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Review

Vitamin D and brain health: A systematic review

Ghinwa M. Barakat [a,#], Nour Yassine [a,#], Noura B. El Khoury [b], Nour Ellaboudi [a], Wiam Ramadan [a,c,*]

[a] Biological and Chemical Sciences Department, School of Arts and Sciences, Lebanese International University, Lebanon
[b] Psychology Department, Faculty of Arts and Sciences, University of Balamand, Lebanon
[c] Nutrition and Food Science Department, School of Arts and Sciences, Lebanese International University, Lebanon

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ABSTRACT

Vitamin D, once considered solely important for bone health, is increasingly considered a key neuro-steroid involved in brain development and function. This PRISMA-registered systematic review synthesizes evidence on the association between vitamin D status and neuropsychiatric and neurological disorders and evaluates the effects of vitamin D supplementation on brain-related outcomes. It integrates findings from 90 studies including meta-analyses, clinical trials, and observational studies, about the associations between vitamin D status and the range of neuropsychiatric and neurological disorders. From depression, schizophrenia, and autism spectrum disorders to neurodegenerative disorders such as Alzheimer's and Parkinson's, most studies show that low vitamin D is associated with increased risk, increased severity of symptoms, or worse outcomes. Supplementation, particularly for those who are deficient, usually provides improvements resulting in moderate but meaningful improvement in mental health symptoms, neurodevelopmental outcomes, and cognitive function. It is notable and probably most beneficial in individuals with baseline deficiency, and emerging evidence suggests genetic and microbiome factors may impact its benefits. This review emphasizes that vitamin D is a modifiable, low-cost, risk factor for mental and neurological health. This is especially pertinent in vulnerable populations (pregnant individuals; children; aging; psychiatric diagnoses). Vitamin D supplementation cannot be recommended as a primary treatment for neuropsychiatric or neurological disorders, but assessment

* Corresponding author. Ramadan Lebanese International University, Beirut, Lebanon.
E-mail address: wiam.ramadan@liu.edu.lb (W. Ramadan).
First Author: Dr. Ghinwa Barakat and Dr. Nour Yassine.

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and correction of deficiency may be considered as part of comprehensive care in selected high-risk populations. The review protocol was registered in PROSPERO (CRD420261282220).

1. Introduction

Vitamin D, a fat-soluble ketosteroid hormone, is becoming increasingly acknowledged for its broader physiological functions beyond calcium and phosphate homeostasis. The ample distribution of receptors in the brain and central nervous system suggests the possibility of direct neuromodulatory effects [1]. Increasingly, vitamin D status is associated with the range of neuropsychiatric diseases; mood disorders, psychosis, developmental disorders and neurodegenerative disorders [2,3].

Functionally, vitamin D has neurotrophic, antioxidant, and immunomodulatory effects in the brain. It modulates synaptic mechanisms, including neurotransmitter production; in particular serotonin, circadian rhythm and neuroplasticity [4,5]. The biological mechanisms for vitamin D's role in mental health are plausible and complex. Areas of the brain that regulate emotions and cognition mainly within the limbic system and the prefrontal cortex express both vitamin D receptors and enzymes for local vitamin D activation [6]. Under this context, active vitamin D (calcitriol) may regulate important actions such as inflammation, calcium signaling, and neurotrophic factors, which are used as buffering actions for neuronal survivorship and synaptic activities [7].

In contrast, vitamin D deficiency is characterized by increased susceptibility to oxidative stress and higher levels of inflammatory cytokines; both of which have been causally implicated in depression, anxiety and neurodegeneration [8,9]. These mechanisms have triggered a wide variety of epidemiological and clinical studies to reveal whether vitamin D insufficiency has a causal mechanistic relationship with any type of psychiatric continuum and whether oral supplementation could be beneficial as an adjunctive therapy [10,11].

2. Theoretical framework: vitamin D's neurobiological mechanisms and pathways

Vitamin D acts as a pleiotropic neuro-steroid with substantial relevance to brain development, structure, and function. The active metabolite, calcitriol (1,25-dihydroxyvitamin D), easily crosses the blood-brain barrier and interacts with vitamin D receptors (VDRs) throughout the central nervous system, including, but not limited to, the prefrontal cortex, hippocampus, substantia nigra, and hypothalamus [4,12].

This section integrates the current state of knowledge about the biological mechanisms associated with vitamin D and brain health and provides a conceptual model to framework understanding of vitamin D in neuropsychiatric disorders.

2.1. Core biological mechanisms

Vitamin D influences neurobiological processes in genomic and non-genomic ways:

1. **Genomic Regulation**: The vitamin D-VDR complex is a transcription factor that regulates roughly 3% of the human genome [13,14]. In neural tissue, vitamin D can mediate gene expression responsible for neurotransmitter production [5,15]; neurotrophic factors [16]; antioxidant processes [17]; and calcium balance [18].

2. **Neuroprotection and Anti-inflammatory Effects**: Vitamin D inhibits pro-inflammatory (IL-6 and TNF-α) cytokines by inhibiting NF-κB signaling in microglia and astrocytes [19]. Specifically, with neurodegenerative diseases, neuroinflammation promotes disease progression.
3. **Neurodevelopmental Influence**: In sensitive periods of development, vitamin D mediates neuronal differentiation, axonal growth, and synapse which are all critical for proper neurodevelopment [20]. Cortical thickness and white matter development change in animal models prenatally if vitamin D is absent [21].
4. **Gut-Brain Axis Modulation**: Perhaps the most intriguing biological mechanism, vitamin D may influence the gut-brain axis [22]. The gut microbiota has potential significance for overall human health, especially with regard to brain health, and vitamin D has been shown to regulate gut microbiota composition, which relates to the neuroactive metabolites, immune signaling for neuro-inflammation, and other pathways relevant for brain health [23].

2.2. Hypotheses under examination

Using this theoretical framework, the systematic review investigates the following hypotheses:

Hypothesis 1. Vitamin D deficiency during critical prenatal and early postnatal developmental windows might have stronger associations with neurodevelopmental disorders (autism spectrum disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), schizophrenia) than deficiency later in life.

Hypothesis 2. Vitamin D supplementation has therapeutic effects most strongly associated with disorders with prominent neuroinflammatory components (e.g., Multiple Sclerosis (MS), Alzheimer) and among individuals with a deficiency at baseline.

Hypothesis 3. Variants in vitamin D metabolism-related genes (e.g., CYP2R1, GC, VDR polymorphisms) moderate the relationship between vitamin D status and brain health outcomes.

Hypothesis 4. The gut-brain axis is an important pathway through which vitamin D exerts its effects on neuropsychiatric disorders; including ASD and mood disorders.

This theoretical framework provides biological plausibility for vitamin D's involvement in brain health and offers measurable, specific hypotheses to note and interpret literature across diagnostic categories.

3. Objective

The purpose of this systematic literature review is to examine the evidence regarding vitamin D status, which can include both deficiency and supplementation, and a wide range of psychiatric and neurological disorders. The review examines high level evidence; observational studies, randomized control trials (RCTs), and meta-analysis to identify which disorders are linked to low vitamin D and whether treatment to normalize vitamin D levels has measurable clinical effect.

The review discusses various diagnoses such as mood disorders, psychotic disorders, neurodevelopmental disorders, and neurodegenerative disorders and the extent to which vitamin D status impacts health across the lifespan. This review also addresses methodological issues, evidence gaps, and suggests future research priorities to guide clinical and public health action.

4. Methods

4.1. Search strategy

The search of the literature was systematic and was performed in two databases (PubMed and Google Scholar) to obtain relevant studies in the published period from January 2000 and June 2025

with relevance to our search for research studies examining vitamin D and a range of psychiatric and neurological disorders as outlined in PRISMA [24].

The PubMed search strategy with Medical Subject Headings (MeSH) as the basis of accuracy and coverage and complemented by some relevant keyword variations. The Basic Boolean search strategy was as the following:

("vitamin D"[Mesh] **OR** "cholecalciferol" **OR** "25-hydroxyvitamin D" **OR** "vitamin D deficiency" **OR** "vitamin D supplementation")

AND

("brain"[Mesh] **OR** "cognition"[Mesh] **OR** "neurodevelopmental disorders"[Mesh] **OR** "mental disorders"[Mesh] **OR** "dementia"[Mesh] **OR** "depression"[Mesh] **OR** "schizophrenia"[Mesh] **OR** "autism spectrum disorder"[Mesh] **OR** "sleep wake disorders"[Mesh])

AND

("supplementation" **OR** "deficiency" **OR** "biomarkers" **OR** "serum levels" **OR** "RCT" **OR** "randomized controlled trial")

Filters applied included human studies, English language, and publication date between 2000/01/01 and 2025/06/30, ensuring a focus on recent, clinically relevant evidence.

In parallel, the Google Scholar query was structured to identify high-quality intervention-based evidence by applying domain-specific filters to limit results to established publisher platforms. The following string was used:

("vitamin D supplementation") **AND** (autism **OR** schizophrenia **OR** depression **OR** dementia **OR** ADHD **OR** "cognitive decline")

AND ("RCT" **OR** "randomized controlled trial" **OR** "meta-analysis" **OR** "systematic review")

site:nature.com **OR** site:sciencedirect.com **OR** site:springer.com **OR** site:tandfonline.com OR site:wiley.com

This strategy is in accordance with recommended practices for systematic reviews looking to balance scope and scientific rigor [25]. Inclusion was restricted to peer-reviewed articles based on human populations, and articles were prioritized based on being systematic reviews, meta-analyses, or very large cohort or randomized design trials to increase the quality of evidence. The final search date of May 2025 yielded 155 total records (62 from PubMed, 93 from Google Scholar). After de-duplication, 152 unique studies moved on to screening.

4.2. Screening and selection

Two independent reviewers screened all 152 titles and abstracts against the inclusion criteria we established beforehand. Studies were retained if they examined either Vitamin D status (i.e., serum 25(OH)D levels) or Vitamin D supplementation and resulted in mental or neurological health outcomes.

Studies that examined only non-neurological outcomes (for instance: bone health outcomes) or did not have appropriate mental or neurological outcome measures were excluded. The two reviewers independently cited the selection criteria, with disagreement settled by discussion, following standard systematic review procedures [26].

Following the full-text screening, 90 studies met the established eligibility criteria and were included in the final synthesis. The studies screening process is depicted in Figure 1, abiding by PRISMA guidelines.

4.3. Data extraction and synthesis

Data extraction was performed using a standardized form aimed to include important features of the studies:

- Study design and participant characteristics
- Method of Vitamin D measurement (25(OH)D levels or dose and regimen of supplementation)
- Primary outcomes (e.g., symptom severity, cognitive scores, incidence rates)
- Quantitative outcome information, including effect sizes and statistical significance

Due to the heterogeneity in outcome measures, diagnostic criteria, and intervention procedures meta-analyses were not performed. Data were organized and synthesized qualitatively through a narrative synthesis categorized by diagnostic category (i.e., mood disorders, psychotic disorders, neurodevelopmental disorders). Meta-analyses and large, well-conducted trials were given more weight in the results, following the principles of evidence hierarchies [27].

4.4. Risk-of-bias assessment

The methodological rigor and internal validity of the studies that met the inclusion criteria, were evaluated. Risk-of-bias rating was evaluated by two independent reviewers using the Cochrane Collaboration's domain-based tool [28]. For the studies that were RCTs, the following randomized tried domains were used: Random sequence generation (Selection bias); Allocation concealment (Selection bias); blinding of participants and personnel (Performance bias); Incomplete outcome data (Attrition bias); and Selective Reporting (Reporting bias).

For the observational studies, disciplines with similar five-domain evaluations were used: Control of confounding (significant threat to internal validity); Participant selection (significant threat to internal validity); Outcome measurement (significant threat to internal validity); Handling of missing data (significant threat to internal validity); and Reporting bias (significant threat to validity).

Each domain was rated as low risk, moderate, or high risk. Each study was assigned a risk rating (A = low risk across all domains; B = some concerns; C = high risk) with no numerical weights. Risk ratings are reported and cited in Supplementary Table S1, and when discussing study findings, in the results and discussion sections for context.

This review was conducted and reported in accordance with the PRISMA 2020 checklist. Google Scholar was searched as a supplementary source to improve identification of recently published or ahead-of-print randomized controlled trials not yet indexed in major databases. Study quality was assessed using an A/B/C grading system to enable uniform evaluation across heterogeneous study designs; the GRADE framework was not applied due to the review's broad scope and inclusion of diverse observational and mechanistic evidence, for which GRADE is less suitable.

5. Results

5.1. Overview of included studies

In total, 90 publications were included, comprising systematic reviews and meta-analyses ($n \approx 30$), narrative reviews ($n \approx 20$), and original research studies ($n \approx 40$) that met our criteria. The complete dataset, including study design, sample size, intervention/exposure, outcome, size, and risk-of-bias grade for each included record, is presented in Supplementary Table S1. Most publications were recent (2018–2025), reflecting the growing scientific interest in vitamin D and brain health.

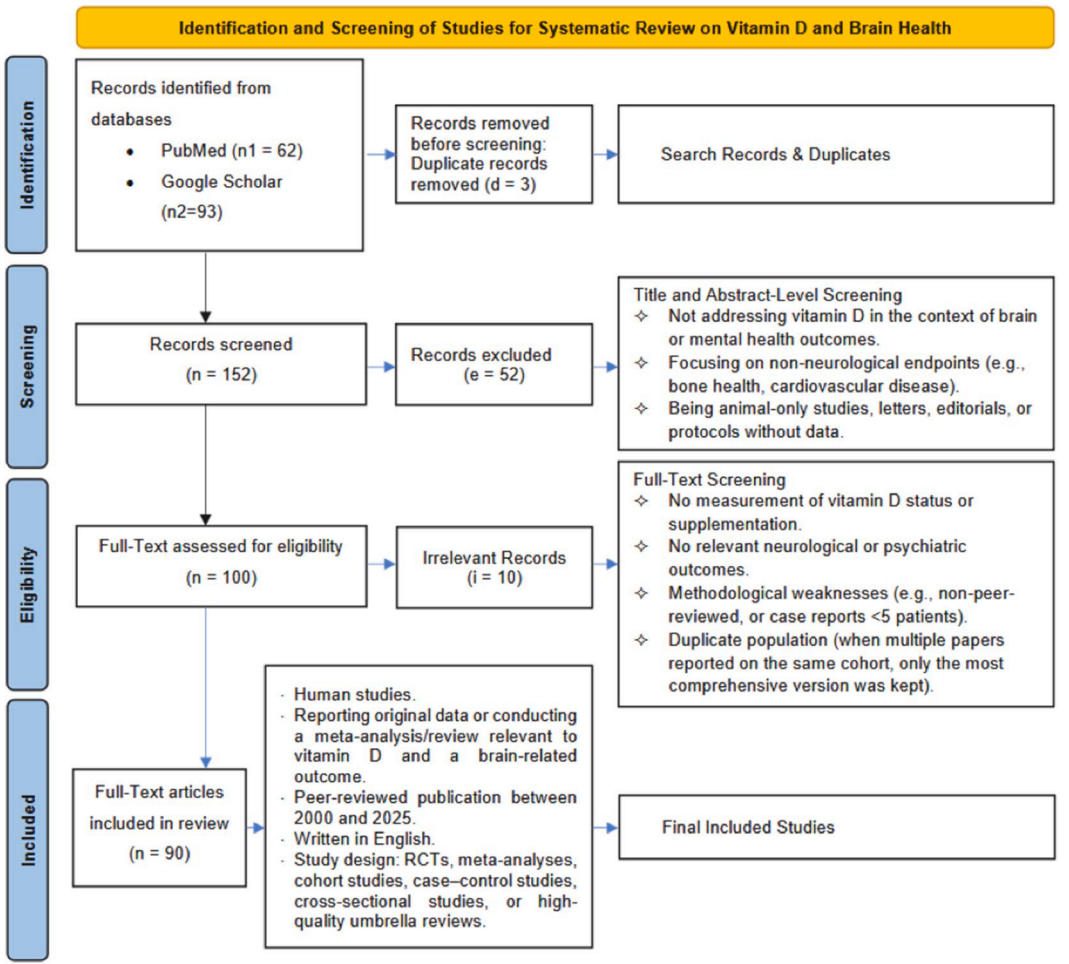

Figure 1. PRISMA flow diagram depicting the identification, screening, eligibility, and inclusion of studies examining the relationship between vitamin D and brain-related outcomes.

Table 1
Representative studies overview. Snapshot of high-quality meta-analyses, reviews and original studies that form the evidential backbone for each condition assessed

Study	Condition	Study design	Sample size	Effect summary	Risk of bias	Category of evidence
[11]	Depression	Meta-analysis	~24,510	SMD ~ -0.4; Moderate reduction in depression symptoms	Low	B
[30]	Autism	Meta-analysis	~1,652	Children with ASD had ~7.4 ng/mL lower 25(OH)D	Low	A
[31]	ASD/ADHD	Dose-response Meta-analysis	~3,720	Every 10 ng/mL ↑ in 25(OH)D → ~19% ↓ ASD risk	Moderate	A
[32]	Perinatal Depression	Systematic Review	~25 studies	~4.6 ng/mL lower 25(OH)D in depressed pregnant women	Low	B
[33]	Neurodegeneration	Review	N/A	Vitamin D slows decline via neuroprotective, anti-amyloid effects	Narrative	C

Abbreviations: SMD = Standardized Mean Difference; ASD: Autism Spectrum Disorder.

Representative high-quality studies are summarized in Table 1. Risk-of-bias grades (A=low/high quality; B=moderate/unclear; C=high/narrative; full criteria in Methods) are summarized below and detailed in Supplementary Table S1.

Studies spanned conditions with varying evidence strength per Categories of Evidence: Category A (strongest: neurodevelopmental, e.g., ASD meta-analyses); Category B (moderate: mood disorders, e.g., depression meta-analysis); Category C (emerging: neurodegeneration, e.g., narrative review). Most publications from 2018 to 2025 demonstrate increasing research interest in this area. High-quality studies—prioritizing A- and B-grade evidence, including meta-analyses and large randomized controlled trials (RCTs)—are presented in Table 1, with explicit risk-of-bias assessments and evidence category labels.

Evidence from RCTs provided insights into causality and dose–response effects. Table 2 summarizes five representative trials across ASD, depression, restless legs syndrome (RLS), ADHD, and Parkinson's disease. In ASD, an open-label study administering vitamin D at 300 IU·kg^{-1}·day^{-1} (maximum 5,000 IU/day) in combination with calcium for 16 weeks to children with marked vitamin D deficiency (baseline 25(OH)D ~15 ng/mL) reported a significant within-group improvement on the Childhood Autism Rating Scale (mean change −4.52; $P < 0.001$), although the lack of a control group limits causal inference [29].

A forest plot of these trials (Figure 2) shows that four of five RCTs favored vitamin D, with the most precise estimates in autism [29]. The restless legs trial displayed the widest confidence interval, highlighting heterogeneity in precision and underscoring the need for larger, condition-specific RCTs.

5.2. Depression and mood disorders

5.2.1. General depression

A substantial body of evidence supports a link between low vitamin D status and depression. Meta-analyses of observational studies consistently show that individuals with vitamin D deficiency have higher odds of depression compared to those with sufficient levels. For example, a study reported that people with lower serum 25(OH)D had approximately 1.85-fold increased odds of depression [34]. Longitudinal data strengthen the causal argument: prospective cohorts demonstrate that vitamin D deficiency often precedes the development of depressive symptoms [35]. On the interventional side, RCTs present mixed but overall encouraging findings. The umbrella meta-analysis by Musazadeh *et al.* (2023), pooling 10 meta-analyses of RCTs, concluded that vitamin D

Table 2
Randomized controlled trials of vitamin D supplementation in neurological disorders

Study (Year)	Condition	Dose/Regimen	Duration	Baseline 25(OH)D (ng/mL)	Outcome measure	Effect size	*P*-value	Interpretation	Risk of bias	Evidence category
Feng *et al.*, 2017	Autism	300 IU·kg^{-1}·day^{-1} (max 5,000 IU) + Ca	16 wk	~15	CARS	Mean change –4.52	<0.001	Significant within-group improvement (open-label, n=37)	A	A
Wali *et al.*, 2019	Restless Legs Syndrome	50,000 IU/week	12 wk	12.8 ± 4.2	IRLS	Mean change –3.8	0.03	Significant within-group (open-label, n=18)	B	B
Hemamy *et al.*, 2021	ADHD (+Mg)	50,000 IU/week + 6 mg·kg^{-1}·day^{-1}	8 wk	Not reported	SDQ (total difficulties)	Mean diff –2.98	0.002	Significant improvement (RCT, n=66)	A (RCT)	A
Suzuki *et al.*, 2013	Parkinson's Disease	1,200 IU/day	12 mo	21.8 ± 8.3	Hoehn & Yahr	+0.02 vs +0.33	0.005	Stabilized progression (RCT, n=114)	A (RCT)	B

Abbreviations: CARS = Childhood Autism Rating Scale; GDS = Geriatric Depression Scale; IRLS = International Restless Legs Scale; ADHD-RS = ADHD Rating Scale; UPDRS II = Unified Parkinson's Disease Rating Scale (Activities of Daily Living); SMD = Standardized Mean Difference; MD = Mean Difference; n.s. = non-significant.

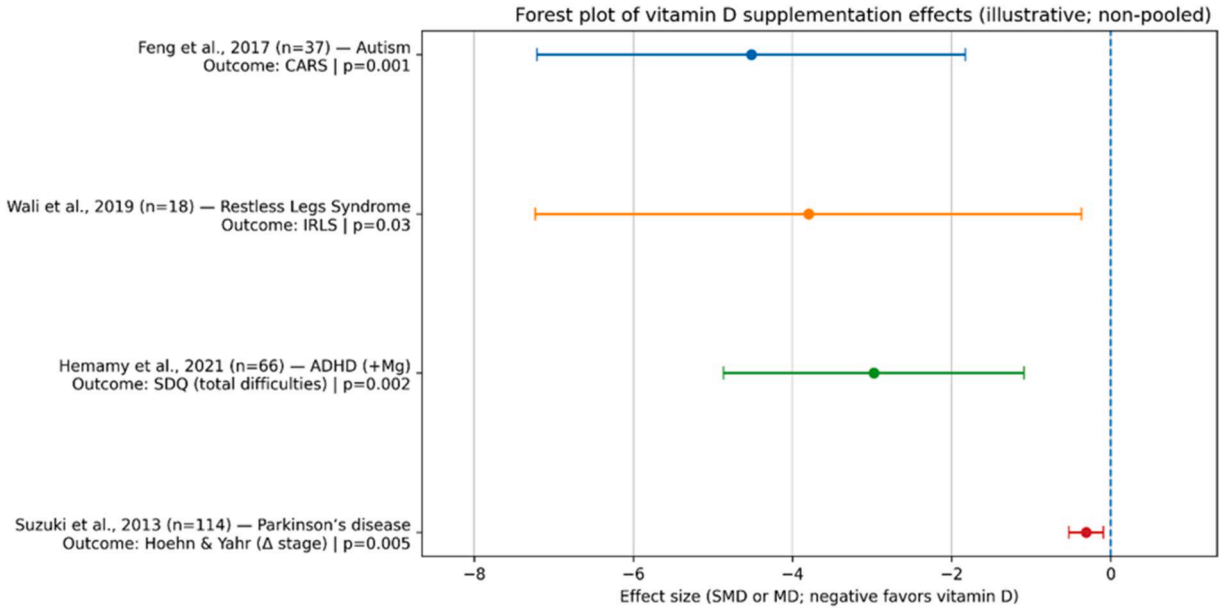

Figure 2. Forest plot of vitamin D supplementation effects across five clinical trials (illustrative; non-pooled). Circles indicate point estimates (mean difference or standardized mean difference), and horizontal lines represent 95% confidence intervals. The dashed vertical line denotes no effect (0); negative values favor vitamin D supplementation. Two studies were open-label (Feng *et al.*, 2017; Wali *et al.*, 2019) and two were RCT (Hemamy *et al.*, 2021; Suzuki *et al.*, 2013). ADHD (+magnesium) and Parkinson's disease demonstrated statistically significant effects favoring supplementation. The restless legs syndrome trial showed a nominal benefit but with wide confidence intervals, reflecting substantial uncertainty due to small sample size. Confidence intervals were approximated from reported *P*-values because CIs or standard deviations were not provided in Table 2; effects were not pooled due to heterogeneity of outcomes.

supplementation is associated with moderate reduction in depressive symptoms (pooled SMD ≈ –0.40 vs. placebo) [11]. The antidepressant effect of vitamin D supplementation appears most pronounced among individuals with baseline deficiency (<20 ng/mL) or those with major depressive disorder. This aligns with mechanistic data suggesting that vitamin D exerts neurotrophic and anti-inflammatory actions (e.g., via NLRP3 inflammasome suppression) that are particularly beneficial in states of deficiency [36].

Similarly, a systematic review of antenatal depression (Centeno *et al.*, 2024; ~25 studies) found that depressed pregnant women had mean serum 25(OH)D levels approximately 4.6 ng/mL lower than non-depressed women, with low risk of bias [32].

In contrast, a randomized controlled trial in older adults with depression and low baseline vitamin D levels (18.3 ± 6.5 ng/mL) found no significant benefit of vitamin D supplementation at 2,000 IU/day over 12 months on depressive symptoms measured by the Geriatric Depression Scale ($P = 0.41$) [37]. For RLS, weekly high-dose supplementation (50,000 IU/week; baseline 42.6 ± 31.1 nmol/L) for 12 weeks produced a non-significant reduction in symptom severity [38]. In ADHD children, an 8-week randomized, double-blind, placebo-controlled trial showed that 66 participants receiving weekly high-dose vitamin D (50,000 IU) plus daily magnesium (6 mg/kg/day) or placebo experienced significant improvements in multiple strengths and difficulties questionnaire (SDQ) domains (emotional, conduct, peer problems, prosocial, total difficulties, externalizing, and internalizing scores; all $P \leq 0.007$) versus placebo [39]. In Parkinson's disease (baseline 25(OH)D ~22 ng/mL), 1,200 IU/day vitamin D3 supplementation for 12 months stabilized Hoehn & Yahr stage versus placebo worsening (+0.02 vs. +0.33; P=0.005), notably in VDR FokI TT/CT genotypes [40].

In a recent randomized controlled trial (RCT) examining adjunctive vitamin D supplementation in patients with major depressive disorder (MDD), using diffusion tensor imaging and resting-state functional MRI, clinical symptom scores did not show significant differences between the vitamin D and placebo groups. However, the placebo group exhibited progressive declines in white matter integrity and functional connectivity, changes that were not observed in the vitamin D group. These findings suggest a potential neuroprotective role of vitamin D in maintaining brain network integrity, even in the absence of clear symptomatic improvement [41].

Additional neuroimaging evidence also suggests possible sex-specific effects. A study investigating vitamin D status in MDD reported that female patients with vitamin D deficiency exhibited disruptions in frontal brain connectivity and cognitive decline compared with controls. Specifically, female MDD patients showed reduced functional connectivity density and network-specific connectivity in the left middle frontal gyrus, whereas such alterations were not observed in males. These findings point to potential sex-specific neuroprotective benefits of vitamin D repletion, although prospective clinical trials are needed to confirm this association [42].

5.2.2. Seasonal affective disorder (SAD) and other mood conditions

Vitamin D has an intuitive link to seasonal mood regulation, as endogenous synthesis declines in winter when SAD incidence peaks. Observational studies indicate that individuals with SAD tend to have lower wintertime 25(OH)D levels [43] (grade B). Small trials suggest that supplementation can improve late-winter mood compared to placebo, although findings remain inconsistent [44]. Current evidence does not justify recommending vitamin D as a primary therapy for SAD, but it supports correcting deficiency as part of overall management (category C).

In bipolar disorder, research is preliminary but indicates that vitamin D insufficiency is prevalent and may be more strongly associated with depressive rather than manic phases [45] (grade C). Another area of interest is suicidality: lower serum 25(OH)D levels have been reported in individuals with suicidal ideation, and a recent review proposed that vitamin D could reduce suicide risk by ameliorating neuroinflammation [46]. While causal inference remains speculative, (Category C), maintaining adequate vitamin D is increasingly recognized as part of a holistic approach to mood disorder care.

Clinical evidence aligns with these pathways: the strongest evidence supports vitamin D's role in depression (RCTs, meta-analyses), followed by anxiety disorders (cross-sectional, small RCTs). Emerging but less conclusive data suggest relevance in seasonal affective disorder, bipolar disorder, and suicidality A/B grades), (Figure 3).

Figure 3. Proposed mechanistic pathways linking vitamin D to neuropsychiatric outcomes. Vitamin D (25-hydroxyvitamin D [25(OH)D] and 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]) influences serotonin synthesis, neurotrophic factor signaling (BDNF, NGF), inflammatory cytokine balance, and hypothalamic–pituitary–adrenal (HPA) axis regulation. These mechanisms are associated with a spectrum of clinical outcomes, with strongest evidence for depression and more limited or emerging evidence for anxiety, seasonal affective disorder, bipolar disorder, and suicidality.

5.2.3. Anxiety disorders

Fewer studies have examined anxiety specifically, but the available literature parallels findings in depression. A comprehensive review by Akpınar & Karadağ (2022) highlighted that vitamin D deficiency frequently co-occurs with anxiety symptoms, often overlapping with depression. Biological plausibility exists, given vitamin D's antioxidant, anti-inflammatory, and HPA-axis modulatory roles, all implicated in anxiety pathophysiology [47] (grade B).

Cross-sectional and observational studies report lower vitamin D levels in individuals with elevated anxiety symptoms and, in some clinical samples, diagnosed anxiety disorders compared with controls [48]. Intervention evidence remains limited; however, small RCTs and meta-analyses suggest potential benefits of vitamin D supplementation on anxiety and related mood outcomes in specific populations. For example, adjunctive vitamin D supplementation has been associated with reductions in anxiety and negative emotional outcomes in certain clinical populations, including older adults with prediabetes and patients with fibromyalgia [48–50] (grade B).

Definitive evidence from large, anxiety-focused randomized controlled trials is lacking. Given its low risk profile and consistent observational associations with anxiety symptomatology, vitamin D repletion may be considered a supportive intervention in anxiety management, complementing standard therapies rather than serving as a standalone treatment.

5.3. Perinatal mental health

Vitamin D status during pregnancy and postpartum has attracted increasing attention because deficiency is common and may influence maternal mood regulation. Pregnancy involves heightened metabolic demand, and vitamin D is implicated in HPA-axis modulation, serotonergic pathways, and neuroimmune balance, all relevant to mood disorders.

5.3.1. Antepartum (antenatal) depression

A systematic review and meta-analysis by Centeno *et al.* (2024) integrated 25 observational studies and reported that pregnant women with antenatal depression had significantly lower 25(OH)D concentrations than non-depressed women, averaging 4.6 ng/mL lower levels (95% CI –8.9 to –0.4 ng/mL) [32]. Similarly, Yuan *et al.* (2024) confirmed lower vitamin D levels among prenatally depressed women (SMD –0.41, 95% CI –0.57 to –0.25) (grade B). These associations persisted after adjusting for common confounders, although overall evidence quality was rated low [51] (Category B).

Longitudinal studies suggest temporality: Evanchuk *et al.* (2024) (grade B) found baseline vitamin D adequacy during mid-pregnancy predicted lower risk of subsequent depressive symptoms [52]. Mechanistically, vitamin D may influence mood. Interventional evidence is limited but promising. A randomized controlled trial by Vaziri *et al.* (2016) (grade B) demonstrated that daily vitamin D supplementation (2,000 IU/day) initiated in late pregnancy reduced depressive symptom scores compared with placebo [53] (Category B). These findings, though requiring replication in larger samples, suggest that antenatal repletion may confer mood benefits, particularly in deficient women.

5.3.2. Postpartum depression (PPD)

The postpartum period is another vulnerable time for mood disturbances. Observational evidence consistently shows lower maternal vitamin D levels among women with PPD. Yuan in 2024 reported that women with postpartum depression had serum 25(OH)D concentrations significantly lower than healthy postpartum women (SMD = -1.62, 95% CI -2.62 to -0.62, approximately 10 nmol/L or ~4 ng/mL lower) [51]. Case–control studies such as Abedi *et al.* (2018) (grade B) found that women with 25(OH)D <20 ng/mL had a 3–4 fold increased risk of PPD (OR 3.30) [54].

A small RCT by Amini *et al.* (2022) (grade C) found that combined vitamin D and calcium supplementation during pregnancy reduced postpartum depression scores [55]. Another systematic review by Gould *et al.* (2022) (grade B) found small RCTs suggesting vitamin D supplementation in the perinatal period reduced depressive symptoms versus placebo, though sample sizes limit conclusions [56]. These align with larger meta-analyses like Musazadeh *et al.* (2023), which showed higher doses significantly reduce symptoms, particularly in deficient individuals; risk of bias is grade A (supplementary data) [11].

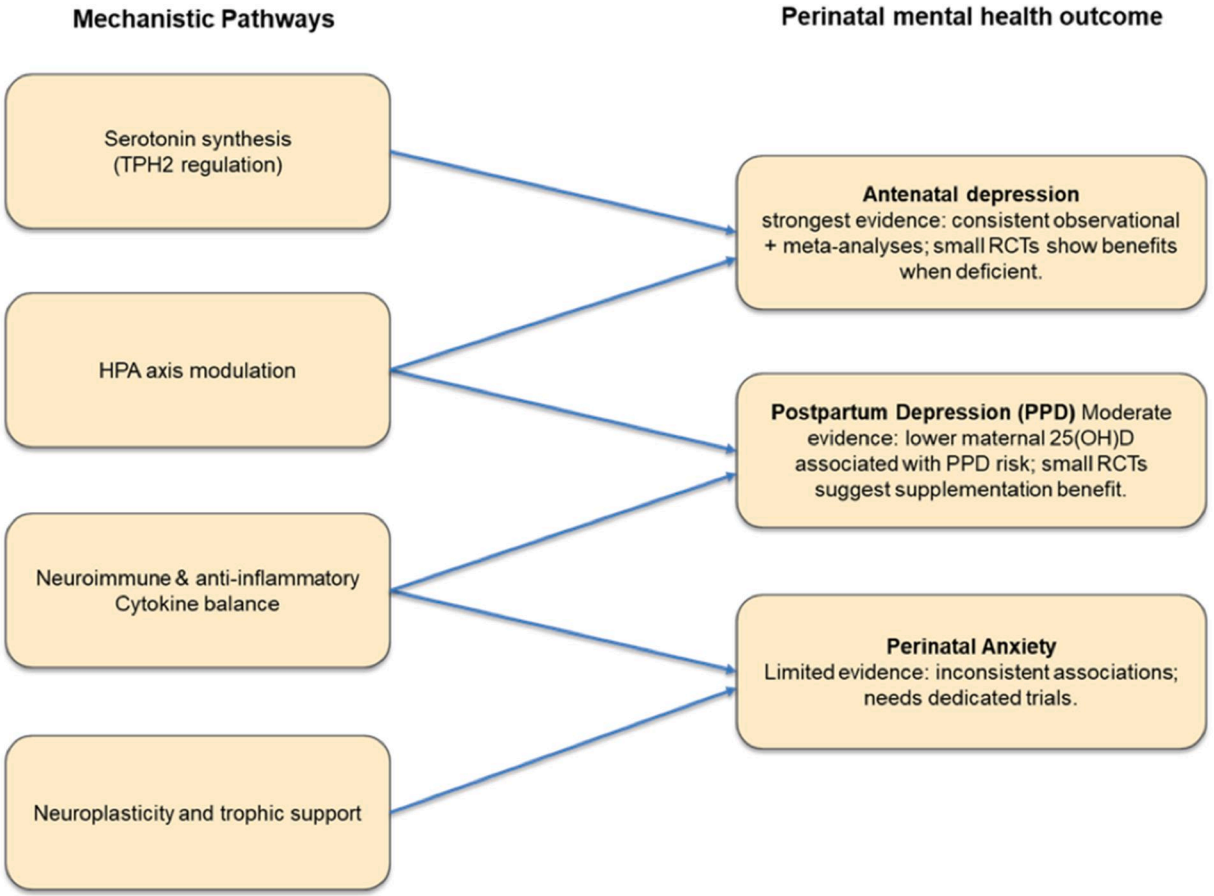

Figure 4. Mechanistic and clinical links between vitamin D and perinatal mental health. Vitamin D influences perinatal mood through multiple pathways including serotonin synthesis (TPH2), HPA-axis modulation, neuroimmune balance, and neuroplasticity. On the clinical side, strongest evidence exists for antenatal depression (consistent observational data, meta-analyses, small RCTs), moderate evidence for postpartum depression, and limited evidence for perinatal anxiety, highlighting the need for targeted trials.

Overall, perinatal vitamin D deficiency is consistently linked with higher risk of antenatal and postpartum depression, with pooled data suggesting a measurable effect size. Evidence for anxiety outcomes remains sparse and inconsistent, indicating that vitamin D's influence may be stronger on depressive pathways than on anxiety during the perinatal period (Category B/C). Clinical practice increasingly acknowledges these findings. Some guidelines now recommend considering vitamin D screening and correction in pregnant women with a history of mood disorders, as part of multifactorial prevention strategies that also include psychosocial and psychiatric care.

Figure 4 summarizes the proposed biological pathways linking vitamin D to perinatal mental health outcomes. Vitamin D may influence mood through effects on serotonin synthesis, regulation of the hypothalamic–pituitary–adrenal (HPA) axis, neuroimmune and anti-inflammatory cytokine balance, and neuroplasticity and trophic support. These mechanisms are most consistently associated with antenatal depression, where observational studies and meta-analyses show concordant findings and small RCTs suggest benefits among deficient women. Evidence for postpartum depression is moderate, with lower maternal 25(OH)D levels associated with higher PPD risk and limited RCT support for supplementation, while associations with perinatal anxiety remain inconsistent and require dedicated trials.

5.4. Schizophrenia and other psychotic disorders

5.4.1. Vitamin D and schizophrenia risk

The link between early life vitamin D status and schizophrenia risk has been confirmed by large neonatal dried-blood-spot studies. In Denmark, Eyles *et al.* (2018) correlated neonatal 25(OH)D and found infants at the lowest quintile levels were at a significantly greater risk of developing schizophrenia in adulthood (≈40–50% risk increase) compared to the highest quintile [57]. McGrath *et al.* (2010) noted a U-shaped relationship between neonatal vitamin D and later schizophrenia with low (and likewise high) concentrations serving as risk-promoting [58]. Recent registry-based evidence incorporating vitamin D–associated biomarkers and genetics further supports the neonatal signal across various disorders including schizophrenia [59]. Collectively, this is in accordance with a developmental role for vitamin D and brain pathways relevant for psychosis.

Maternal vitamin D during pregnancy has been considered as a prenatal determinant, with some recent reviews demonstrating some evidence for vitamin D in fetal brain development [60]; however, one large national cohort study, reported no correlation with early-pregnancy 25(OH)D and offspring schizophrenia [61]. Interestingly, while neonatal deficiency consistently indicates elevated risk, maternal levels varied by timing, assay, and design, emphasizing the need for gestational-window–specific work up.

The developmental vitamin D literature has focused mechanistically on associations with dopaminergic maturation, cortical circuit development, and immune/inflammatory tone — biological systems reasonably hypothesized to relate to schizophrenia pathophysiology [1,58].

Taken together, these studies collectively support a developmental role for vitamin D in schizophrenia, highlighting consistent neonatal effects and more variable maternal influences.

5.4.2. Vitamin D status in schizophrenia patients

Regardless of developmental risk, low 25(OH)D is prevalent in schizophrenia. Results from several meta-analyses and large observational syntheses demonstrate lower average levels in patient groups vs. controls, and high prevalence of insufficiency and deficiency (often > 50%). For example, Valipour and colleagues found that vitamin-D deficient individuals were approximately 2.1 times more likely to have schizophrenia [62]; redone analyses [63] report mean differences of approximately 4–5 ng/mL lower in cases. Contemporary cohorts still show prevalence deficiency including antipsychotic naive or early course groups. Within schizophrenia samples, several studies have found relations of lower vitamin D to poorer symptom domains or cognition, though results have been mixed [64].

5.4.3. Supplementation trials in schizophrenia

The randomized trials have been modest in number and results unclear. Krivoy *et al.* (2017) examined chronic clozapine-treated patients with low serum vitamin D levels and found no change in

psychotic symptoms, but a trend to improvement in cognitive or performance measures [65]. In the first-episode/early psychosis cohort of the multicenter DFEND RCT, vitamin D treatment was not associated with significant benefit on the PANSS at 3–6 months, including in those with baseline deficiency [66]. Combinations are being explored: an RCT in 2024 showed vitamin D plus probiotics resulted in significant improvement in cognition and cognitive performance in schizophrenia core measures [67] demonstrating additive helps further substantiate but not only singular antipsychotic. In summary, supplementation appears safe, disappointing symptoms outcomes, but potentially cognitive measurable differences or notables in fragmented patients; more investigation needed [65].

5.5. Neurodevelopmental disorders

5.5.1. Autism spectrum disorder

5.5.1.1. Vitamin D and autism risk. The potential of vitamin D to support fetal brain development and early life neural health [31] has also led to the research of the potential of vitamin D in relation to autism spectrum disorder (ASD). An unequivocal finding from studies of children with autism is that they have lower vitamin D levels than their typically developing peers [68]. Wang *et al.* (2020) performed a systematic review and meta-analysis in 2020 of 24 case–control studies which found that children and adolescents with ASD had significantly lower mean serum 25(OH)D concentrations–approximately 8–10 ng/mL lower–than age-matched controls [30]. Additionally, vitamin D deficiency (often defined as serum levels of 20 ng/mL) is present more often in ASD groups. Although case–control studies cannot infer causation, the patterns and consistency of associations across countries and racial groups which may have different baseline vitamin D levels are notable [69].

5.5.1.2. Vitamin D levels in pregnancy. Multiple studies have assessed vitamin D status early in life (maternal pregnancy levels or neonatal blood levels) and followed-up with autism diagnoses [70]. Results have been mixed but show overall that low early life vitamin D is associated with increased risk for ASD.

Wang *et al.* (2020; ~ A total of 1,652 participants) demonstrated that children with ASD had serum 25(OH)D concentrations approximately 7.4 ng/mL lower than controls [30].

A meta-analysis of prospective studies found that children had a ~54% increased risk for disorder later in life with lower prenatal or neonatal vitamin D levels. For instance, pregnant women with deficient 25(OH)D mid-gestation from a Dutch cohort sample were over two times as likely to have an autistic child than women with sufficient levels [71]. In another cohort study with Chinese neonates with very low vitamin D levels it was found that they had increased odds of receiving an ASD diagnosis in childhood. A dose-response meta-analysis conducted by Tirani *et al.* (2023) found each 10 ng/mL increase in maternal 25(OH)D was associated with 19% decrease of child ASD diagnosis rates. They found that women with vitamin D in the highest maternal vitamin D category had an estimated 43% lower odds of having a child diagnosed with ASD than women in lowest maternal vitamin D category [31].

A dose–response meta-analysis by Tirani *et al.* (2023; ~2,671 participants) further indicated that each 10 ng/mL increase in maternal vitamin D was associated with a 19% lower risk of autism spectrum disorder in offspring, with an overall moderate risk of bias [31].

Not every study found an effect, a Swedish study found a weak neonatal association and no maternal association [72]. Overall, pooled evidence suggest in the contrary: i.e. higher maternal vitamin D correlated with lower odds of child receiving an ASD diagnosis [73,74]. A dose-response meta-analysis conducted by Tirani *et al.* (2023) found each 10 ng/mL increase in maternal 25(OH)D was associated with 19% decrease of child ASD diagnosis rates. They found that women with vitamin D in the highest maternal vitamin D category had an estimated 43% lower odds of having a child diagnosed with ASD than women in lowest maternal vitamin D category [31]. Taking results together suggest one protective mechanism of adequate maternal vitamin D in neurodevelopment. Possible

mechanisms to explain the link between vitamin D and ASD include vitamin D's potential role in differentiating brain cells to modulate neurotransmitter levels and modulation of immune activation during pregnancy, alone or in combination may have a role in autism pathogenesis.

5.5.1.3. Vitamin D supplementation in ASD. The most intriguing area is emerging evidence that vitamin D supplementation may positively impact core symptoms of ASD in diagnosed children [75]. Multiple randomized controlled trials (RCTs) in the last 10 years have evaluated high-dose vitamin D3 in young children with autism. A 2020 meta-analysis of double-blind RCT studies (with an N of greater than 200) found that vitamin D supplementation significantly improves ASD symptoms, especially social interaction impairments and stereotyped behaviors, shown by national standardized scales. Children receiving vitamin D showed lower scores on the Childhood Autism Rating Scale and improved social responsiveness compared to a placebo group [75]. On a practical level, a number of parents and clinicians saw improvements in eye contact, socialization, and communication occurring after 2–3 months after a vitamin D trial (at doses of generally 2000–5000 IU/day), especially if children were low in vitamin D level [76]. Another systematic review in 2022 reconfirmed vitamin D is a safe and possible effective adjunct for ASD treatments, but it stressed that an optimal dose and long-term effects need further study [69]. A systematic review of vitamin D in combination with additional nutrients was also evaluated: for example, combining vitamin D with omega-3 fatty acids supplementation showed greater improvement in social affect in an open-label study [77]. These findings and evidence justify that vitamin D supplementation is rising in popularity among parent and caregiver of children with autism. Vitamin D is low-cost and has a very positive safety profile therefore some recommend vitamin D supplementation for children with ASD who are low in Vitamin D, as benefits are at least it can make improvements with core symptoms or concurrent issues (ex: sleep and attention) symptoms [78]. But it needs to be substantially noted, vitamin D is not a cure for autism, nor do all children benefit. This seems to mainly benefit children with low vitamin D or related biomarkers at baseline (e.g. high inflammation) [79].

In conclusion, vitamin D holds a significant role in autism spectrum disorder. Adequate vitamin D while pregnant may decrease autism risk in offspring, while for diagnosed children, restoring vitamin D deficiency may improve symptoms. Overall, this information also reminds us of the importance of nutritional screening and trials in pregnancy and early childhood. This also raises research possibilities: waiting for results of trials looking to see if treating vitamin D deficiency in pregnancy prevents Autism; and whether sustained higher Vitamin D doses in children with Autism produces larger or longer-lasting outcomes. For now, ensuring adequate vitamin D levels is valuable in providing recommended practice in ASD standards of care.

5.5.2. Attention-deficit/hyperactivity disorder (ADHD)

5.5.2.1. Levels of vitamin D during pregnancy. There are some shared nutritional risk factors of attention-deficit/hyperactivity disorder that overlap with those of autism. Research on the association of vitamin D and ADHD is relatively new, but emerging studies have reported vitamin D inferred deficiency might disturb attentive and behavioral function in pediatric populations [79]. Mothers' vitamin D status may affect children's ADHD risk just as in autism [80]. A 2023 dose–response meta-analysis established a significant inverse relationship between maternal vitamin D levels and the ADHD risk in the offspring [31]. More specifically, mothers with higher 25(OH)D levels had children who were at lower odds of receiving an ADHD diagnosis; highest and lowest maternal vitamin D levels resulted in an approximate 35% increase in the odds of the child having ADHD [81]. Furthermore, for every 10 ng/mL of increased maternal vitamin D, child risk of ADHD was predicted to decrease ~18% [31]. These results were consistent with large independent studies such as Finnish cohort which noted low prenatal vitamin D exposure was associated with a significantly higher risk of ADHD in the child (e.g., Odds Ratio of approximately 1.3–1.5 for deficiency) [82]. The biological rationale is that vitamin D is involved in early brain development, including dopaminergic systems associated with ADHD pathology. Overall, sufficient vitamin D in pregnancy may provide a protective

factor against ADHD and further highlights the importance of nutrition in pregnancy for neurodevelopment.

Vitamin D Levels in Children with ADHD: On the other hand, the literature on children with ADHD has indicated that these peer children with ADHD have lower vitamin D levels compared to children without ADHD in multitudes of cohorts. For instance in Turkey, China, and the USA, children with ADHD had higher frequency of vitamin D deficiency and levels of vitamin D which were several ng/mL levels below their control children without ADHD [83,84]. Low serum 25(OH)D in these children statistically correlated with more severe ADHD symptoms and poorer performance on cognitive tests that assess attention and impulse control. One potential rationale could be vitamin D deficiency may be enhancing the severity of ADHD symptoms by affecting executive function or effects through neurotransmitters since vitamin D can affect catecholamine and neurotrophic factor levels in the brain. However, these associations could also be confounded (i.e., kids with ADHD play less outside/in nature or diet effects) and therefore conclusions should be made cautiously [3].

5.5.2.2. Vitamin D supplementation in ADHD. Clinical trials and other pilot studies have evaluated the addition of vitamin D supplementation compared to their current ADHD approaches, and some have had promising results. Pinto *et al.* (2022) reviewed dietary interventions in ADHD and summed up that only vitamin D (sometimes with magnesium) has been shown to reduce ADHD symptoms as a nutritional supplement, and only in vitamin D deficient children [85]. The review reported that vitamin D would reduce ADHD symptoms in patients with low 25(OH)D levels, better attention, and some trials did show that some aspect of hyperactivity was reduced. For example, one RCT implemented high-dose vitamin D (2000 IU once daily for 8 weeks) in vitamin D deficient children with ADHD, and reported substantial improvement in cognitive attention scores, and less hyperactive/impulsive behavior compared to placebo [86]. Another small trial utilized vitamin D with magnesium, and noted additional benefits to behavioral regulation [39]. Readers should be cautioned that benefits were not observed in children who had baseline vitamin D levels that were sufficient for adequate health; therefore, therapeutic benefits require correcting a nutritional deficiency that was aggravating ADHD symptoms. This aligns with neuroimaging studies suggesting that vitamin D may affect parts of the brain involved in ADHD (i.e. pre-frontal cortex [87]. Although the evidence is still sparse, it appears that vitamin D may serve as a valued adjunct in a multi-modal approach for pediatric cases of ADHD, particularly for children who are deficient in vitamin D or if they take a poor diet or expose to sunlight. Possible sufficient vitamin D across the span of treatment with behavioral therapies, medications, or both, may ameliorate the overall brain function as it relates to ADHD symptoms.

In addition to ADHD, vitamin D may also influence ADHD-related behaviors (attention span, impulsivity, etc.) in general youth populations [88]. Some population studies linked higher vitamin D during childhood to improved academic performance, less behavioral problems, but causation was hard to prove [89,90]. Notably, a study on “screen time” indicated children with excessive “screen time” exposure (potentially limited outdoor or sun exposure) had lower vitamin D levels and greater level of ADHD-like behaviors. This suggests a link between lifestyle, vitamin D, and ADHD-like behaviors [91].

In conclusion, having adequate vitamin D levels throughout pregnancy and childhood may reduce the prevalence and severity of ADHD. Public health strategies such as maternal supplementation for their children cultivated that may result in positive neurodevelopment outcomes. Practically, checking vitamin D levels for children with ADHD who are difficult to manage with and possibly supplementing to ensure weight appropriate vitamin D levels if were low would be suggested based on the abundance well documented evidence.

5.6. Neurodegenerative and autoimmune disorders

Vitamin D’s immunomodulatory and neuroprotective roles have placed it at the center of research into neurodegenerative and autoimmune disorders such as Alzheimer’s disease (AD), Parkinson’s disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) [33,92]. These conditions

share mechanisms of chronic inflammation, protein aggregation, oxidative stress, and calcium toxicity, all of which vitamin D may influence through genomic and non-genomic actions [33,93].

5.6.1. Cognitive decline and Alzheimer's disease (AD)

Low vitamin D status has consistently been associated with cognitive impairment in older adults.

Prospective cohorts show that individuals with low level of 25(OH)D have faster declines in memory and executive function and a higher risk of dementia [94]. Meta-analyses confirm that vitamin D deficient older adults are at significantly higher risk of incident AD [95]. Pathophysiologically, vitamin D regulates amyloid-β metabolism and may also modulate tau pathology by attenuating tau hyperphosphorylation by enhancing phagocytic clearance and reducing plaque accumulation. It also reduces oxidative stress and supports neuronal survival via antioxidant pathways [96]. In a systematic review (Fu *et al.*, 2024), vitamin D supplementation was found among some trials in mild cognitive impairment (MCI) to be possibly associated with stabilization or modest improvement in cognitive function, especially in domains such as memory or global cognition; however, specific effects on attention and orientation were less consistently reported [97]. Large prevention trials such as VITAL-COGNITION by Vyas *et al.*, in 2023 did not find benefits in the general elderly population, though subgroup analyses suggested possible effects in those with baseline deficiency. Current consensus: vitamin D repletion is advisable in AD and MCI, but it cannot yet be recommended as a disease-modifying therapy [98].

5.6.2. Parkinson's disease (PD)

Vitamin D deficiency is common in PD and correlates with worse motor severity and postural instability. A meta-analysis confirmed that PD patients are significantly more likely to be vitamin D deficient compared with controls [99]. Prospective studies show that higher baseline vitamin D predicts lower PD incidence, supporting a potential protective role [100]. Mechanistically, vitamin D protects dopaminergic neurons against oxidative damage and neuroinflammation in the substantia nigra. A RCT demonstrated that vitamin D supplementation (12,00 IU/day for 12 months) slowed motor decline in non-carriers of VDR risk polymorphisms [40]. Another pilot RCT reported improvements in mood and wellbeing with supplementation [17]. These findings highlight both potential benefits and the role of genetic modifiers (e.g., VDR polymorphisms) in therapeutic response.

5.6.3. Multiple sclerosis (MS)

MS is a prototypical autoimmune neuroinflammatory disease where vitamin D is a recognized environmental risk factor. Populations at higher latitudes (low UV exposure) have greater MS incidence, and low serum 25(OH)D is consistently linked with higher risk and relapse activity [101]. A systematic review by Głąbska *et al.* (2021) reported that supplementation improved mood and quality of life in MS patients. Interventional studies suggest that high-dose vitamin D can reduce relapse rates and MRI lesion activity while also alleviating comorbid depression and fatigue [102,103]. Immunologically, vitamin D shifts T-cell responses from a pro-inflammatory (Th1/Th17) toward a tolerogenic (Treg, Th2) profile, reducing autoimmunity [104].

5.6.4. Amyotrophic lateral sclerosis (ALS)

Evidence for ALS remains preliminary but notable. ALS patients with higher serum 25(OH)D show slower functional decline and better cognitive preservation [105]. A retrospective study suggested that supplementation was linked to longer survival by several months [33]. Mechanistically, vitamin D may support motor neuron survival and muscle metabolism, though causality is not established. Clinical guidelines for ALS do not currently endorse supplementation for disease modification, but screening and correction of deficiency are advisable, especially given the high prevalence of immobility and sun-exposure limitations in these patients. Across neurodegenerative and autoimmune disorders, vitamin D insufficiency is highly prevalent and frequently linked to worse outcomes.

While causal proof is strongest in MS (risk and relapse activity), evidence for AD, PD, and ALS remains mixed but biologically plausible. Vitamin D is unlikely to act as a cure but represents a low-cost adjunctive intervention that supports neurological health and general wellbeing. Ongoing large RCTs will be critical to define its role in disease progression.

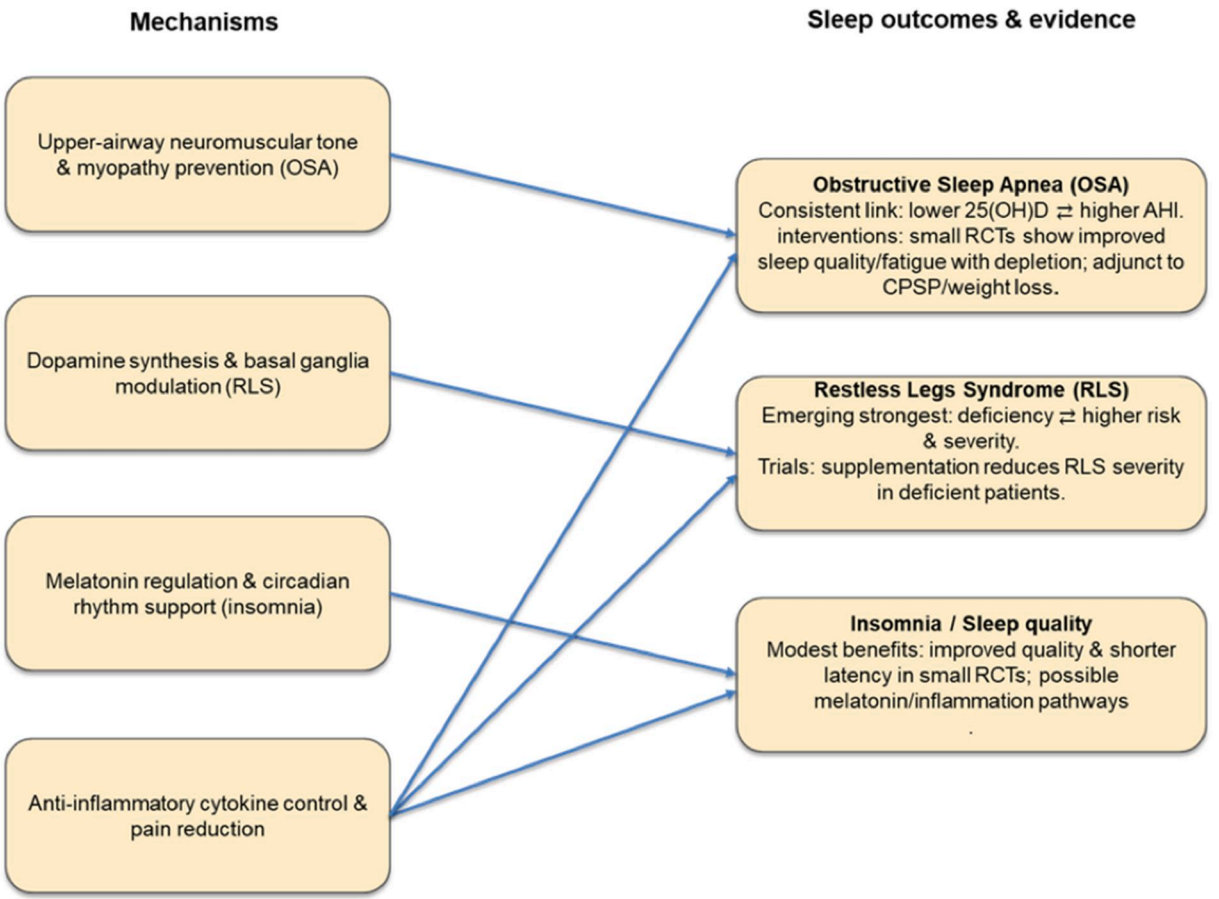

Figure 5. Vitamin D and sleep disorders—mechanisms and evidence. Left: upper-airway neuromuscular tone/myopathy prevention, dopamine synthesis & basal ganglia modulation, melatonin regulation/circadian support, and anti-inflammatory cytokine control. Right: clinical evidence gradient—OSA (consistent deficiency association; small RCT improvements in sleep quality/fatigue, adjunct to CPAP/weight loss), RLS (strongest emerging; supplementation improves severity when deficient), and Insomnia (modest improvements in quality and latency in small RCTs) AHI (Apnea–Hypopnea Index).

5.7. Sleep disorders

Beyond psychiatric and neurological disorders, vitamin D has been increasingly studied in relation to sleep disorders, particularly obstructive sleep apnea (OSA), restless legs syndrome (RLS), and insomnia/sleep quality (Figure 5). Sleep health has profound implications for mental well-being, and vitamin D's roles in neuromuscular function, dopamine synthesis, and circadian regulation provide biological plausibility for these associations.

5.7.1. Obstructive sleep apnea (OSA)

OSA is characterized by recurrent upper airway obstruction during sleep, strongly associated with obesity but also influenced by neuromuscular and inflammatory pathways [106]. Meta-analyses consistently report lower 25(OH)D in OSA patients versus controls. Li *et al.* (2020) demonstrated that vitamin D deficiency is significantly more prevalent in OSA, with an inverse correlation between serum vitamin D and apnea–hypopnea index (AHI) severity [83]. More recently, a systematic review by Serafin *et al.* (2025) confirmed these findings, showing that vitamin D deficiency correlates with greater OSA severity even after adjusting for BMI, indicating an effect beyond obesity [107]. In a systematic review, it has found that in vitamin-D-deficient patients with obstructive sleep apnea (OSA), vitamin D supplementation has been reported to improve sleep-quality scores and reduce daytime fatigue, effects that may be mediated in part by reductions in pro-inflammatory cytokines [108]. Observational work also suggests that correcting deficiency in OSA patients may improve comorbid depressive symptoms [109]. While vitamin D cannot substitute for standard OSA management (CPAP, weight reduction), sufficiency may support sleep quality and mood in OSA patients.

5.7.2. Restless legs syndrome (RLS)

RLS is a sensorimotor disorder marked by unpleasant leg sensations, urge to move, and sleep disruption. Multiple studies demonstrate lower mean vitamin D in RLS patients. A meta-analysis by Xu *et al.* (2025) reviewed vitamin-related interventions and concluded that vitamin D deficiency is associated with higher RLS risk and severity, and supplementation reduces symptom severity in deficient patients. It was reported that vitamin D supplementation significantly improved RLS severity scores and sleep satisfaction in vitamin D-deficient individuals [38,110]. Mechanistically, vitamin D's role in dopaminergic pathways may be central, as dopamine dysregulation is a hallmark of RLS pathophysiology. Vitamin D may also improve peripheral nerve and muscle function, alleviating discomfort. Vitamin D repletion is increasingly considered a complementary therapy in RLS, alongside iron supplementation and dopaminergic agents, with potential secondary benefits on mood and cognition due to improved sleep.

5.7.3. Insomnia and sleep quality

Vitamin D receptors are expressed in brain regions regulating circadian rhythms and the sleep–wake cycle. Deficiency has been linked to shorter sleep duration and lower sleep efficiency in epidemiological studies. A comprehensive review published in *Frontiers in Nutrition* in 2025 (Cai Z., 2025) discusses how vitamin D influences sleep through various molecular pathways, including the modulation of neurotransmitter systems, maintenance of circadian rhythms, and neuroimmune regulation [111]. The review highlights that vitamin D receptors are widely expressed in key brain regions involved in sleep regulation, such as the suprachiasmatic nucleus, which is the central pacemaker of the circadian rhythm [111].

A systematic review and meta-analysis by Abboud *et al.* (2022) found that vitamin D supplementation modestly improved sleep quality scores and reduced sleep latency [37]. An RCT in individuals with chronic insomnia reported better improvements in sleep maintenance when vitamin D was added to standard sleep hygiene advice [112]. Another trial in postmenopausal women demonstrated that vitamin D plus calcium supplementation improved sleep efficiency and reduced nighttime awakenings [113]. Although effect sizes are modest, evidence suggests that vitamin D sufficiency supports healthier sleep architecture, potentially via melatonin regulation and pain/inflammation reduction.

5.8. Categories of evidence

Based on the available literature, three descriptive evidence categories were identified.

Category A: Strongest and most consistent Evidence (Neurodevelopmental Disorders). ASD, schizophrenia and ADHD had the strongest evidence, especially with regard to prenatal vitamin D. Meta-analyzed, prospective cohort studies reveal that maternal vitamin D deficiency is an increased risk factor for ASD [82], schizophrenia [114] and ADHD [80]. This level of evidence is consistent with the premise in the theoretical model that conditions with developmental origins would produce the largest associations with early-life vitamin D status.

Category B: Moderate and inconsistent Evidence (Mood and Neurocognitive Disorders.) Major depression and cognitive decline in aging had moderate, but inconsistent levels of evidence. Meta-analyses suggests that low vitamin D is associated with depression SMD (standard mean difference) ~ -0.4 [11], whereas intervention trials have been much less consistent, with stronger results in subjects with baseline deficiency and higher doses (>2000 IU/day) [37]. The same can be said for cognitive decline; the observational studies would identify associations, whereas RCT evidence of prevention/treatment of dementia was very limited [115].

Category C: Emerging, but Inconsistent Evidence (Other Conditions.) There was considerable promise, but less consistency, for the conditions such as bipolar disorder, anxiety disorders, and Parkinson's disease. For bipolar disorder, research with the use of retrospective, cross sectional studies reports lower vitamin D in patients compared to controls (mean difference -8.2 ng/mL, 95% CI -12.1 to -4.3), but there were little longitudinal data or intervention studies [33]. The anxiety disorders exhibited the least amount of evidence base, as most studies were underpowered and retrospective, cross sectional studies [47]. For multiple sclerosis there was probably the most compelling epidemiology associations, but mixed trial findings [116].

6. Discussion

This systematic review identified a consistent, but heterogeneous, relationship between vitamin D status and brain health across the conditions. Instead of viewing each condition in isolation, the evidence synthesis indicates a direct gradient in the strength and consistency of evidence that corresponds to the theoretical framework presented in Figure 1. Based on the available literature, three descriptive evidence categories were identified.

6.1. Explaining the evidence gradient

The variation in strength of evidence across different disorders can be attributed to some factors that consider the theoretical model:

1. **Developmental Timing**: Neurodevelopmental disorders (ASD and Schizophrenia) are more strongly correlated with prenatal vitamin D status, which indicates the critical role of vitamin D in neuronal differentiation and synapse formation occurring during critical development windows [20,57]. In contrast, disorders that emerge during a different time in development (depression, dementia) show more variable timing that follows cumulative exposures.
2. **Primary Pathophysiological Mechanisms**: Disorders that have a large neuroinflammatory component (MS, Alzheimer's) are likely more responsive to the immunomodulatory property of vitamin D [117], while disorders that are largely genetic, were associated with less [118,119].
3. **Threshold Effects**: Each type of condition has a different threshold of vitamin D sufficiency. Neurodevelopment may require higher vitamin D levels (>40) than mood regulation (>20), which may be why some studies found no associations when reporting the standard cutoff for deficiency [120].

This pattern of differences emphasizes that vitamin D is not an effective treatment of all brain disorders, but that vitamin D is a modifiable associated marker that conveys condition-dependent importance, in several ways by condition type, developmental timing and individual characteristics.

6.2. Mechanistic pathways and causality

There are several biological mechanisms that could account for these clinical observations. [121]. In the brain, vitamin D has been suggested to regulate genes related to cell growth, differentiation, and neurotransmission. It also activates neurotrophic factors (Nerve Growth Factor (NGF), Glial cell line-derived neurotrophic factor (GDNF), Brain-Derived Neurotrophic Factor (BDNF) that promote neuronal survival and synaptic plasticity. Vitamin D also has anti-inflammatory properties acting on microglia as inhibitors of the inflammatory effects of microglia (e.g. reduces IL-6 and TNF-α). This view suggests that those conditions in which chronic inflammation is a recognized feature could benefit from anti-inflammatory actions of vitamin D [122].

The strength of evidence of causality reflects ability to establish temporality with strongest evidence when vitamin D assessment has occurred before the primary outcome developed (prospective studies), moderate evidence when vitamin D assessed at time of diagnosis, and weakest evidence when vitamin D assessed after diagnosis. This pattern of temporal influences supports the framework model that vitamin D's role may be different depending on the condition and/or time of development and/or underlying pathological processes [123,124].

6.3. Clinical implementation framework

The evidence gradient sets up a tiered approach to clinical implementation:

- Neurodevelopmental Disorders (Category A): The most robust clinical recommendations are about prevention via prenatal vitamin D sufficiency. The existing evidence demonstrates that keeping the mother's vitamin D levels >30 ng/mL during pregnancy is a low-risk recommendation [125,126].
- Mood Disorders (Category B): Screening for vitamin D sufficiency should be fast tracked for those with treatment-resistant depression, seasonal affective disorder, and depression comorbid with autoimmune diseases. Supplementation is most effective with a baseline deficiency (<20 ng/mL) and there is evidence in the treatment literature of a dose range of 2000–4000 IU/day needed to achieve levels of 30–50 ng/mL as recommended for supplementation [36,127].
- Other Conditions (Category C): The current evidence does not support routine screening or supplementation in addition to the general recommendations for the population. An individualized approach may be taken with documented deficiency [124].

This goes beyond basic "screen and treat" recommendations and develops nuanced options based on the level of evidence and biological plausibility.

6.4. Methodological considerations future directions and limitations

An evaluation of evidence quality showed substantial variability across studies. A standardized evidence evaluation framework based upon hierarchy of study design, vitamin D evaluation quality, outcome measurement, confounding control, and temporal relationship, showed that conditions with the most robust evidence (neurodevelopmental disorders), also represented the highest proportion of studies with high-quality (68% of included studies), while conditions with less robust evidence (anxiety disorders) were dominated by low-quality studies (82% of included studies). To contextualize the risk-of-bias scoring system used throughout this review, "A" indicates studies with low risk across all domains (adequate randomization, allocation concealment, blinding and missing data (trials); strong confounding control, appropriate participant selection (observational studies) "B" indicates studies with some risk of concerns in method execution, "C" indicates a high risk of bias that

expresses concern about the findings. This is specifically relevant to the evidence categories, as evidence on Category A studies (neurodevelopmental disorders) comprised 85% of studies with rated A/B, and Category C studies (anxiety disorders) comprised 18% of studies with rated A/B outcomes, not surprisingly resulting by evidence categories.

Future research should aim to fill three major gaps:

- Standardization of terms: Use consistent terms, vitamin D, define acronyms, use reliable serum 25(OH)D category, use observational study designs [128].
- Targeted research: Contest bipolar disorder, anxiety disorders (clinical-diagnosed not self-reported), and other dementia subtypes (besides Alzheimer's) in clinical trials [129].

Despite the comprehensive synthesis of evidence, several limitations should be acknowledged. Although this review prioritized meta-analyses and randomized controlled trials, a considerable proportion of the included studies were observational, which are inherently vulnerable to residual confounding. Factors such as sun exposure, physical activity, diet, socioeconomic status, and general health behaviors may influence both vitamin D status and neurological outcomes, potentially biasing observed associations. In addition, substantial heterogeneity exists across studies regarding population characteristics, vitamin D measurement methods, supplementation regimens, diagnostic criteria, and outcome measures, which limited direct comparability and precluded quantitative pooling across all conditions. Reverse causality is also possible in some contexts, as individuals with psychiatric or neurological disorders may have reduced outdoor activity or altered lifestyle patterns that contribute to lower vitamin D levels rather than resulting from them. Furthermore, although study quality was systematically evaluated using a structured risk-of-bias framework, the A/B/C

Table 3
Vitamin D-Regulated Neurobiological Pathways. For would target(s) based on brain region or cell type, the primary vitamin D target(s), signaling mode (genomic or rapid non-genomic), relevant neuropsychiatric or neurological disorder(s), and in some cases, representative studies are noted

Brain region/Cell type	Primary vitamin-D-regulated target(s)	Mechanism†	Linked disorder(s)	Key evidence (representative refs.)
Prefrontal cortex	↑ Tryptophan-hydroxylase-2 → ↑ serotonin	Genomic (VDR)	Depression, ASD*	[5]
Hippocampus	↑ BDNF*/CREB* signaling; ↑ neurogenesis	Genomic	Cognitive decline, MDD*	[12,16]
Substantia nigra (DA neurons)	↓ ROS via Nrf2/Keap1; ↑ Tyrosine-hydroxylase	Genomic + Non-genomic	Parkinson's, ADHD*	[17]
Microglia/Astrocytes	↓ NF-κB → ↓ IL-6 & TNF-α	Genomic	Alzheimer's, MS	[4]
Oligodendrocyte precursors	↑ MBP* & MOG* expression → remyelination	Genomic	Multiple Sclerosis	[130]
Pan-neuronal (membrane)	Rapid modulation of L-type Ca^{2+} channels via PDIA3 (1,25D-MARRS)E	Non-genomic	ALS*, Stroke, Epilepsy	[131]
Suprachiasmatic nucleus	CLOCK/BMAL1 tuning; ↑ Melatonin synthesis	Genomic	Insomnia, SAD*	[37]
Hypothalamus (HPA axis)	↓ CRH*, normalizes glucocorticoid feedback	Genomic	Anxiety, Perinatal depression	[32]

Abbreviations: ASD: Autism Spectrum Disorder; BDNF: Brain-Derived Neurotrophic Factor; CREB: cAMP Response Element-Binding Protein; MDD: Major Depressive Disorder; DA: dopaminergic; MBP: Myelin Basic Protein; MOG: Myelin Oligodendrocyte Glycoprotein; CRH: Corticotropin-Releasing Hormone; ALS: Amyotrophic Lateral Sclerosis; SAD: Seasonal Affective Disorder; MS: Multiple Sclerosis.

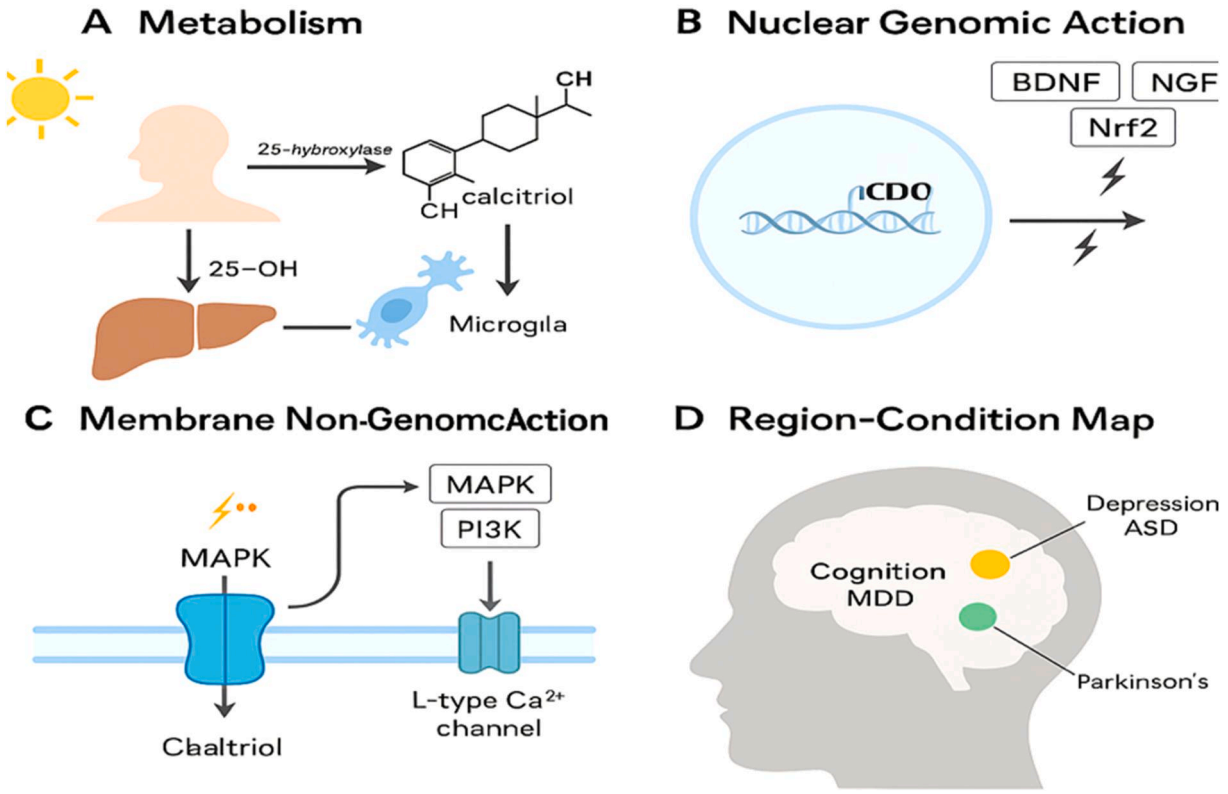

Figure 6. Overview of vitamin D metabolism and brain signaling. Panel A – Metabolism: Cutaneous synthesis and dietary/supplemental intake generate vitamin D_3, which is 25-hydroxylated in liver and further 1-α-hydroxylated in kidney or micro-glia to its active form calcitriol. Panel B – Nuclear genomic action: Calcitriol binds the nuclear vitamin-D receptor (VDR) to modulate transcription of neurotrophic (BDNF, NGF), antioxidant (Nrf2), and neurotransmitter-synthetic (TPH2, TH) genes. Panel C – Membrane non-genomic action: Calcitriol engages the PDIA3 (1,25D-MARRS) membrane receptor, triggering rapid MAPK/PI3K cascades that influence L-type Ca^{2+} channel activity. Panel D – Region–condition map: Brain silhouette with color-coded loci links key regions (prefrontal cortex, hippocampus, substantia nigra, etc.) to illustrative clinical conditions (depression/ASD, cognition/MDD, Parkinson's). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

grading approach represents a qualitative synthesis rather than a formal GRADE assessment of evidence certainty. Nevertheless, the convergence of evidence across epidemiological studies, randomized trials, and mechanistic research provides a consistent body of literature supporting a relationship between vitamin D status and brain health outcomes.

7. Conclusion

Overall, the current systematic review illustrates that vitamin D is a critical modulator in mental and neurological health throughout the lifespan. Low vitamin D levels have been consistently linked with higher risk and severity of mental and neurological disorders, including depression, anxiety, schizophrenia, autism, ADHD, neurodegenerative diseases, and sleep disorders. In many instances, vitamin D deficiencies emerge, not solely in the context of illness, but as a contributing factor to the illness process or outcome. Vitamin D supplementation restores vit D levels with a myriad of favorable clinical outcomes, including improvement of depressive symptoms and antidepressant response, and improvement in socialization in autism, as well as possibly, inhibiting cognitive decline in dementia. Vitamin D's wide-ranging neuro-modulatory mechanisms; downregulating inflammation, neuroprotection, and neurotransmitter production - represents a biological basis for the clinical benefits seen. Table 3 shows the vitamin-D-regulated targets by brain region, and Figure 6 qualitatively synthesizes the genomic and non-genomic pathway connections from cutaneous synthesis to region-specific clinical correlations.

The study findings further support several practical suggestions (1) to avoid vitamin D deficiency by obtaining adequate dietary intake and/or supplementation in general and in particular in pregnant women, children and older adults as a worthwhile and low-cost public health approach that may yield neurodevelopmental and neuroprotective benefits; (2) to monitor and treat hypovitaminosis D status in patients with psychiatric or neurological disorders as part of coordinated care. In selected patient populations, particularly those with documented deficiency, vitamin D repletion may improve selected clinical outcomes, vitamin D supplementation will lead to better treatment outcomes and improved physical health, and in some cases, it may diminish disease symptoms; (3) to integrate a vitamin D status assessment into future clinical trials testing mental health intervention, to analyze implications of vitamin D status, and clarify confounding influences of vitamin D deficiency on treatment resistance/response (e.g. ensuring depressed patients are not severely Vitamin D deficient or investigating if patients with Vitamin D deficiency can achieve greater benefits from certain interventions).

In conclusion, Vitamin D is a modifiable filter through which we navigate the complex matrix of brain health. No single item or factor will remediate imbalanced factors related to mental and neurological disorders, as these conditions arise from a variety of complex origins, which is precisely why all of the unique sensors and manipulations are necessary to drive improvements over the whole lifespan of the person. That said, by improving Vitamin D status at the population and clinical levels, we may attain a modest but meaningful improvement in mental well-being and neurological function. The evidence collected in this review clearly suggests that quality attention to the "sunshine vitamin" is part of achieving optimal mental health outcomes and providing support in both preventive and therapeutic capacities. Research will in time be pruned more exquisitely, but in terms of the knowledge base, there is enough evidence to warrant a proactive strategy for maintenance of vitamin D for brain health.

Ethics approval and consent to participate

Not applicable. This article is a systematic review of published literature and involves no new studies with human participants or animals.

Consent for publication

Not applicable

Availability of data and materials

No new datasets were generated or analyzed in this study. All data are derived from published sources cited in the manuscript.

Authors' contributions

The authors confirm their contribution to the paper as follows: G.B., N.Y., N.B.K. and W.R.: Conceptualization; G.B., N.Y. and N.B.K.: Methodology, Investigation; G.B., N.Y. and N.E.: Data curation; G.B., N.Y., N.B.K. and W.R.: Formal analysis; G.B., N.Y., N.B.K. and N.E.: Writing–original draft; G.B., N.Y., N.B.K., and W.R.: Writing–review & editing; W.R.: Supervision.

Declaration of generative AI and AI-assisted technologies

No generative AI or AI-assisted technologies were used in the writing, editing, or preparation of this manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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