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eISSN 2450-3118 · Open Access · Peer-reviewed

apcz.umk.pl/QS Nicolaus Copernicus University in Toruń

Cite as: CZECHOWSKA, Małgorzata, KASZNICKI, Michał, SKRZYPEK, Emilia, ŁĄCKI, Jakub, ROGOZIŃSKA, Alicja, BEŚKA, Wiktor, JACKOWIAK, Karol, KALISIAK, Michał, MICEK, Natalia and KAMELA, Mikołaj. Vitamin D and the Serotonergic Pathway in Depression: Genomic Mechanisms, Clinical Evidence, and Implications for Sport and Physical Activity — A Narrative Review. Quality in Sport. 2026;57:72508. https://doi.org/10.12775/QS.2026.57.72508

ARTICLE TIMELINE

Received: 24.05.2026. Revised: 25.05.2026. Accepted: 31.05.2026. Published: 10.06.2026.

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines: Medical Sciences; Health Sciences.

Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Nauki medyczne; Nauki o zdrowiu.

Vitamin D and the Serotonergic Pathway in Depression: Genomic Mechanisms, Clinical Evidence, and Implications for Sport and Physical Activity — A Narrative Review

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Abstract

Background and Purpose: Vitamin D, acting through the vitamin D receptor (VDR), may directly regulate brain serotonin synthesis, linking vitamin D deficiency to depression. This review examines the serotonergic hypothesis of vitamin D action, evaluates supporting evidence, and considers implications for athletes.

Materials and Methods: PubMed, Scopus, Google Scholar, and the Cochrane Library were searched for articles published between 2010 and 2026 using terms related to vitamin D, serotonin, TPH2, VDR, depression, and physical activity.

Results: Calcitriol upregulates tryptophan hydroxylase 2 (TPH2), represses the serotonin transporter (SLC6A4) and monoamine oxidase A, together constituting a three-node serotonergic regulatory circuit. Meta-analyses of RCTs confirm vitamin D reduces depressive symptoms (SMD = −0.36 to −0.57), with dose-dependent effects peaking near 8,000 IU/day. Effects are strongest in deficient individuals with existing depression. VDR polymorphisms, particularly FokI, modulate the neuropsychiatric impact of deficiency. Athletes exhibit high rates of insufficiency and may benefit given overlapping exercise-vitamin D effects on serotonin.

Conclusions: The serotonergic hypothesis offers a defined molecular account connecting vitamin D and depression. Future research should prioritize CSF serotonin metabolite measurements, genotype-stratified trials, and sport-specific cohort studies.

Keywords: vitamin D, serotonin, tryptophan hydroxylase 2, vitamin D receptor, depression, athletes, physical activity, VDR polymorphisms, calcitriol

1. Introduction

Major depressive disorder (MDD) is among the most prevalent psychiatric conditions worldwide, affecting over 280 million individuals globally and ranking as the leading cause of disability according to the World Health Organization [WHO, 2023]. Despite decades of pharmacological research, first-line antidepressant therapies — predominantly selective serotonin reuptake inhibitors (SSRIs) — achieve full remission in only 30–50% of patients, with significant residual symptoms, delayed onset of action, and adverse effects limiting their clinical utility [Rush et al., 2006; Cipriani et al., 2018]. This gap has driven the search for modifiable risk factors and biological mechanisms that could improve outcomes.

In parallel, the global prevalence of vitamin D deficiency has reached widespread proportions. An estimated one billion people worldwide exhibit serum 25-hydroxyvitamin D [25(OH)D] concentrations below 50 nmol/L, the threshold commonly regarded as indicative of insufficiency [Holick, 2007; Amrein et al., 2020]. Hypovitaminosis D is not limited to elderly or institutionalized groups but also affects otherwise healthy young adults, including competitive and recreational athletes, particularly those training indoors, residing at high latitudes, or possessing darker skin pigmentation [Farrokhyar et al., 2015; Owens et al., 2018]. The overlap between these two conditions has prompted investigation into whether the link is causal. Epidemiological studies have consistently demonstrated an inverse association between serum 25(OH)D concentrations and the risk of depressive symptoms, with a meta-analysis by Anglin et al. [2013] reporting that individuals in the lowest vitamin D tertile exhibited a significantly elevated hazard of depression compared to those in the highest tertile. While observational data cannot establish causality, the discovery of vitamin D receptors (VDRs) throughout the human brain, including in regions implicated in mood regulation — the prefrontal cortex, hippocampus, cingulate gyrus, and, the dorsal raphe nucleus — has provided a clear neuroanatomical basis for direct central nervous system (CNS) effects of this secosteroid hormone [Eyles et al., 2005; Eyles, 2020].

Among the several mechanistic hypotheses advanced to explain the antidepressant potential of vitamin D, the serotonergic hypothesis stands out for its molecular specificity and its pharmacological analogy to SSRIs. The core proposition is that 1,25-dihydroxyvitamin D3

(calcitriol), the hormonally active metabolite of vitamin D, directly regulates the transcription of genes encoding the key enzymes and transporters of the serotonin system — specifically tryptophan hydroxylase 2 (TPH2), the serotonin reuptake transporter (SERT, encoded by SLC6A4), and monoamine oxidase A (MAO-A) [Kaneko et al., 2015; Sabir et al., 2018]. Under this framework, vitamin D acts as a genomic regulator of serotonin homeostasis, through a mechanism complementary to SSRI pharmacotherapy.

The present narrative review aims to synthesize the current molecular, preclinical, and clinical evidence supporting the serotonergic hypothesis of vitamin D action in depression, to evaluate the strength and limitations of this evidence, and to discuss its relevance for sport and exercise science — a domain in which vitamin D deficiency and mood disturbances frequently co-occur.

2. Aim

The aim of this review is to examine the hypothesis that vitamin D regulates brain serotonin homeostasis through VDR-mediated genomic actions, and to evaluate whether the available clinical evidence supports a causal role for vitamin D in the modulation of depressive symptoms. A secondary aim is to consider the implications of this hypothesis for physically active individuals and athletes, in whom both vitamin D insufficiency and exercise-related modulation of serotonergic neurotransmission are well documented.

3. Materials and methods

This narrative review was based on a structured literature search conducted in PubMed/MEDLINE, Scopus, Google Scholar, and the Cochrane Library. The search strategy employed the following terms and their combinations: “vitamin D,” “calcitriol,” “1,25-dihydroxyvitamin D3,” “serotonin,” “5-hydroxytryptamine,” “tryptophan hydroxylase 2,” “TPH2,” “vitamin D receptor,” “VDR,” “depression,” “depressive disorder,” “SERT,” “SLC6A4,” “monoamine oxidase,” “VDR polymorphism,” “FokI,” “athletes,” “exercise,” and “physical activity.” The search was restricted to articles published in English between January 2010 and March 2026. Reference lists of retrieved articles were hand-searched for additional relevant publications. Preference was given to randomized controlled trials (RCTs), systematic reviews, meta-analyses, and mechanistic studies employing chromatin immunoprecipitation (ChIP), reporter gene assays, or validated animal models. Narrative and expert reviews were included where they provided integrative context. No formal risk-of-bias assessment was performed, consistent with the narrative nature of this review.

4. Vitamin D metabolism in the central nervous system

4.1. Transport of vitamin D across the blood-brain barrier

The biological activity of vitamin D in the brain requires that its precursor metabolites gain access to neural tissue. Circulating 25(OH)D, the principal storage form, is transported bound to vitamin D-binding protein (DBP) in the systemic circulation and enters the CNS via the blood-brain barrier (BBB) and the choroid plexus. Two primary mechanisms have been identified: passive diffusion of free (unbound) 25(OH)D across endothelial cell membranes and receptor-mediated endocytosis of the DBP-25(OH)D complex via the megalin/cubilin (LRP2) receptor system expressed on the choroid plexus epithelium and brain capillary endothelium [Gall and Szekely, 2021; Khatibi and MacDonald, 2026]. The megalin pathway is important here because it allows internalization of protein-bound 25(OH)D, which constitutes the vast majority of circulating vitamin D metabolites.

Once within neural tissue, 25(OH)D undergoes local hydroxylation to the active hormone 1,25(OH)2D3 (calcitriol) by the enzyme 25-hydroxyvitamin D-1alpha-hydroxylase (CYP27B1). CYP27B1 expression has been demonstrated in multiple brain regions in both rodents and humans, including the hypothalamus, cerebellum, cortex, hippocampus, and substantia nigra, with strongest immunostaining observed in the supraoptic and paraventricular hypothalamic nuclei and in large dopaminergic neurons of the substantia nigra [Eyles et al., 2005; Gall and Szekely, 2021]. This local activation pathway is important because it enables paracrine and autocrine regulation of vitamin D-responsive genes within the brain, independent of renal 1alpha-hydroxylation and systemic calcitriol concentrations.

More detail on the cellular compartmentalization of vitamin D metabolism in the brain has emerged from studies employing purified neural cell cultures. Landel et al. [2018] demonstrated that CYP27B1, the activating enzyme, is expressed predominantly in microglia, while CYP24A1, the catabolic enzyme responsible for calcitriol inactivation, is localized primarily to astrocytes. This glial compartmentalization creates a regulatory circuit in which microglia serve as the principal site of local calcitriol synthesis and astrocytes govern its catabolism — a spatial organization distinct from the renal feedback loop [Eyles, 2020; Landel et al., 2018]. This matters clinically: neuroinflammatory states, which are common in depression, may upregulate CYP24A1 in astrocytes, potentially depleting local calcitriol even when systemic serum 25(OH)D levels appear adequate — a mechanism that could contribute to brain-specific vitamin D resistance in depressed individuals.

4.2. VDR distribution in the brain

The vitamin D receptor, a member of the nuclear receptor superfamily of ligand-activated transcription factors, is widely expressed throughout the human brain. Immunohistochemical and in situ hybridization studies have identified VDR expression in the prefrontal cortex, hippocampus, hypothalamus, amygdala, substantia nigra, and — directly relevant to the serotonergic hypothesis — the dorsal raphe nucleus (DRN) [Eyles et al., 2005; Eyles, 2020]. The DRN is the principal source of serotonergic projections to the forebrain and is implicated in mood regulation, sleep-wake cycling, and the pathophysiology of MDD. The co-localization of VDR with serotonergic neurons in the DRN provides a neuroanatomical substrate for vitamin D-mediated regulation of serotonin synthesis.

VDR functions as a heterodimer with the retinoid X receptor (RXR), binding to specific DNA sequences known as vitamin D response elements (VDREs) in the promoter regions of target genes. Upon binding calcitriol, the VDR-RXR complex recruits coactivator proteins and the basal transcription machinery, thereby modulating gene transcription [Haussler et al., 2013]. This genomic mechanism is the primary pathway through which vitamin D exerts its effects on serotonin-related gene expression.

5. The serotonergic hypothesis: molecular mechanisms

5.1. VDR-mediated upregulation of tryptophan hydroxylase 2

The central claim in the serotonergic hypothesis is the demonstration that calcitriol directly activates transcription of the TPH2 gene, which encodes the rate-limiting enzyme for serotonin biosynthesis in the brain. TPH2 catalyzes the hydroxylation of L-tryptophan to 5-hydroxytryptophan, the immediate precursor of serotonin (5-hydroxytryptamine, 5-HT). TPH2 is the brain-specific isoform, distinct from the peripheral isoform TPH1, which governs serotonin production in the gut and pineal gland [Walther and Bader, 2003]. This isoform specificity renders the vitamin D-TPH2 interaction a CNS-selective mechanism.

The key genomic evidence came from Kaneko et al. [2015], who identified two functional VDREs at positions -7 kb and -10 kb in the human TPH2 promoter region. Using chromatin immunoprecipitation (ChIP) and electrophoretic mobility shift assays, the investigators demonstrated that VDR-RXR heterodimers bind to these elements in a calcitriol-dependent manner. Reporter gene assays confirmed that both VDREs drove transcriptional activation in response to 1,25(OH)2D3. Functionally, treatment with 10 nM calcitriol induced TPH2 mRNA expression 2.2-fold in human U87 glioblastoma cells and 47.8-fold in rat RN46A-B14

serotonergic raphe neurons — a cell line that closely models the neuronal population of interest [Kaneko et al., 2015]. The size of this response in serotonergic neurons suggests the VDR-TPH2 axis is biologically meaningful.

These findings were preceded and conceptually framed by the hypothesis of Patrick and Ames [2014], who proposed that calcitriol activates TPH2 transcription at a vitamin D response element and that this mechanism could explain the epidemiological associations between vitamin D deficiency and neuropsychiatric disorders, including depression and autism spectrum disorder. The Patrick-Ames model predicted that vitamin D insufficiency would lead to reduced brain serotonin synthesis, with downstream consequences for mood, impulse control, and executive function — predictions that have since found partial empirical support.

5.2. Regulation of the serotonin reuptake transporter (SERT/SLC6A4)

The serotonergic hypothesis extends beyond synthesis to include synaptic availability. Sabir et al. [2018], in a analysis of vitamin D-regulated genes in the serotonin pathway using rat serotonergic RN46A-B14 neurons, demonstrated that treatment with 10 nM 1,25(OH)2D3 repressed SLC6A4 (SERT) mRNA expression by approximately 59% ($P = 0.0001$). SERT is the molecular target of SSRIs; it mediates the reuptake of 5-HT from the synaptic cleft into the presynaptic neuron, thereby terminating serotonergic signaling. SERT repression by calcitriol functionally mimics the pharmacological blockade by SSRIs, though through a transcriptional rather than protein-level mechanism [Sabir et al., 2018].

SERT repression by calcitriol was selective for serotonergic neurons; the effect was not replicated in human U87 glioblastoma cells, suggesting cell-type specificity that may reflect the particular chromatin landscape and cofactor environment of serotonergic neurons. The direction and magnitude of SERT regulation by calcitriol may thus vary by brain region and cell type, a complexity that requires further investigation. Still, the fact that vitamin D affects serotonin reuptake dynamics adds a second regulatory node to the serotonergic loop, beyond TPH2-mediated synthesis.

5.3. Modulation of monoamine oxidase A

Serotonin is catabolized primarily by monoamine oxidase A (MAO-A), a mitochondrial enzyme that oxidatively deaminates 5-HT to 5-hydroxyindoleacetic acid (5-HIAA). Sabir et al. [2018] further demonstrated that treatment of serotonergic RN46A-B14 neurons with 10 nM 1,25(OH)2D3 repressed MAO-A mRNA expression by approximately 51% ($P = 0.015$), while MAO-B expression remained unaffected. In silico analysis identified candidate VDREs (DR3

motifs) in the human MAO-A gene at approximately +776 bp, with additional ChIP-seq-confirmed VDR binding regions, providing a plausible genomic mechanism for this regulation [Sabir et al., 2018]. The net functional consequence of these concurrent actions — TPH2 induction, SERT repression, and MAO-A repression — was a measurable increase in serotonin accumulation in cell culture, reaching 2.9-fold above baseline at 10 nM calcitriol ($P < 0.05$), with a time-dependent trajectory (1.7-fold at 24 hours; 2.0-fold at 72 hours) [Sabir et al., 2018]. One caveat: the dose-response curve for these effects was biphasic (inverted-U shaped), with only the 10 nM concentration proving effective; both 1 nM and 100 nM concentrations failed to produce significant effects. This narrow therapeutic window in vitro echoes the U-shaped epidemiological curves observed for vitamin D and various health outcomes and suggests that achieving optimal brain calcitriol concentrations may require precise supplementation strategies.

Furthermore, a potential discrepancy exists between the in vitro and in vivo evidence regarding MAO-A regulation. Jiang et al. [2014], in a study of chronic calcitriol administration in rats, observed MAO-A mRNA induction in the prefrontal cortex — a direction opposite to the repression reported by Sabir et al. [2018] in isolated serotonergic neurons. This discrepancy likely reflects the difference between effects in purified serotonergic neurons versus whole-brain tissue containing multiple cell types with distinct VDR signaling programs, and reinforces the need for region-specific and cell-type-specific analyses in future studies.

Despite this limitation, the triad of regulatory actions identified in serotonergic neurons a "complete serotonergic modulatory loop" — a regulatory program where a single endocrine signal (calcitriol) coordinates serotonin production, synaptic availability, and turnover. In practice, SSRIs act only at the level of reuptake, and MAO inhibitors act only at the level of catabolism**;** vitamin D operates simultaneously across multiple nodes of serotonin homeostasis.

5.4. Pharmacological analogy to selective serotonin reuptake inhibitors

The mechanistic parallels between vitamin D and SSRIs warrant direct comparison. Both agents increase the net concentration of serotonin available for postsynaptic signaling in the brain, but they achieve this outcome through fundamentally different molecular strategies. SSRIs block the SERT transporter protein, inhibiting reuptake and thereby prolonging the duration of serotonin action in the synaptic cleft. Vitamin D, by contrast, acts upstream — enhancing de novo synthesis of serotonin via TPH2 upregulation — while simultaneously modulating SERT expression and MAO-A activity [Bostan et al., 2025].

This distinction has clinical implications. First, the mechanisms are non-redundant and

potentially synergistic: vitamin D supplementation could, in principle, augment the efficacy of SSRI therapy by increasing the total pool of serotonin available for synaptic release, while the SSRI ensures that released serotonin remains in the synaptic cleft. Preliminary clinical evidence supports this proposition. Khoraminya et al. [2013], in a double-blind RCT of 42 patients with MDD, found that the combination of fluoxetine (20 mg/day) plus vitamin D3 (1,500 IU/day) produced significantly greater improvement in depressive symptoms than fluoxetine alone, with the superiority of the combination evident from week 4 onward. This accelerated onset suggests that vitamin D-mediated enhancement of serotonin synthesis may complement the reuptake blockade of the SSRI, resulting in earlier therapeutic benefit [Khoraminya et al., 2013; Bostan et al., 2025].

Second, vitamin D supplementation may offer antidepressant benefits in individuals who are non-responsive or intolerant to SSRIs, provided that their depressive pathophysiology involves serotonergic dysfunction related to substrate (serotonin) deficiency rather than transporter-level abnormalities [Bostan et al., 2025]. Third, the genomic nature of vitamin D's action implies a slower onset but potentially more sustained effect on serotonin homeostasis compared to the acute pharmacodynamic action of SSRIs.

6. Clinical evidence

6.1. Meta-analyses of vitamin D supplementation and depression

The clinical evidence linking vitamin D supplementation to improvements in depressive symptoms has been evaluated in multiple systematic reviews and meta-analyses. Results were initially mixed but have become more consistently positive in better-designed recent trials.

Mikola et al. [2023], in a meta-analysis published in Critical Reviews in Food Science and Nutrition, synthesized data from randomized controlled trials (RCTs) investigating the effect of vitamin D supplementation on depressive symptoms in adults. The analysis demonstrated a statistically significant reduction in depressive symptoms in vitamin D-supplemented groups compared to placebo, with the effect most pronounced in trials that enrolled participants with clinically diagnosed depressive disorder and in those with documented baseline vitamin D deficiency.

Wang et al. [2023], in a meta-analysis published in the Journal of Affective Disorders, further confirmed that vitamin D supplementation significantly reduced depressive symptoms in adults with primary depression, particularly when baseline 25(OH)D concentrations were below 50 nmol/L. This finding aligns with the mechanistic prediction that serotonergic benefits of

vitamin D should be contingent upon achieving sufficient substrate for CNS calcitriol synthesis. Srifuengfung et al. [2023], in a systematic review and meta-analysis of 18 RCTs enrolling 1,980 depressed patients (Nutrition), reported that vitamin D supplementation was significantly superior to placebo (SMD = -0.49; 95% CI: -0.75 to -0.23), with adults responding substantially better than children and adolescents. Of note, intermittent high-dose (bolus) regimens were more effective than daily oral dosing, and more severe depression tended to respond better (P = 0.053), consistent with a floor effect in mildly symptomatic individuals.

The most detailed dose-response data came from the meta-analysis of Ghaemi et al. [2025], published in Psychological Medicine, which synthesized data from 31 RCTs encompassing 24,189 participants. The analysis demonstrated that each 1,000 IU/day increment in vitamin D3 supplementation was associated with an SMD of -0.32 (95% CI: -0.43 to -0.22; GRADE certainty: moderate). In the subgroup with existing depressive symptoms, the effect was larger (SMD = -0.57; 95% CI: -0.69 to -0.44; 15 trials). The dose-response curve revealed that antidepressant effects increased proportionally up to approximately 8,000 IU/day (SMD = -2.04; 95% CI: -3.77 to -0.31) — a large effect size — after which a plateau was reached. However, a temporal attenuation was also observed: while short-term (<=8 weeks; SMD = -0.45) and medium-term (8-24 weeks; SMD = -0.47) trials showed significant benefits, long-term trials (>52 weeks) did not (SMD = +0.14; non-significant) [Ghaemi et al., 2025]. This attenuation at longer durations **i**s difficult to reconcile with the serotonergic hypothesis, which would predict sustained benefits as long as calcitriol-dependent TPH2 transcription remains active.

Musazadeh et al. [2023], in an umbrella meta-analysis pooling 10 RCT-based meta-analyses and 4 cohort-based meta-analyses (Pharmacological Research), reported a pooled SMD of -0.40 (95% CI: -0.60 to -0.21) for the effect of vitamin D supplementation on depression across all RCT meta-analyses, alongside a pooled odds ratio of 1.60 (95% CI: 1.08-2.36) linking lower 25(OH)D concentrations to higher odds of depression in cohort studies. The heterogeneity (I2 approximately 89-91%) across both bodies of evidence reinforces the need for better-defined target populations and standardized outcome measures.

Most recently, Wang et al. [2025], in a meta-analysis of 20 RCTs published in Frontiers in Psychiatry, confirmed a moderate but statistically significant improvement in depressive symptoms (pooled SMD = -0.36; 95% CI: -0.52 to -0.20; P < 0.00001) and recommended that future investigations incorporate biomarkers of serotonin pathway activity and VDR gene polymorphism data to advance the mechanistic understanding of vitamin D’s antidepressant effects.

Regarding the direct measurement of serotonin, the meta-analysis by Alimohammadi-Kamalabadi et al. [2024], published in Health Science Reports, synthesized data from 6 RCTs encompassing 356 participants and found no significant change in serum serotonin levels following vitamin D supplementation (SMD = 0.24 ng/mL; 95% CI: -0.28 to 0.75; P > 0.10). This null finding requires qualification, though, because all included studies measured peripheral (platelet-derived) serotonin, which is synthesized by TPH1 in enterochromaffin cells and does not cross the BBB. Peripheral serotonin pools are largely independent of central serotonergic neurotransmission, and unchanged serum 5-HT levels do not preclude altered brain serotonin dynamics. To date, no human supplementation trial has measured cerebrospinal fluid 5-HIAA — the gold-standard index of central serotonin turnover — a gap that limits mechanistic conclusions.

6.2. The VITAL-DEP trial and its implications

The clinical evidence must be weighed against the null findings of the VITAL-DEP (Vitamin D and Omega-3 Trial — Depression Endpoint Prevention) study, the largest RCT to date examining vitamin D and depression [Okereke et al., 2020]. This ancillary study of the VITAL trial randomized 18,353 adults aged 50 years or older to receive either 2,000 IU/day of vitamin D3 or placebo over a median follow-up of 5.3 years. The primary outcome — incidence of depression or clinically relevant depressive symptoms — did not differ between groups (hazard ratio 0.97; 95% CI: 0.87-1.09).

However, several design features of the VITAL-DEP trial limit its relevance to the serotonergic hypothesis. First, participants were not selected for baseline vitamin D deficiency; the mean baseline 25(OH)D was approximately 77 nmol/L, well above the threshold of insufficiency. In a population with largely replete vitamin D status, the serotonergic mechanism — which depends on local calcitriol synthesis from 25(OH)D substrate — would not be expected to produce measurable effects, as the enzymatic pathway is already adequately supplied. Second, the dose of 2,000 IU/day, while sufficient for skeletal health, may be suboptimal for achieving the CNS calcitriol concentrations necessary to activate VDR-mediated TPH2 transcription in the brain, particularly given the attenuation of vitamin D transport across the BBB with aging. Third, the trial examined depression prevention in a general population, not treatment of existing depression — a fundamentally different clinical question with different mechanistic requirements.

In contrast, Kaviani et al. [2022], in a randomized, double-blind, placebo-controlled trial published in BMC Psychiatry, administered 50,000 IU of vitamin D3 biweekly for 8 weeks to

adults with mild-to-moderate depression and documented vitamin D deficiency. The vitamin D group exhibited a significantly greater reduction in Beck Depression Inventory-II (BDI-II) scores (mean change: -11.75 +/- 7.08) compared to placebo (-3.61 +/- 4.95; P = 0.003). Serum concentrations of interleukin-1beta (IL-1beta), interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP) did not change significantly in either group, suggesting that the antidepressant effect was not mediated through anti-inflammatory pathways and was, by elimination, more consistent with a serotonergic mechanism [Kaviani et al., 2022].

6.3. Dose-response considerations and baseline vitamin D status

The antidepressant efficacy of vitamin D supplementation is modulated by two variables: the dose administered and the recipient's baseline vitamin D status. The dose-response meta-analysis by Ghaemi et al. [2025] provides the most detailed quantitative framework: the antidepressant effect increases linearly from 1,000 IU/day (SMD = -0.32) through approximately 8,000 IU/day (SMD = -2.04), after which a plateau is reached. Trials employing higher doses (>=4,000 IU/day or equivalent bolus regimens) and enrolling vitamin D-deficient participants (baseline 25(OH)D < 50 nmol/L) have consistently reported larger effect sizes compared to studies using lower doses in replete populations [Mikola et al., 2023; Wang et al., 2023; Ghaemi et al., 2025]. Supporting this, Bahrami et al. [2018] reported significant reductions in depression scores in adolescent girls receiving 50,000 IU/week (approximately 7,143 IU/day equivalent) for 9 weeks, and Tarikere Satyanarayana et al. [2024], in an RCT of 451 rural adolescents, found that 2,250 IU/day for 9 weeks significantly reduced BDI-II scores compared to a 250 IU/day control.

This dose-response pattern is consistent with the serotonergic hypothesis. The in vitro data of Sabir et al. [2018] indicate that the calcitriol concentration required for optimal TPH2 induction is approximately 10 nM — a concentration that corresponds to serum 1,25(OH)2D3 levels achievable with supplementation doses of 4,000-8,000 IU/day in most adults. In vitamin D-deficient individuals, supplementation that raises 25(OH)D into the sufficient range would increase local calcitriol production by CYP27B1 in brain microglia, thereby enhancing TPH2 expression. In vitamin D-replete individuals, the VDR-mediated pathway may already be saturated, rendering additional supplementation ineffective — precisely the pattern observed in the literature.

The moderating role of baseline vitamin D status, however, remains paradoxical and contested. The VITAL-DEP trial found no benefit even in its deficient subgroup (25(OH)D < 50 nmol/L; only 11.6% of participants), and Guzek et al. [2023], in a systematic review of 8 RCTs, noted

that studies explicitly requiring deficiency as an inclusion criterion paradoxically tended to show null results, while mixed-status populations showed benefit. This counterintuitive pattern may reflect regression to the mean, floor effects in individuals with very low 25(OH)D, or the possibility that the clinical threshold for serotonergic benefit differs from the conventional skeletal health threshold.

6.4. Evidence from preclinical serotonin biomarker studies

Direct evidence that vitamin D supplementation alters brain serotonergic activity in vivo remains limited but suggestive. Jiang et al. [2014], in a study of chronic calcitriol administration in rats (50 and 100 ng/kg/day for 6 weeks), demonstrated that calcitriol treatment enhanced VDR protein levels in the brain without altering serum calcium or phosphate, and was associated with alterations in monoamine neurotransmitter concentrations, including serotonin. More recently, Wang et al. [2025] reported sex-specific effects of vitamin D on autistic behavior and gastrointestinal symptoms in a valproic acid-induced autism rat model. Male rats with vitamin D deficiency exhibited decreased 5-HT levels, decreased VDR expression, and decreased TPH activity in both intestinal and brain tissues; vitamin D supplementation reversed these changes and alleviated behavioral symptoms. Female rats showed no significant changes in any of these parameters, revealing a sex-specific dimension of vitamin D-serotonin coupling that has implications for the design and interpretation of clinical trials [Wang et al., 2025]. This sex specificity aligns with the subgroup analyses of Xie et al. [2022], who found stronger antidepressant effects of vitamin D supplementation in female human participants.

Worth noting, the Eyles group's assessment of developmental vitamin D (DVD) deficiency models has identified dopaminergic — rather than serotonergic — alterations as the most robust in vivo phenotype. Kesby et al. [2017] found that serotonin decreases in DVD-deficient neonatal rats were limited to striatal subregions, whereas dopamine alterations were more widespread and glutamine reductions were ubiquitous (12-24% across all brain regions). Eyles [2020] explicitly noted that evidence for vitamin D's effect on brain serotonin in vivo "remains only at the in vitro level" — a point that should temper conclusions drawn from the cell culture data of Kaneko et al. [2015] and Sabir et al. [2018].

These findings support the biological plausibility of vitamin D-mediated serotonergic regulation in vivo but reinforce the need for direct measurement of central serotonin metabolites — specifically 5-HIAA in cerebrospinal fluid — in human supplementation trials, an experiment that has never been conducted.

7. Genetic variability: VDR polymorphisms and inter-individual response

7.1. Functional polymorphisms of the VDR gene

The VDR gene harbors several common polymorphisms that alter the structure and transcriptional efficiency of the encoded receptor, with potential consequences for the magnitude of vitamin D's serotonergic effects. The most extensively studied polymorphisms include FokI (rs2228570), BsmI (rs1544410), TaqI (rs731236), and ApaI (rs7975232).

The FokI polymorphism is located in exon 2 of the VDR gene and results in a structural difference in the VDR protein itself. The C-allele (designated "F") produces a VDR protein that is three amino acids shorter and exhibits approximately 1.7-fold greater transcriptional activity than the longer variant produced by the T-allele ("f") [Arai et al., 1997; Uitterlinden et al., 2004]. This difference directly impacts the capacity of calcitriol to activate target gene transcription, including, presumably, TPH2 and SLC6A4. Carriers of the ff genotype would therefore be predicted to exhibit attenuated serotonergic responses to vitamin D supplementation compared to FF homozygotes.

7.2. VDR polymorphisms and depression: emerging evidence

The evidence linking VDR polymorphisms to depression is emerging, with findings that emphasize gene-environment interactions and haplotype-level effects rather than simple single-SNP associations.

Da Silva Sabiao et al. [2024], in a population-based study of 1,637 Brazilian adults (Scientific Reports), investigated the interaction between FokI polymorphism and vitamin D deficiency in relation to symptoms of mental disorders. The study found that vitamin D deficiency alone was not directly associated with depression symptoms; however, individuals with vitamin D deficiency who carried one or two copies of the FokI altered allele (f/ff genotype) exhibited significantly higher prevalence of depressive symptoms compared to those with sufficient vitamin D and the FF genotype. This gene-environment interaction was specific to depression and was not observed for anxiety symptoms, providing direct human evidence that VDR genetic variation determines the neuropsychiatric threshold at which vitamin D deficiency becomes symptomatic [da Silva Sabiao et al., 2024].

A parallel finding by Menezes-Junior et al. [2024], in a cross-sectional study of 1,674 Brazilian adults, demonstrated that the FokI ff genotype conferred an odds ratio of 1.49 (95% CI: 1.05-2.12) for poor sleep quality, with a synergistic effect when combined with vitamin D deficiency

(OR = 2.19; 95% CI: 1.27-3.76). Given that sleep disruption is a cardinal feature of depression, this finding provides indirect support for the role of FokI in mood-relevant neurobiological outcomes.

Beyond individual SNPs, haplotype-level analyses have revealed more consistent associations. Lye et al. [2021], in a matched case-control study of 300 MDD cases and 300 controls from Malaysia, found that no individual BsmI, ApaI, or TaqI SNP was significantly associated with MDD risk after adjustment for confounders. However, the TAC (BAt) haplotype — comprising specific alleles at BsmI, ApaI, and TaqI — was significantly associated with increased MDD risk. This haplotype finding was independently corroborated by Kuningas et al. [2009], who in the Leiden 85-plus Study (n = 563) identified the BAt haplotype as a risk factor for worse cognitive function and depressive symptoms in the elderly. The convergence of these findings across ethnically and geographically distinct cohorts strengthens the case for haplotype-level VDR effects on neuropsychiatric outcomes.

In vitro pharmacogenomic evidence has also emerged. Gizzi and Albi [2024], using HN9.10e embryonic hippocampal cell lines, demonstrated that cells with favorable FokI/ApaI genotype combinations (AA/CC) responded robustly to vitamin D3 treatment, cells with heterozygous genotypes showed intermediate responses, and cells with unfavorable genotype combinations (GG/AA) failed to respond at all. Although a parallel in vivo study in adolescents yielded null results, the in vitro data suggest that VDR genotype qualitatively determines whether vitamin D supplementation can elicit a cellular response — a finding with clear pharmacogenomic implications.

Regarding post-stroke depression, Sun et al. [2023] found that while no individual VDR SNP was associated with depression risk, a specific 5-SNP VDR haplotype (CCGAA) was strongly protective (OR = 0.14; 95% CI: 0.03-0.65; P = 0.010), and the CYP27B1 rs10877012 G/G genotype was independently protective (OR = 0.41; 95% CI: 0.18-0.92) — implicating not only VDR signaling but also local vitamin D activation capacity in depression susceptibility.

A systematic review by Grant and Athreya [2025], which evaluated 390 pharmacogenetic studies of antidepressants, found that VDR is not currently represented on any of the 34 clinical pharmacogenetic panels used for antidepressant prescribing. This is a notable gap. The mechanistic rationale for genotype-stratified vitamin D supplementation is strong, but prospective genotype-stratified RCTs have not yet been conducted. Such trials would directly test the serotonergic hypothesis and could move vitamin D pharmacogenomics closer to precision psychiatry — as with the genotype-guided prescribing of SSRIs based on CYP2D6 polymorphisms.

8. Implications for sport and physical activity

8.1. Vitamin D deficiency in athletes

Vitamin D deficiency and insufficiency are prevalent among athletes and physically active populations, despite the common perception that outdoor activity confers adequate sun exposure. A systematic review by Farrokhyar et al. [2015] found that 56% of athletes had inadequate vitamin D levels (25(OH)D < 80 nmol/L), with indoor-sport athletes, those at higher latitudes, and athletes with darker skin pigmentation at greatest risk. Owens et al. [2018] reported similarly high rates of insufficiency in professional football (soccer) players in the United Kingdom, with seasonal nadirs during winter months.

These findings are directly relevant to the serotonergic hypothesis. If vitamin D deficiency impairs TPH2-mediated serotonin synthesis in the brain, then vitamin D-insufficient athletes may be at elevated risk for subclinical serotonergic dysfunction, manifesting as mood disturbances, impaired recovery from training stress, poor sleep quality, and suboptimal cognitive performance — all recognized barriers to athletic performance.

8.2. Convergent pathways: exercise, vitamin D, and serotonin

Physical exercise is itself a potent modulator of brain serotonin levels. Acute exercise increases tryptophan availability to the brain by promoting competition at the large neutral amino acid transporter, while chronic exercise training upregulates TPH2 expression and serotonin turnover in the DRN [Meeusen and De Meirleir, 1995; Klempin et al., 2013]. These effects are believed to contribute substantially to the well-documented antidepressant efficacy of regular physical activity.

That exercise and vitamin D both act on serotonin synthesis raises the question of whether the two interventions may act synergistically on TPH2 expression, with exercise promoting enzymatic activity through substrate availability and neural signaling mechanisms, while vitamin D promotes transcription of the TPH2 gene through VDR-mediated genomic action. This possibility was partially explored by Kazemi et al. [2023], who demonstrated that maternal vitamin D supplementation combined with treadmill exercise attenuated vitamin D deficiency-induced anxiety- and depressive-like behaviors in offspring rats, suggesting additive or synergistic neuroprotective effects.

Arabshahi et al. [2024], in a cross-sectional study published in Frontiers in Nutrition, examined the association between dietary vitamin D intake and the risk of depression, anxiety, and sleep

disorders in physically active adults. The results indicated that higher vitamin D intake was associated with lower odds of depressive and anxiety symptoms in this population, supporting the relevance of vitamin D status for mental health in active individuals.

Tomlinson et al. [2021] specifically investigated depression in collegiate runners and soccer players in relation to serum 25(OH)D levels, finding that student-athletes with lower vitamin D concentrations exhibited higher depression scores — an observation consistent with the serotonergic hypothesis and pointing to the potential for vitamin D optimization as a mental health intervention in sport.

8.3. Practical considerations

For sports medicine practitioners and coaches, the serotonergic hypothesis carries several practical implications. First, routine screening of 25(OH)D levels in athletes should be considered not only for musculoskeletal health but also for mental health optimization. Second, supplementation protocols aimed at achieving 25(OH)D concentrations of at least 75-100 nmol/L may be warranted in deficient athletes, with attention to the dose-response relationships identified in the clinical literature. Third, the interaction between exercise and vitamin D on serotonergic pathways suggests that combined interventions — structured physical activity programs with concurrent vitamin D optimization — may provide synergistic mood benefits, particularly during winter months or in athletes confined to indoor training environments.

9. Testable predictions and future directions

The serotonergic hypothesis generates several specific, falsifiable predictions that should guide future research:

First, vitamin D3 supplementation in deficient individuals should produce measurable increases in cerebrospinal fluid 5-HIAA (the primary serotonin metabolite), with the magnitude of increase correlating with the achieved rise in 25(OH)D concentration. To date, no human supplementation trial has measured CSF serotonin metabolites as a primary endpoint — a gap in the evidence base.

Second, TPH2 mRNA expression in post-mortem human brain tissue from the dorsal raphe nucleus should correlate positively with ante-mortem serum 25(OH)D status. Post-mortem transcriptomic studies incorporating vitamin D status data would provide direct evidence for the genomic regulation of serotonin synthesis in the human brain.

Third, individuals carrying VDR polymorphisms associated with reduced transcriptional

efficiency (e.g., FokI ff genotype) should exhibit an attenuated antidepressant response to vitamin D3 supplementation compared to those with the more active FF genotype. Genotype-stratified RCTs are needed to test this prediction.

Fourth, the antidepressant effect of vitamin D3 supplementation should be partially attenuated by acute tryptophan depletion challenge, as reduced substrate availability would limit the benefit of enhanced TPH2 expression. This experimental paradigm, well established in serotonin research, has not yet been applied to vitamin D intervention studies.

Fifth, in athlete populations, seasonal variation in 25(OH)D levels should correlate with seasonal variation in mood disturbances, mediated through serotonergic mechanisms, and this relationship should be attenuated by vitamin D supplementation during winter months.

The hypothesis would be substantially weakened if: (a) vitamin D3 supplementation fails to alter CSF serotonin metabolites in deficient individuals under controlled conditions; (b) VDR knockout animal models show no changes in brain TPH2 expression or serotonin levels; or (c) selective TPH2 inhibition abolishes the antidepressant behavioral effects of calcitriol in validated animal models of depression.

10. Discussion

The serotonergic hypothesis of vitamin D action in depression is supported by converging lines of genomic, preclinical, and clinical evidence. The identification of functional VDREs in the TPH2 promoter [Kaneko et al., 2015], the demonstration that calcitriol regulates SERT and MAO-A expression [Sabir et al., 2018], the localization of VDR to serotonergic neurons in the dorsal raphe nucleus [Eyles, 2020], and the capacity of the brain to synthesize calcitriol locally via CYP27B1 collectively establish a biologically plausible pathway through which vitamin D status could directly influence brain serotonin homeostasis.

The clinical evidence, while not uniformly positive, is increasingly supportive when the methodological heterogeneity of the trial literature is taken into account. The apparent discrepancy between the null result of the VITAL-DEP trial [Okereke et al., 2020] and the positive findings of targeted supplementation studies [Kaviani et al., 2022; Mikola et al., 2023; Wang et al., 2023] is reconciled by recognizing that the serotonergic mechanism is substrate-dependent: it requires that vitamin D status be insufficient at baseline for supplementation to produce a meaningful increase in local calcitriol availability. Trials that enrolled vitamin D-replete populations and administered moderate doses would not be expected to observe serotonergic benefits, and they did not.

The observation by Kaviani et al. [2022] that vitamin D supplementation improved depressive symptoms without altering inflammatory biomarkers (IL-1beta, IL-6, hs-CRP) effectively rules out the anti-inflammatory hypothesis as the sole explanation for the observed antidepressant effect and strengthens the case for a serotonergic mechanism by exclusion. This finding does not, however, exclude contributions from other vitamin D-dependent pathways, including upregulation of brain-derived neurotrophic factor (BDNF), modulation of the hypothalamic-pituitary-adrenal (HPA) axis, or neuroprotective actions mediated through calcium signaling.

Several limitations of the current evidence base must be acknowledged, and it is worth noting that the serotonergic pathway is likely one of several parallel mechanisms — alongside dopaminergic, neuroinflammatory, and neurotrophic pathways — through which vitamin D influences mood and behavior.

First, the direct evidence that vitamin D supplementation alters central serotonin metabolism in humans is absent; all mechanistic data derive from in vitro systems and animal models, and the translation of VDR-mediated TPH2 transcription from cell culture to the intact human brain remains to be confirmed. The in vitro data, while striking in magnitude (33-fold TPH2 induction in serotonergic neurons), were obtained in rat embryonic cell lines at a single calcitriol concentration (10 nM), with a biphasic dose-response that complicates clinical translation [Sabir et al., 2018]. No human brain tissue ChIP-seq data confirming VDRE occupancy at the TPH2 locus in serotonergic neurons have been published.

Second, the measurement of peripheral serotonin concentrations, which has been attempted in some studies [Alimohammadi-Kamalabadi et al., 2024], is of uncertain relevance to central serotonergic function, as peripheral and central serotonin pools are largely independent. The meta-analysis by Alimohammadi-Kamalabadi et al. [2024] found no significant change in serum serotonin following vitamin D supplementation (6 RCTs, 356 participants), and a study by Khalighi Sikaroudi and Shidfar [2020] demonstrated improvement in depression scores without any change in serum 5-HT or 5-HIAA — a dissociation that is consistent with the serotonergic hypothesis (if the effects are central) but equally consistent with non-serotonergic mechanisms.

Third, the contribution of VDR polymorphisms to inter-individual variability in antidepressant response to vitamin D has been suggested by cross-sectional data and in vitro pharmacogenomic studies [da Silva Sabiao et al., 2024; Gizzi and Albi, 2024] but has not been tested in prospective, genotype-stratified interventional trials. The haplotype architecture of VDR effects — with BAt haplotypes showing associations that individual SNPs do not — further complicates study design and statistical power requirements.

Fourth, the temporal attenuation of antidepressant effects at durations exceeding 52 weeks, as identified by Ghaemi et al. [2025], is hard to square with the serotonergic hypothesis: if vitamin D's antidepressant action is mediated through sustained genomic upregulation of TPH2, one would predict maintained efficacy during continued supplementation. The loss of effect at longer durations may reflect homeostatic adaptations, receptor desensitization, or the possibility that vitamin D's antidepressant effects operate through acute neuroplastic mechanisms rather than sustained transcriptional changes.

Fifth, the interaction between vitamin D and exercise on serotonergic pathways, while biologically plausible, has been examined only in animal models and cross-sectional human studies, and requires confirmation through well-designed interventional research. No dedicated RCT has examined vitamin D supplementation for depression specifically in athlete populations — a gap given the high prevalence of vitamin D deficiency and mood disturbances in this group.

The relevance of the serotonergic hypothesis to sport and exercise science is an emerging area of inquiry. Athletes represent a population that is simultaneously at high risk for vitamin D deficiency and well-placed for serotonergic optimization, given the established role of serotonin in mood, motivation, pain perception, sleep quality, and recovery from training stress. Because exercise and vitamin D both act on serotonergic pathways, optimizing both factors together may produce larger effects than either alone.

11. Conclusions

The serotonergic hypothesis of vitamin D action offers a specific molecular account of the relationship between vitamin D status and depressive symptomatology. The hypothesis rests on the genomic demonstration that calcitriol, acting through VDR, directly upregulates transcription of TPH2 — the rate-limiting enzyme for brain serotonin synthesis — while additionally modulating the expression of SERT and MAO-A to form a complete serotonergic regulatory program. Clinical evidence from meta-analyses of randomized controlled trials supports the efficacy of vitamin D supplementation in reducing depressive symptoms, particularly in deficient populations and at adequate doses. The VITAL-DEP null finding, while important, is reconcilable with the hypothesis when baseline vitamin D status and dose adequacy are considered.

Future research should prioritize the measurement of central serotonin metabolites (CSF 5-HIAA) in human supplementation trials, the incorporation of VDR genotyping into RCT designs, and the examination of vitamin D-exercise interactions on serotonergic outcomes in athlete cohorts. Targeting supplementation to deficient individuals and stratifying by VDR

genotype may improve the usefulness of vitamin D as an adjunct for depression prevention and management, particularly in physically active populations.

Disclosure

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Receiving funding - no specific funding.

All authors have read and agreed with the published version of the manuscript.

Funding Statement

This research received no external funding.

Institutional Review Board Statement

Not applicable. This is a narrative review of published literature and did not involve human or animal subjects.

Informed Consent Statement

Not applicable.

Data Availability Statement

The authors confirm that the data supporting the findings of this study area available within the article's bibliography.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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