing it into KYNA before it can reach the CNS. This sophisticated muscular buffering mechanism demonstrates that the neuroprotective potential of exercise is

systemic, acting as a shield for the brain against the neurotoxic consequences of chronic stress and inflammation [23, 25].

3.5. The Gut-Brain Axis and Microbiome Influence

The gut-brain axis is a bidirectional, specialized communication pathway that integrates the central and enteric nervous systems through neural (primarily the vagus nerve), endocrine, and immunological mechanisms. In depression pathophysiology, particular emphasis is placed on intestinal dysbiosis and pathological epithelial permeability, often referred to as "leaky gut syndrome". Reduced expression of tight junction proteins, such as occludin and claudin, allows bacterial endotoxins—primarily lipopolysaccharides (LPS) from Gram-negative bacteria—to translocate into the general circulation. This induces metabolic endotoxemia, which activates Toll-like receptor 4 (TLR4) on immune cells, triggering a massive pro-inflammatory cytokine cascade. These mediators cross the BBB and stimulate microglia to produce neurotoxic metabolites, directly inhibiting neurogenesis and triggering affective symptoms [10, 26].

Current scientific discourse highlights lifestyle interventions, particularly structured physical exercise, as a primary modulator of gut-brain axis reactivity to stress. Regular activity has emerged as a potent, non-pharmacological stimulator of gut microbiome diversification and optimization. Endurance training, through shifts in visceral blood flow and gastrointestinal motility, forces an adaptation of the intestinal environment. Microbiological analyses show that long-term exercise promotes favorable phylogenetic modifications, such as lowering the Firmicutes-to-Bacteroidetes ratio and increasing the proliferation of protective commensal strains like Akkermansia muciniphila and Faecalibacterium prausnitzii [27].

These bacteria are the primary source of short-chain fatty acids (SCFAs), including butyrate, propionate, and acetate, produced during fiber fermentation. Butyrate, in particular, serves a critical trophic function as the preferred energy source for colonocytes. Its elevated concentration stimulates epithelial regeneration and significantly increases the expression of tight junction proteins. This effectively seals the intestinal barrier, cutting off the influx of endotoxins and dampening systemic inflammation [26, 27].

Furthermore, SCFAs exhibit direct neurotropic effects; upon entering the bloodstream, they can cross the BBB to act as endogenous HDAC inhibitors, mechanistically enhancing BDNF expression. They also cooperate in stimulating the afferent fibers of the vagus nerve, which transmits anti-inflammatory signals directly to limbic structures. This integrated

mechanism underscores that the therapeutic impact of exercise on mood begins at the level of the intestinal barrier [27].

3.6. Clinical Efficacy in the Light of Evidence-Based Medicine (EBM)

In the era of Evidence-Based Medicine (EBM), assessing the efficacy of non-pharmacological interventions requires verification from the highest levels of the evidence hierarchy. Recent network meta-analyses of hundreds of randomized controlled trials (RCTs) unequivocally show that structured physical exercise has a large, measurable clinical effect size in treating mild-to-moderate depressive episodes. This finding remains statistically significant even after rigorous adjustments for publication bias, which often inflates the perceived efficacy of traditional pharmacotherapy in psychiatric literature. Analyses of exercise dose optimization indicate that efficacy is clearly tied to metabolic engagement. High-intensity interval training (HIIT) and organized aerobic exercise protocols yield therapeutic benefits—measured by objective decreases in HDRS or MADRS scores—that are fully comparable to, and in some cohorts even superior to, standard first-line treatments like cognitive-behavioral therapy (CBT) and SSRI monotherapy [28, 29, 30].

From a clinical perspective, the universality of this intervention across different affective phenotypes is noteworthy. While its role in unipolar depression (MDD) is well-established, new data highlight its promising profile in treating bipolar disorder (BD). Rigorous analyses indicate that properly planned exercise significantly reduces depressive and sub-depressive symptoms in BD patients without inducing the "phase switch" toward hypomania, mania, or mixed states—a risk often associated with traditional antidepressants. This safety profile makes physical exercise a preferred intervention for mood stabilization in bipolar patients [31, 32].

From a holistic and internal medicine standpoint, the value of exercise goes far beyond psychiatric symptom control, directly addressing the "mortality gap". Patients with severe mental illness (SMI) have a life expectancy 10 to 20 years shorter than the general population. The leading cause of this premature mortality is not suicide, but a dramatically increased incidence of cardiometabolic diseases (including metabolic syndrome, ischemic heart disease, and type 2 diabetes), resulting from both the pathophysiology of depression (chronic inflammation, hypercortisolemia) and the iatrogenic effects of long-term psychopharmacotherapy. Implementing "exercise is medicine" is one of the few interventions that may simultaneously address depressive symptoms and reduce cardiovascular risk. This

leads to improved insulin sensitivity, normalized lipid profiles, and lower blood pressure, which in the long term translates into significantly lower somatic mortality rates [33].

4. Discussion and Limitations

The scientific evidence synthesized in this review underscores a definitive departure from the isolated, neurocentric model previously dominant in our understanding of depression and its therapeutic interventions. The emerging picture of exercise neurobiology proves that the antidepressant benefits of movement do not stem from the activation of a single signaling pathway, but rather represent a highly integrated, pleiotropic systemic response. This paradigm shift involves recognizing that tissues traditionally defined as peripheral—specifically contracting skeletal muscles and the gut microbiota—function as primary, active modulators of the central nervous system.

This phenomenon, described in the literature as "organ cross-talk," redefines physical activity. When muscles take on the role of an endocrine organ, detoxifying the blood of kynurenine, and the gut produces neuroactive short-chain fatty acids, exercise ceases to be merely a behavioral recommendation. Instead, it becomes a precise immunometabolic tool that targets the very biological roots of affective disorders.

Despite these robust and rigorously documented pathophysiological foundations, the full translation of these mechanisms into standard clinical practice faces several research barriers, necessitating a cautious approach when formulating categorical therapeutic conclusions. A critical appraisal of the present material requires acknowledging the inherent limitations of this review. It must be explicitly stated that the chosen methodology of a narrative review, while allowing for a holistic view of complex biological pathways, lacks the quantitative rigor of a statistical meta-analysis and remains susceptible to selection bias.

Furthermore, the primary studies analyzed exhibit significant methodological heterogeneity. Variations in the FITT (Frequency, Intensity, Time, Type) parameters across different research protocols—ranging from low-intensity aerobic interventions (e.g., walking) to resistance training and extreme high-intensity interval training (HIIT)—make direct comparisons of effect sizes challenging. Additionally, the clinical populations assessed often vary in their sociodemographic profiles, pharmacological history (drug-naive vs. chronic polypharmacy), and the prevalence of somatic comorbidities. This fundamental diversity in the literature means that a single, universal algorithm or a standardized "exercise prescription" is currently unattainable. The concept of personalized medicine suggests that a patient’s ultimate

neurobiological response to a specific type of exercise remains highly individualized, contingent upon their genetic polymorphisms, baseline inflammatory profile, and degree of intestinal dysbiosis. Future research should therefore focus on the precise identification of predictive biomarkers to allow for the targeted matching of training parameters to specific depressive phenotypes.

5. Conclusions

Based on this narrative synthesis of current literature and evidence-based medicine (EBM) data, the following conclusions can be drawn:

Neurobiological Pleiotropy: The antidepressant effect of structured physical activity is not the result of a single signaling pathway but relies on integrated neurochemical optimization. This includes restoring physiological negative feedback within a disorganized HPA axis, regulating monoaminergic pathways (with a focus on the reward system), and potently stimulating BDNF expression, which facilitates reparative neurogenesis in hippocampal structures.

The New Immunometabolic Paradigm (Organ Cross-Talk): The phenomenon of multi-organ signaling proves the peripheral basis of the therapeutic effect of exercise. Contracting skeletal muscles—via PGC-1α1-dependent conversion of neurotoxic kynurenine into kynurenic acid—serve as an endogenous filter protecting the central nervous system from the deleterious effects of stress. Concurrently, exercise reinforces the intestinal barrier by diversifying the microbiome, thereby reducing endotoxin translocation and dampening systemic neuroinflammation.

High Clinical Efficacy (EBM): Exercise interventions of appropriate volume (including aerobic and HIIT) demonstrate statistically and clinically significant effect sizes, comparable to standard pharmacotherapy and cognitive-behavioral therapy (CBT) in mild and moderate episodes. Their high safety profile justifies their application in both unipolar and bipolar affective disorders.

Addressing the Mortality Gap: Physical activity represents a unique therapeutic intervention that simultaneously alleviates psychiatric symptoms and radically lowers global cardiovascular risk. Implementing the "exercise is medicine" framework is essential to reversing the premature mortality of patients with affective disorders, necessitating its absolute integration into standard clinical algorithms for psychiatric treatment.

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Conceptualization: Arkadiusz Psiuk
Methodology: Joanna Szymocha, Jarosław Tsukerman
Investigation: Joanna Szymocha, Arkadiusz Psiuk, Igor Smędowski, Aleksandra Wojas, Jarosław Tsukerman
Resources: Aleksandra Wojas
Writing-rough preparation: Arkadiusz Psiuk
Writing-review and editing: Joanna Szymocha, Arkadiusz Psiuk, Aleksandra Wojas, Jarosław Tsukerman, Igor Smędowski
Supervision: Arkadiusz Psiuk, Aleksandra Wojas
Project administration: Igor Smędowski

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