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The Synergy of physical activity and vitamin D_3 supplementation as a potential strategy to support depression treatment: biological mechanisms and intervention perspectives

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ABSTRACT

Depression affects over 20 million people globally, causing disability and socio-economic burdens. First-line treatments fail in 30-50% of patients. Novel approaches targeting neuroinflammation and synaptic deficits are needed. Physical activity and vitamin D3 show promise for treatment-resistant depression. Evaluate effectiveness of vitamin D3 & mechanisms, and combined physical activity & vitamin D3 supplementation on depression symptom management. Conducted structured systematic PubMed/Google Scholar search (from 2015) for RCT, full research observational studies, and meta-analyses, with keywords (depression, physical activity, vitamin D3, neuroinflammation, combined-interventions and mental health). Included English peer-reviewed human studies. Physical training reduced symptoms by 20-30%. This has been accounted for through upregulation of BDNF, normalization of HPA, and reduced inflammation. Vitamin D3 supplementation (≥2800 IU/day) in vitamin D deficient groups (<50 nmol/L) was associated with an improvement in mood. This has been accounted for through enhanced production of serotonin and suppressed neuroinflammation. Combined interventions had greater symptom reduction then the monotherapy's, such as physical activity and Vitamin D3, from combinations in treatment-resistant cases. Combined physical activity and Vitamin D3 may provide an optimal combined treatment strategy for depression. Treatment must be personalized depending upon deficiency, status and severity. Research moving forward must focus on research of large-scale randomized controlled trials (RCTs) to provide solid evidence, followed by public health integrated interventions to transmit and work with knowledge findings on the implementation of findings.

Keywords: Depression, Physical activity, Vitamin D3, Neuroinflammation, Combined interventions, Mental health.

1. INTRODUCTION

Depression is a condition that affects over 20 million individuals worldwide and a leading cause of disability. There are primary socio-economic costs linked to depression: the costs of care, reducing productivity, and the burden on social support. Moreover, the cost of care is increasing, productivity is declining, and absenteeism is increasing (Ménard et al., 2016). Treatments for depression include cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) in front-line treatments. Even with advancements in therapeutics, about 30-50% of patients show suboptimal, or no response to any current treatment modalities. After cycles of treatment, the odds of remission remain at around ~50% (Cuijpers et al., 2019; Arathimos et al., 2021).

The side effects of pharmacotherapy compound these problems. Some of these adverse effects include weight gain, emotional blunting, risk of addiction, and accessibility of psychotherapy for poorer people in terms of economic limitations. There is a need to investigate some therapies that may enhance available treatment modalities. As a result, we should actively seek to research new areas that are currently not well-studied. Mechanisms such as oxidative stress, neuroinflammation, and synaptic deficits should be investigated. Treatment-resistant depression is often associated with these (Ménard et al., 2016). Women are twice as likely as men to experience depression. This statistic is one reason why interventions should be tailored and take into account hormonal, social and environmental factors (Salk et al., 2017).

A body of epidemiological and clinical evidence indicates a protective role of physical activity against depression. Meta-analyses have confirmed that physical exercise can decrease depression severity by 20-30% through the regulation of exercise. When considering mild to moderate depression, aerobic exercise (running) was shown to have therapeutic benefit, while resistance training (weight lifting) had benefit equivalent to first-line antidepressant medications (Suneson et al., 2021; Rodriguez-Ayllon et al., 2019). Additionally, Suneson et al., (2021) described a reduced inflammatory response after activities like yoga. Programs for the aging population have targeted pro-inflammatory markers (e.g., IL-6) and positively impacted mood.

Evidence showed that physical activity increased neurogenesis in the hippocampus. Lastly, the predominant underlying mechanisms involved BDNF modulation, stabilization of the HPA axis, and an anti-inflammation component (by downregulating metabolic activity of proinflammatory cytokines) (Lubans et al., 2016; Schuch et al., 2021). Physical activity also increases social connection and when done in a structured group format has been shown to contribute to an increased feeling of self-efficacy. Exercise in organized groups enhances feelings of self-efficacy. Interventions such as the ones described may enhance the therapeutic responses to antidepressants in adolescents and geriatric populations (McDowell et al., 2017). Contreras-Osorio et al., (2022) showed a significant change in executive function and emotional resilience after 12 weeks of moderate intensity exercise in patients with major depressive disorder within a randomized controlled trial.

Vitamin D3 deficiency is present in nearly 50% of the world, especially in high-latitude countries, and urban areas with low sun exposure. Vitamin D3 deficiency is also expected to augment the risk of depressive disorders by as high as 75% (Ohrnberger et al., 2017). Sometimes several observational studies also indicate that the number of depressive symptoms and serum levels less than 50 nmol/l shows negative correlation with serum levels of 25-OH D (Xie et al., 2022; Satyanarayana et al., 2024). As a rule, Vitamin D3 has several modes of action on mood, such as positively affecting serotonin synthesis (e.g., through stimulation of brain tryptophan hydroxylase 2 (TPH2)), antagonizing some proinflammatory cytokines like TNF-alpha, and protecting against glutamate neurotoxicity (Kandola et al., 2019; Menéndez et al., 2024). There is evidence to establish that depressive symptoms occur with low serum 25 hydroxyvitamin D and that the most serious severity of anhedonia and fatigue occurred with levels < 50 nmol/l (Xie et al., 2022; Satyanarayana et al., 2024).

Vitamin D3 regulates mood, including serotonin production (via stimulating brain TPH2), inhibits proinflammatory cytokines (i.e., TNF-α) and protects from glutamate toxicity (Kandola et al., 2019; Menéndez et al., 2024). Mixed findings were demonstrated from randomized controlled trials (RCTs). Evidence showed that supplementation in vitamin D3 deficient population (adolescents and elderly) significantly improved mood. In contrast, in nondeficient populations, the effects were minimal, suggesting targeting supplementation in groups associated with deficiencies (Satyanarayana et al., 2024; Alavi et al., 2019). Genetic studies have indicated that vitamin D3 receptor polymorphisms influence susceptibility to treatment-resistant depression (Merlo et al., 2023).

Physical activity and D3 intake exhibit synergistic effects. Combining both exercise and vitamin D3 treatment will optimize the positive effects on an antidepressant treatment. Importantly, exercise supports brain health through brain-derived neurotrophic factor (BDNF) release that improves neuroplasticity and neuroprotective processes. Relatedly, vitamin D3 lessens oxidative stress and increases serotonin level which can collectively improve cognitive function. The outcome has been associated with activation of the erythrocyte nuclear factor 2 (Nrf2) pathway (Hansen et al., 2019; Gujral et al., 2017). A meta-analysis from Musazadeh et al., (2023)

illustrated that multitherapies in older adults reduced depressive symptoms by 40% compated to monotherapies. In addithion, outdoor exercise strengthens the cutaneous production of vitamin D3, reserving deficiency. To date, it seems that multimodal approaches are particularly easy in populations witsh concomitant inflammation or metabolic disturbance (Menéndez et al., 2024; Beurel et al., 2020).

2. REVIEW METHODS

A search in literature was conducted through digital databases like PubMed and Google Scholar. The review included clinical trials, systematic reviews, and meta-analyses that focused on the effects of physical activity and vitamin D3 supplementation on depression published after 2015. Keywords used in the search included: depression, physical activity, vitamin D3, neuroinflammation, combined interventions, and mental health. The number of records identified through the database search was 170. 156 records were then screened. Thirty-four articles in languages other than English, animal studies, and non-peer-reviewed articles were excluded. 122 articles were assessed for eligibility. 92 records were excluded. Thirty studies were included that were relevant to the purpose of this review (figure 1).

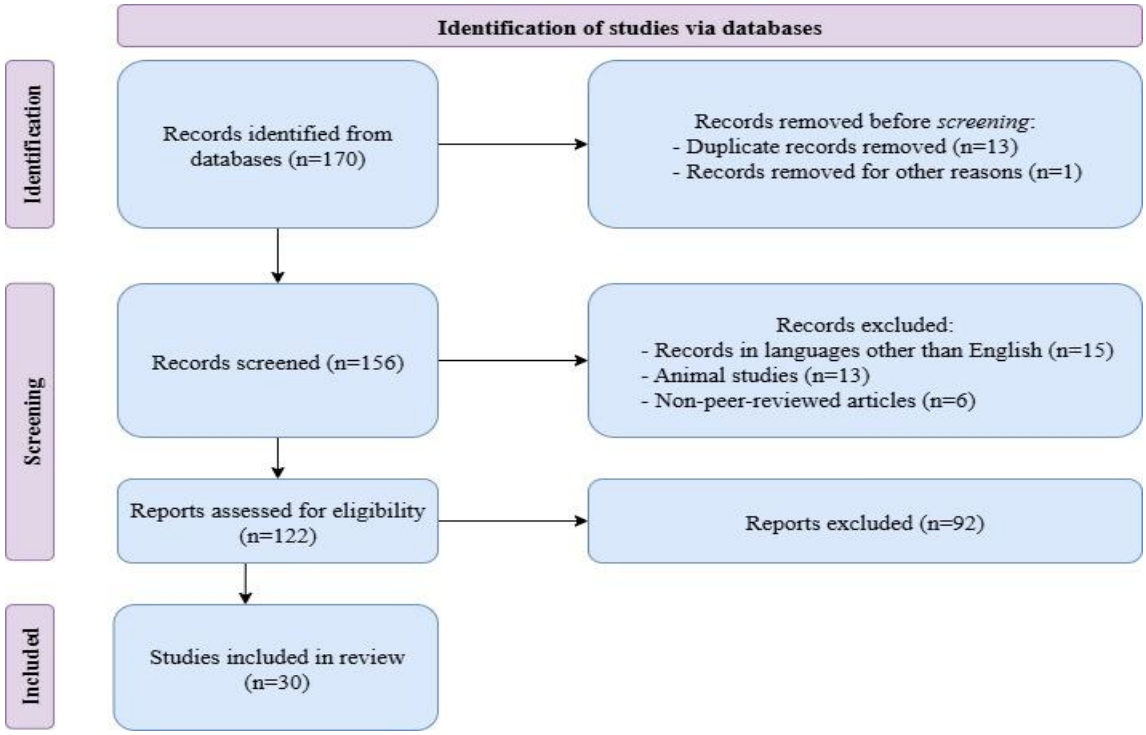

Fig. 1: PRISMA consort chart of selected studies

3. RESULTS AND DISCUSSION

Meta-analyses of randomized controlled trials (RCPTs) demonstrate that high-dose vitamin D3 supplementation (≥2800 IU/day for ≥8 weeks) reduces symptoms of depression. This vitamin D3 effect of a dose-dependent relationship on depression is particularly apparent in those with vitamin D3 deficiencies (Contreras-Osorio et al., 2022). Vitamin D3 supplementation demonstrates clinically meaningful efficacy as an adjunct therapy, especially for those patients who were deficient. However, there is evidence to suggest that with exercise or combined with exercise, the effect may be equivalent or exceed some standard treatments of antidepressant therapy in specific population samples (Xie et al., 2022; Philippot et al., 2022). Philippot et al., (2022) observed synergistic antidepressant effects in deficient adults: 32% reduction in HAM-D score with combined aerobic movement (3x/week, vigorous or moderate) and high-dose vitamin D3 (only supplying 3000 IU/day), compared to 19% reduction with vitamin D3 supplementation alone. There is evidence why these therapies would results in mechanisms such as exercise related increases in neurogenesis with the anti-inflammatory effects of vitamin D3, and both therapies modify serotonin synthesis or central to regulate HPA axis (Beurel et al., 2020; Casseb et al., 2019).

Subgroup analysis showed that patients with severe deficiency (serum 25(OH)D <12 ng/mL) or treatment-resistant depression may have derived the best benefit. The impact of Lifestyle Interventions on Depression Outcomes is presented in Table 1.

Table 1: Impact of Lifestyle Interventions on Depression Outcomes

Factor	Impact on Depression	Key Details	Supporting Articles
Vitamin D3 Alone	Reduces symptoms, especially in deficient patients	≥2800 IU/day for ≥8 weeks. Dose-dependent effect. Up to 19% HAM-D reduction.	Contreras-Osorio et al., (2022); Philippot et al., (2022)
Exercise Alone	Supports mood regulation	≥150 min/week moderate aerobic (e.g., jogging/swimming) OR mind-body (e.g., yoga/tai chi).	Musazadeh et al., (2023)
Combined Therapy	Synergistic effect: Superior to Vitamin D3 alone; may match/exceed antidepressants	32% HAM-D reduction (vs. 19% with D3 alone) with exercise + 3000 IU/day.	Xie et al., (2022); Philippot et al., (2022)

The best integration of Vitamin D3 with exercise will depend on individualized protocol specifications based on baseline deficiency status and severity of depressive symptomatology. It is recommended to take 2000-4000 IU of vitamin D3 used daily. This dose increases serum 25-hydroxyvitamin D [25(OH)D] to ≥ 30 nanograms per milliliter (ng/mL). It has been demonstrated that realizing either recommended dosing, while completing either aerobic or mind body movement activities (≥150 minutes/week at a moderate level of intensity such as jogging, swimming) will support mood regulation (Musazadeh et al., 2023). Increased physiological demands necessitate doses up to 4000 IU/day in adolescents and older populations. Increased metabolic requirement during growth and reduced skin synthesis in old age (Alavi et al., 2019). Satyanarayana et al., (2024) randomized controlled study found that rural adolescents who received vitamin D3 4000 IU/day for 12 weeks showed a 25% greater reduction in depressive symptoms than adolescents who received vitamin D3 2000 IU/day. Additionally, the severity of depression guides dosing of vitamin D3. Individuals with moderate-to-severe depressive symptoms may find value in acceleration (e.g. vitamin D3 50,000 IU/week for 4 to 8 weeks) and maintenance (Hansen et al., 2019). Exercise programs must be tailored according to the patients' readiness levels: deconditioned individuals should start walking for 10-minutes before progressing intensity and duration in their activity, as this was associated with improvement around adherence (Musazadeh et al., 2023). Clinicians can monitor patient outcomes with validated measures (e.g., PHQ-9), and may change the treatment frequency every 2-weeks (Akpınar and Karadağ, 2022).

It is important for exercise program design to consider the mental health risk factors associated with depression, such as low motivation, fatigue, psychomotor agitation/retardation, and other comorbidity risk (e.g. cardiovascular deconditioning, obesity, osteoporosis). For this reason, lower-impact modes of activity (e.g. walking, swimming, or using an elliptical) should be introduced first, and with supervised and progressive exposure (i.e. increasing duration by 5-10% each week) to minimize injury risk and any feelings of early stage discouragement (Contreras-Osorio et al., 2022; López-Torres, 2019). Two days a week of resistance training can help develop musculoskeletal capacity by increasing bone density, musculature, and the strength of connective tissue. Health professionals should complete pre-exercise evaluation (e.g., PAR-Q+) to assess if there are contraindications of any kind. Be on the lookout for increased suicidal ideation risk among severely depressed patients at early activation phases; careful monitoring is required. Targeted Dosing and Exercise Strategies for Depression Management are presented in Table 2.

Table 2: Targeted Dosing and Exercise Strategies for Depression Management

Factor	Impact on Depression	Key Details	Supporting Articles
Vitamin D3 Dosing:			
• Severe deficiency	Greatest symptom reduction	Accelerated dosing: 50,000 IU/week for 4–8 weeks then maintenance.	Hansen et al., (2019)
• Adolescents	25% greater reduction vs. lower dose	4000 IU/day (vs. 2000 IU/day).	Satyanarayana et al., (2024)

• Older adults	Addresses higher metabolic needs	Up to 4000 IU/day (reduced skin synthesis).	Alavi et al., (2019)
Exercise Prescription	Safe progression improves adherence	Start low (e.g., 10-min walks); increase duration/intensity 5–10% weekly. Low-impact first (walking/swimming).	Musazadeh et al., (2023); Contreras-Osorio et al., (2022); López-Torres et al., (2019)

Biological Mechanisms

Adult hippocampal neurogenesis is an important neuroplasticity mechanism that allows the support of mood stabilizers, and cognitive function as the neuroplasticity processes are engaged by physical exercise (Okereke et al., 2020). One aspect of physical activity (PA) that allows BDNF neuroprotection is through the mechanisms of neuroprotection, which help keep limited and help support neuronal survival (Rodriguez-Ayllon et al., 2019; Kandola et al., 2019). Another neurobiological mechanism linked to physical activity (PA) are the areas of the hypothalamic-pituitary-adrenal (HPA) axis; one of the many dysregulations seen in depression is along the HPA axis. In relation to PA, the regularity of PA increases glucocorticoid receptor sensitivity and glucocorticoid receptor feedback inhibition and this can positively influence the actions of the axis itself which may result in decreased absolute values of circulating cortisol and attenuated physiologic responses to chronic stress (Salk et al., 2017; McDowell et al., 2017).

In addition, PA may attenuate elevated levels of circulating proinflammatory cytokines that are elevated in relation to the inflammatory processes tied to neuroinflammation and neuronal degradation seen in depressive circuitry such as IL-6, TNF-α, etc… (Alavi et al., 2019; Beurel et al., 2020). The combination of the different mechanisms around neurotrophic support, neuroendocrine balance, and inflammation provide a reasoning for the effects seen and medications, or antidepressants seen with PA. Importantly, these biological mechanisms sync with the conclusions drawn from clinical trials. Meta-analyses indicated that the studies consistently demonstrated the anti-depressant symptoms with PA for all ages and populations (Philippot et al., 2022; López-Torres et al., 2019).

Vitamin D3 acts as a secosteroid hormone with key neuroregulatory function. It has multiple mechanisms of action to help regulate mood. It will indirectly regulate serotonin production by upregulating tryptophan hydroxylase-2 (TPH-2). TPH-2 is the enzyme that turns tryptophan into serotonin (within the brain). Low serotonin levels are pathophysiologically linked to the pathology of depression (Gujral et al., 2017; Swainson et al., 2023). Vitamin D3 also has a strong anti-inflammatory action and it inhibits nuclear factor kappa B (NF-κB), which is the master regulator of pro-inflammatory signaling pathways that contribute to neuroinflammation and oxidative stress in depression (Menéndez et al., 2024; Gujral et al., 2017). The neuroprotective actions of vitamin D include: stabilizing mitochondria; enhancing antioxidant defenses (e.g., glutathione synthesis), and prevention of cellular damage due to ROS (Casseb et al., 2019). There is evidence from both epidemiological and clinical studies linking vitamin D deficiency with higher rates of depression. Further the data suggest that supplementation improves depression symptoms, especially for individuals who are deficient at baseline (Arathimos et al., 2021; Hansen et al., 2019). Satyanarayana et al., (2024) demonstrated in a cluster randomized controlled trial that high-dose vitamin D3 supplementation (2250 IU/day) significantly lowered Beck Depression Inventory (BDI-II) scores in rural adolescents, and thus provided evidence of its therapeutic potential with those at risk of nutritional vulnerability.

There may be additional synergistic effects of combining physical activity and vitamin D3 supplementation relevant to depression that act through overlapping and complementary mechanisms. For instance, both exercise and vitamin D3 supplementation can enhance BDNF signaling pathways, and combining exercise and vitamin D3 interventions yielded stronger BDNF signaling responses than those achieved with either alone. The reasons for this synergistic effect are likely twofold: firstly, vitamin D3 supplementation improves exercise-mediated BDNF expression, and exercise leads to greater expression of brain vitamin D receptor (VDR) density, leading to an additive effect through self-reinforcement that boosts neuroplasticity (Merlo et al., 2023; Mousa et al., 2018). In addition, exercise and vitamin D3 supplementation have anti-inflammatory effects as well, both of which have an additive effect by inducing exercise-mediated myokines (such as interleukin-10) and suppression of NF-κB signaling to diminish neuroinflammatory cascades, to reduce neuron endogenous trauma induced by cytokines (Menéndez et al., 2024; Beurel et al., 2020). Lastly, the complementary effects of exercise and vitamin D3 on oxidative stress (exercise promoted endogenous antioxidant enzymes such as superoxide dismutase; vitamin D3 scavenges free radicals and stabilizes mitochondrial electron transport chains) can act synergistically as well (McDowell et al., 2017; Merlo et al., 2023), as shown through preclinical models- e.g., exercise amplified the efficacy of vitamin D3-generated-hippocampal neurogenesis and exercise alone may amplify the significance of VDR signaling suggesting a two-way interaction that would ideally maximize neuroprotective/promoting efficacy (Mousa et al., 2018). From a clinical standpoint, this multi-target intervention may maximize treatment response for treatment-resistant depression through simultaneous engagement of three

fundamental pathophysiological inputs: neurotrophic deficiency, chronic inflammation, and oxidative stress. This polypharmacological approach modifies the underlying neurobiology of treatment-resistant depression, providing better outcomes where singular treatment options have proven ineffective (Musazadeh et al., 2023; Beurel et al., 2020).

Challenges and Limitations

It is not possible to reach definitive evidence about the personal effects of exercise and vitamin D3 supplementation on depression. First, many included studies had very heterogeneous methodologies, which makes comparison difficult and confuses the results. The interventions in the included studies were very heterogeneous in their design and delivery. As a result, a clear and meaningful comparison was not feasible. Interventions for exercise included mind-body procedures (e.g. yoga) to structured resistance training. Due to their differences, we are unable to assess or compare the efficacy of these procedures, as they may implicate different neurobiological pathways (e.g., stress-relief effectiveness versus effect on neurotrophic activity of physical activity) (Suneson et al., 2021; Merlo et al., 2023). For instance, aerobic exercise consistently showed antidepressant effects in adolescents (Lubans et al., 2016). Yoga appears to have a positive effect via the activation of the parasympathetic nervous system and by tempering stress response and ability to modulate autonomic tone (Menéndez et al., 2024). Inconsistency in study outcomes prevents direct comparison of methodology. Other inconsistency involves vitamin D3 dosing regimens, with some studies using 2000 IU per day and others 50,000 IU per week. The duration of treatment is highly variable across studies, ranging from weeks to a couple of years, which introduces temporal heterogeneity, making it difficult to interpret the findings (Alavi et al., 2019; Okereke et al., 2020). Differences in dosing regimen, and measurement approach, and therefore preventing good threshold levels, also produced varied outcome results for mood (McDowell et al., 2017; Swainson et al., 2023). For example, Alavi et al., (2019) described remarkable reductions in depression with 50,000 IU/week in older adults, while Okereke et al., (2020) found no benefit to the older adults with monthly long-term doses. They suggest that dose and frequency may have an effect on efficacy.

Causal inferences are influenced by confounding factors. There are many critical confounders that are not accounted for in current studies related to depression, including diet variables, such as omega-3 fatty acids, and geographical parameters relating to vitamin D production and UV rays. Not accounting for these factors undermines the validity of the clinical outcomes due to unrecognized bias (Kandola et al., 2019; López-Torres et al., 2019). Comorbidities often found in depression, such as chronic inflammation and obesity can also confound the responses to interventions. For example, in overweight patients or those with obesity, vitamin D can become sequestered in adipose tissue resulting in bioavailability challenges (McDowell et al., 2017). For those struggling with chronic inflammation, perhaps exercise has the greatest anti-inflammatory effect on those with the most significant levels of cytokines (Ohrnberger et al., 2017; Peng et al., 2015). Existing trials exploring diet and exercise do not fully account for gender differences in their pathophysiology and/or treatment response, such as hormonal modulation of vitamin D metabolism (Salk et al., 2017).

A gap of major concern is the lack of long-term compliance data especially for combined exercise and supplementation interventions. Most trials are acute (<12 weeks) and little to no attention is placed on the sustainability of exercise and dietary supplements in real-world settings (Philippot et al., 2022; López-Torres et al., 2019). To progress real-world evidence, pragmatic trials must be held that utilize three elements; remote-monitoring technologies, exercise groups, and biomarker dosing (e.g., 25[OH]D levels at baseline need to be stratified) to provide ecological validity (Satyanarayana et al., 2024, Beurel et al., 2020). Additionally, hypotheses about causality could be examined by mechanistic studies (Mendelian randomization or neuroimaging) and future umbrella reviews can help clarify discrepancies in calculated aggregated data (Arathimos et al., 2021; Menéndez et al., 2024). Translation to improve non-pharmacological treatment of depression will likely remain disjointed until these flaws are overcome.

Future Research Directions

Future studies must incorporate large-scale randomized controlled trials (RCTs). Real-world effectiveness trials are the gold standard for evaluating interventions targeting depression's heterogeneous etiologic pathways, resolving biological vulnerabilities and environmental precipitants. Depressive disorders are complex. Therefore, the use of a monotherapy option is expected to have less than optimal results. Consequently, future studies must reconceptualize depression as being biopsychosocially integrated, while looking at neuroendocrine pathways, cognitive-affective dynamics, as well as socio-economic context concurrently. It is proposed that studies would benefit from a randomised design using a vitamin D supplement in combination with a specific aerobic exercise, or a pharmacotherapy and cognitive-behavioral techniques (Swainson et al., 2022). Methodologically, studies must intentionally recruit subgroups of underrepresented demographic populations (e.g., race, socio-economic status) as cohorts to ensure external validity in

subsequent studies. Future studies must also systematically consider age and gender differences, as well as socioeconomic factors, when available, in both prospective studies. From a scientific basis, this is what the evidence advocates for in order to provide demographically tailored treatments. Future studies will also be focused on providing an evaluation of health system barriers for implementing obesity treatments, including medication compliance, financial circumstances, and health inequities (Salk et al., 2017, López-Torres et al., 2019).

Identifying treatment pathway mechanisms requires amalgamating state-of-the-art neuroimaging (MRI/PET) with a concurrent measurement of molecular biomarkers of neurobiological target modulation. There are two clinically significant biomarkers: brain-derived neurotrophic factor (BDNF), which supports neuroplasticity, and C-reactive protein (CRP), a clinically validated inflammation biomarker. These biomarkers can illustrate, in physiological terms, how a given intervention will neurobiologically counteract depression (Suneson et al., 2021; Kandola et al., 2019). Exercise enhances vitamin D3-mediated BDNF neurotrophic signaling and decreases neuroinflammation by downregulating pro-inflammatory cytokines (e.g., IL-6, TNF-α) in response to acute and chronic exercise. This intervention restores connections from the prefrontal cortex and parts of the hippocampus (Menéndez et al., 2024; Beurel et al., 2020). Using longitudinal studies of ongoing changes in these biomarkers would help determine symptom relief and associated changes in neurobiological targets. The possibilities with multi-omic evaluations (e.g., epigenetics, metabolomics, etc.) will help in understanding new therapeutic pathways (including gut-brain axis modulation and mitochondrial bioenergetics optimization) to mechanistically target pathways for future interventions (Salk et al., 2017; Gujral et al., 2017).

Advancing future treatment strategies will require genetic and molecular profiling of individuals with depression to practice precision psychiatry. A person's pharmacogenomic variability (for example, VDR and CYP polymorphisms) influences the efficacy of supplementation. Genotyping of CYP2R1 will inform each person's capacity for vitamin D metabolism in relation to precision dosing for vitamin D supplementation that considers biochemical individuality and gives the clinician the tools of precision psychiatry (Arathimos et al., 2021). An expansion of pharmacogenomic investigations of (i) variants in serotonin transporter genes or (ii) variants in genes involved in inflammatory pathways, would permit clinical researchers to avoid the trial-and-error prescription of antidepressants. This action will allow for improved drug selection (Musazadeh et al., 2023). Processing of newly collected data should be based on artificial intelligence. Algorithms should utilize integrated genetic, biomarker, and clinical information to develop personalized therapeutic interventions for individual patients (Musazadeh et al., 2023). These areas of investigation are open to ethical issues. The issues are privacy protection, equitable access, and potential for genetic alienation. These remain ongoing issues in research and development. Paths that can supply research solutions to these issues would increase remission rates and improve the quality of life for patients.

4. CONCLUSION

The integration of physical activity and vitamin D3 supplementation has the potential to improve therapeutic outcomes in depression, but collaboration across disciplines is needed. A multidisciplinary professional team, consisting of psychiatrists who can identify risk groups and give clinical guidance, dieticians who can implement food measures to increase vitamin D3 levels, and those responsible for creating physical activity programs can be beneficial.

Author's Contributions

Sebastian Polok- Conceptualization, Formal analysis, Writing - rough preparation, Writing - review and editing, Project administration.
Małgorzata Wasilewska- Software, Resources, Data Curation, Check
Krzysztof Pietrzak- Metodology, Investigation, Writing - rough preparation
Adriana Potoczek- Formal analysis, Investigation, Supervision
All authors have read and agreed with the published version of the manuscript

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Informed consent

Not applicable.

Ethical approval
Not applicable.

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Conflict of interest
The authors declare that there is no conflict of interest.

Data and materials availability
All data associated with this study will be available based on the reasonable request to corresponding author.

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