Diplomarbeit

Vitamin D and Calcium Metabolism in Bipolar Disorder: A Scoping Review of Contradictory Evidence

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Univ.-Prof.in PDin Dr.in Eva Maria Reininghaus MBA

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Graz, 19. April 2026

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Graz, 19. April 2026 Amirzhan Kulmagambetov eh.

Danksagungen (optional)

Mein besonderer Dank gilt Univ.-Prof.in PDin Dr.in Eva Maria Reininghaus, MBA, sowie Dr.in med.univ. Adelina Tmava-Berisha für die engagierte Betreuung, die wertvollen fachlichen Anregungen und die konstruktiven Rückmeldungen während der Erstellung dieser Arbeit.

Zusammenfassung in Deutsch (maximal 5000 Zeichen)

Hintergrund:
Dieser Scoping-Review fasste die Evidenz zu Vitamin D, Parathormon (PTH) und Serumkalzium bei bipolarer Störung zusammen, um deren potenziellen klinischen Nutzen zu evaluieren.

Methoden:
Eine systematische PubMed-Suche identifizierte Originalstudien, die Biomarker des Kalziumstoffwechsels (Vitamin D, PTH, Serumkalzium) ausschließlich in Populationen mit bipolarer Störung untersuchten. Aufgrund erheblicher methodischer Heterogenität wurden die Ergebnisse narrativ synthetisiert.

Ergebnisse:
Vierzehn Studien erfüllten die Einschlusskriterien, mit kleinen Stichprobengrößen (Median n=55) und überwiegend querschnittlichen Studiendesigns. Vergleiche der Vitamin-D-Spiegel zwischen Patient*innen mit bipolarer Störung und Kontrollpersonen zeigten widersprüchliche Ergebnisse: Drei Studien berichteten signifikant niedrigere Werte bei Patient*innen, zwei fanden signifikant höhere Werte, und drei zeigten keine Unterschiede. Die Definitionen eines Vitamin-D-Mangels variierten erheblich (<25 bis <50 nmol/L), was sinnvolle Vergleiche verhinderte. Vier kognitive Studien zeigten inkonsistente Zusammenhänge mit Vitamin D, darunter negative Korrelationen, altersabhängige Effekte oder keine Assoziationen. Zwei kleine Supplementationsstudien mit Vitamin D bei bipolaren Spektrumstörungen lieferten widersprüchliche Ergebnisse in unterschiedlichen Populationen, eine bei Jugendlichen und eine bei Erwachsenen. Daten zu PTH und Kalzium waren spärlich und inkonsistent.

Limitationen:
Zu den Limitationen gehörten die Nutzung nur einer Datenbank, erhebliche Studienheterogenität sowie eine unzureichende Kontrolle von Störfaktoren, einschließlich saisonaler Variationen.

Schlussfolgerungen:
Die Evidenz zu Biomarkern des Kalziumstoffwechsels bei bipolarer Störung ist widersprüchlich und methodisch limitiert. Grundlegende Inkonsistenzen im Vitamin-D-Status zwischen Patient*innen und Kontrollpersonen sowie widersprüchliche Supplementationsdaten lassen keine klinischen Empfehlungen zu. Ein routinemäßiges Vitamin-D-Screening speziell zur Behandlung der bipolaren Störung kann nicht unterstützt werden. Große, standardisierte Studien sind erforderlich, bevor eine klinische Anwendung gerechtfertigt ist.

Abstract in Englisch (maximal 5000 Zeichen)

Background:
This scoping review synthesized evidence on vitamin D, parathyroid hormone (PTH), and serum calcium in bipolar disorder (BD) to evaluate their potential clinical utility.

Methods:
A systematic PubMed search identified original studies examining calcium metabolism biomarkers (vitamin D, PTH, serum calcium) exclusively in BD populations. Findings were synthesized narratively due to substantial methodological heterogeneity.

Results:
Fourteen studies met inclusion criteria, with small sample sizes (median n=55) and predominantly cross-sectional designs. Vitamin D comparisons between BD patients and controls yielded contradictory results: three studies reported significantly lower levels in BD patients, two found significantly higher levels, and three found no differences. Vitamin D deficiency definitions varied widely (<25 to <50 nmol/L), precluding meaningful comparisons. Four cognition studies showed inconsistent associations with vitamin D, with negative correlations, age-dependent effects, or no associations reported. Two small vitamin D supplementation studies in bipolar spectrum disorders yielded contradictory results in distinct populations, with one in youth and the other in adults. Data on PTH and calcium were sparse and inconsistent.

Limitations:
Study limitations included a single database search, substantial study heterogeneity, and inadequate control for confounders, including seasonal variation.

Conclusions:
Evidence on calcium metabolism biomarkers in BD is contradictory and methodologically limited. Fundamental inconsistencies in vitamin D status between BD patients and controls, combined with conflicting supplementation data, preclude clinical recommendations. Routine vitamin D screening specifically for BD management cannot be supported. Large-scale, standardized studies are needed before clinical application.

Angaben von bereits erfolgten Veröffentlichungen (bei Bedarf)

- ## Bei Veröffentlichungen:

Das im Rahmen dieser Diplomarbeit erstellte Manuskript wurde zur Veröffentlichung angenommen:

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Inhaltsverzeichnis

Vitamin D and Calcium Metabolism in Bipolar Disorder: A Scoping Review of Contradictory Evidence

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Abstract

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recommendations. Routine vitamin D screening specifically for BD management cannot be supported. Large-scale, standardized studies are needed before clinical application.

Keywords: bipolar disorder, calcium, vitamin D, parathyroid hormone

Introduction

Bipolar disorder (BD) is a chronic recurrent mood disorder characterized by episodes ranging from acute depression to mania, affecting approximately 40 million people worldwide [1,2]. Despite advances in treatment, many patients continue to experience residual symptoms and functional impairment, highlighting the need for novel therapeutic approaches and biomarkers.

Recent research has increasingly focused on calcium metabolism in psychiatric disorders, particularly in relation to vitamin D and its regulatory systems [3]. Calcium homeostasis involves a complex network of serum calcium, parathyroid hormone (PTH), and vitamin D metabolites. When serum calcium decreases, PTH secretion increases, enhancing calcium resorption and stimulating production of active vitamin D [1,25$(OH)_2$D], which binds to vitamin D receptors (VDRs) and increases intestinal calcium absorption [4].

Vitamin D synthesis requires two sequential hydroxylations: first in the liver, producing 25(OH)D, then in the kidneys, forming the active hormone 1,25$(OH)_2$D [5]. Beyond calcium homeostasis, vitamin D exhibits diverse neurobiological functions including neuroprotection, inflammation suppression, and modulation of serotonin synthesis [6,7]. In addition to that, VDRs are widely expressed in the central nervous system and contribute to immunomodulatory and neuroprotective effects [8].

The intersection of calcium signaling and BD pathophysiology has garnered considerable attention. Meta-analytic evidence suggests elevated intracellular calcium concentrations in patients with BD [9], while genetic studies have implicated calcium channel genes in BD susceptibility [10]. Patient-derived stem cell studies suggest altered calcium signaling in BD neurons that responds to lithium, which is frequently used as mood-stabilizer in BD treatment

[11]. Additionally, stress-induced cortisol elevation may increase synaptic glutamate and intracellular calcium, potentially contributing to manic episodes [12].

Previous research has identified associations between vitamin D deficiency and psychiatric conditions, including BD [3, 13]. Studies suggest that insufficient vitamin D levels may negatively influence cognition through VDRs in brain regions responsible for memory and executive function [14]. However, research on calcium metabolism in BD remains methodologically inconsistent, with studies employing heterogeneous populations, varying diagnostic criteria, different vitamin D assays, and inconsistent deficiency thresholds.

The present scoping review systematically synthesizes research conducted exclusively in BD populations, focusing on vitamin D, PTH, and serum calcium. Our objective was to evaluate current evidence regarding these biomarkers in BD pathophysiology, clinical presentation, and therapeutic applications. However, it is important to note that the peripheral biomarkers such as 25(OH)D, PTH, and serum calcium do not necessarily reflect potential mechanisms in the central nervous system that are implicated in BD. Therefore, we do not presume a direct correlation between them. We hypothesized that hypovitaminosis D, elevated PTH, and hypocalcemia would be associated with greater symptom severity and cognitive impairment in BD, and explored whether vitamin D supplementation represents a viable adjunctive therapeutic strategy.

Methods

This scoping review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [15]. The protocol was registered on the Open Science Framework at https://doi.org/10.17605/OSF.IO/GQ6JU.

A systematic search was conducted in PubMed from database inception to 26 August 2024 using the following search string: "bipolar disorder" AND ("vitamin D" OR "parathyroid hormone" OR "serum calcium"). No publication date limits were applied. The search was restricted to English-language articles, and no additional filters were used. Reference lists of included studies were screened for potentially relevant publications. While additional databases such as Embase and PsycINFO would strengthen the search, resource constraints limited the search to PubMed, representing a methodological limitation that may have resulted in incomplete evidence synthesis. Furthermore, the incomplete capture of the evidence base could have contributed to the exclusion of endocrinology-focused or non-psychiatric journals that in turn may have influenced heterogeneity and contradictory findings in the final review.

Studies were included if they were original research articles examining vitamin D, parathyroid hormone, or serum calcium in individuals with BD and published in English. Exclusion criteria were non-original research, case reports ($n<10$), animal studies, mixed psychiatric populations without extractable BD-specific data, and multivitamin studies without specific vitamin D data.

Study Selection and Data Extraction

Figure 1 presents the PRISMA-ScR study selection process [16]. The PubMed search yielded 171 records. After removing 12 duplicates, 159 records were screened, and 143 were excluded based on title and abstract. Sixteen full-text articles were assessed, with 2 excluded (multivitamin study, mixed diagnoses), resulting in 14 included studies.

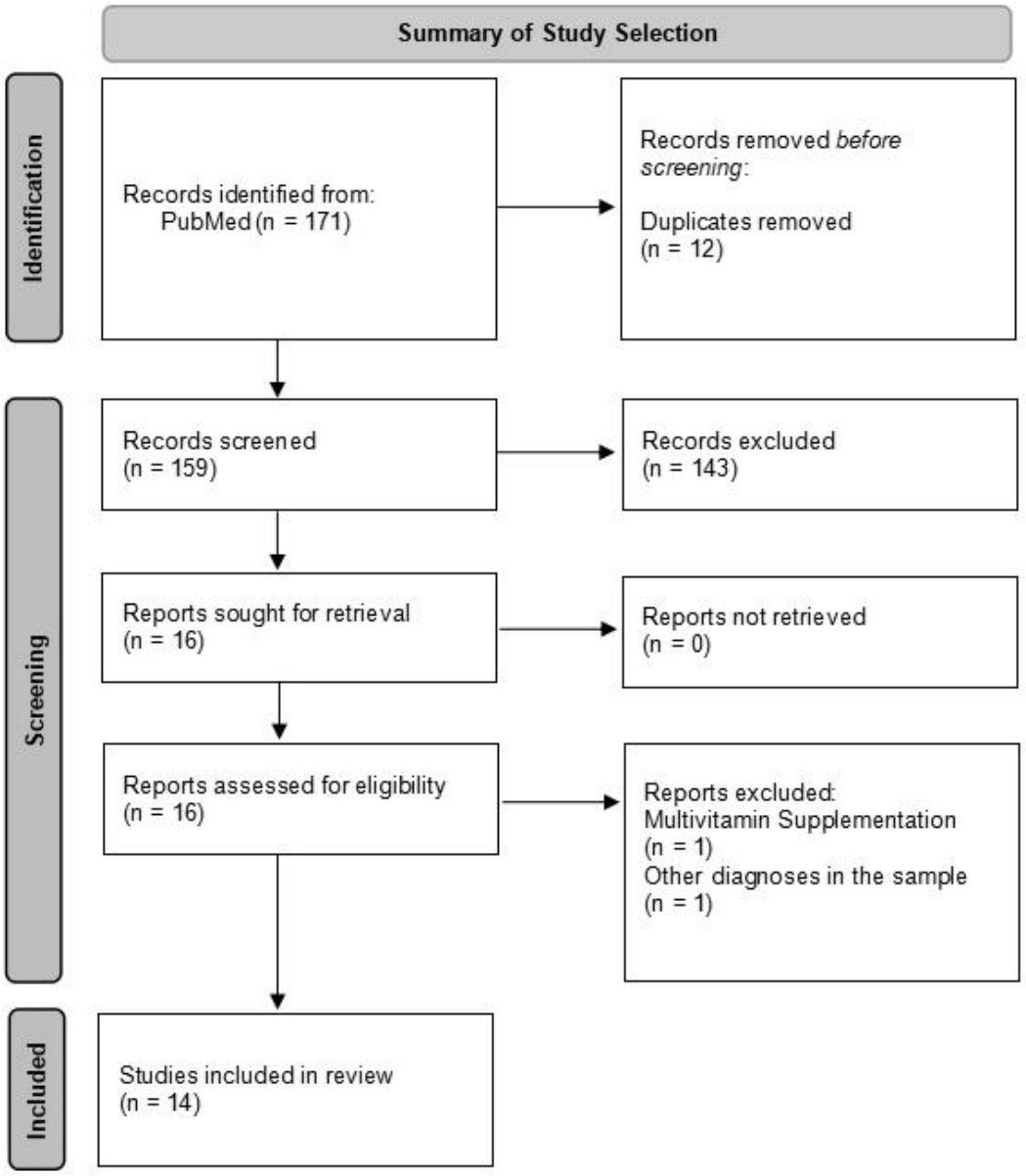

Figure 1. PRISMA-ScR study selection process

Two reviewers independently screened titles, abstracts, and full-text articles. Disagreements were resolved through discussion. Inter-rater agreement was substantial ($\kappa = 0.78$ for screening, $\kappa = 0.82$ for full-text review). Data were extracted on study characteristics, biomarker levels, vitamin D deficiency definitions, and clinical outcomes. Values were standardized using conversion factors (vitamin D: 1 ng/mL = 2.5 nmol/L; PTH: 1 pg/mL = 0.106 pmol/L; calcium: 1 mg/dL = 0.25 mmol/L). Two studies (Leser et al., 2023; Späth et al., 2023) utilized overlapping populations but examined different outcomes and were both included.

Due to heterogeneous study populations, biomarker measurement methods, and vitamin D deficiency definitions (ranging from <25 to <50 nmol/L), meta-analysis was not feasible. Results are presented as narrative synthesis organized by: (1) vitamin D levels in BD vs controls, (2) vitamin D and cognition, (3) vitamin D supplementation, and (4) PTH and calcium in BD.

Results

Fourteen studies met inclusion criteria, with significant heterogeneity in study populations, methodological approaches, and findings. Tables 1-4 present detailed study characteristics and biomarker data. The evidence base was characterized by small sample sizes (median n = 55, range n = 16-199), predominantly cross-sectional designs (n = 11), and substantial methodological diversity in vitamin D deficiency definitions, mood states assessed, and outcome measures used.

Vitamin D Status and Disease Activity

Studies examining vitamin D status in BD patients compared to mentally healthy controls, along with associations between vitamin D and mood symptoms, yielded highly inconsistent

results (Table 1). Three studies reported significantly lower vitamin D levels in BD patients: Altunsoy et al. [17] found lower levels in acute mania patients compared to controls (37.90 ± 18.70 vs 55.78 ± 22.00 nmol/L, $p = 0.002$), Astaneh et al. [18] reported lower levels in manic and mixed episodes ($p < 0.05$), and İmre et al. [19] observed lower levels in manic patients (26.15 ± 12.33 vs 41.08 ± 13.20 nmol/L, $p < 0.001$).

Among the studies finding lower vitamin D levels in BD patients, several demonstrated significant associations with mood symptom severity. Altunsoy et al. [17] found strong negative correlations between vitamin D levels and both Young Mania Rating Scale (YMRS) scores ($r = -0.641$, $p < 0.001$) and Clinical Global Impression Scale - Severity (CGI-S) scores ($r = -0.559$, $p = 0.003$) in patients with acute mania. The remission group did not differ significantly from either the healthy control or the acute mania episode groups in vitamin D levels. Astaneh et al. [18] reported comprehensive associations between vitamin D and multiple symptom domains, with vitamin D levels negatively associated with CGI-S ($r = -0.311$, $p = 0.028$), YMRS ($r = -0.464$, $p = 0.001$), and Hamilton Depression Rating Scale (HAM-D) scores ($r = -0.393$, $p = 0.005$).

Notably, gender-specific analyses revealed important differences. Astaneh et al. [18] found that after gender-specific analysis, the difference between patient groups and controls was significant only in males, despite both groups showing lower vitamin D levels overall. The control group in this study consisted of first-degree relatives of the patients. In the subgroup with disease duration of ≥10 years, mixed BD patients had significantly lower vitamin D levels compared to acute-phase bipolar mania patients ($p < 0.05$).

İmre et al. [19] provided unique longitudinal data, comparing vitamin D levels in BD patients during manic episode before treatment and in post-treatment remission. Vitamin D levels in post-treatment euthymic patients were significantly increased compared to the pre-treatment

patient group ($p < 0.001$). However, this finding is confounded by the fact that patients with low vitamin D levels received an unspecified regimen of vitamin D supplementation during inpatient treatment ($n = 19$, 55.8% of the sample).

In direct contradiction, two studies found higher vitamin D levels in BD patients. Li et al. (2023)[20] reported significantly higher levels in BD patients compared to controls (45.90 ± 17.68 vs 39.05 ± 9.15 nmol/L, $p = 0.043$), while Li et al. (2022) [21] initially found higher levels (46.10 ± 20.15 vs 40.95 ± 11.30 nmol/L, $p = 0.041$), though statistical significance was lost after Bonferroni correction. Li et al. (2022) reported that vitamin D levels of males in the BD group were significantly higher than those of females ($p < 0.001$), indicating important sex differences in vitamin D status among BD patients. Notably, neither Li et al. study found significant correlations between vitamin D levels and mood rating scales (HAM-D, YMRS, Hypomania Checklist).

Three studies found no significant differences between groups in vitamin D levels. Leser et al. [22] reported similar levels in patients with BD and controls (56.37 ± 23.64 vs 57.29 ± 23.95 nmol/L), Van Rheenen et al. [23] found no differences, and Späth et al. [24] reported no overall group differences. However, Späth et al. [24] found negative correlations between YMRS scores and vitamin D metabolites, including $24,25(OH)_2D$ ($r = -0.154$, $p = 0.040$) and vitamin D metabolite ratio (VMR) ($r = -0.238$, $p = 0.015$), despite the absence of group differences. Van Rheenen et al. [23] found no associations between vitamin D levels and either YMRS ($F(1,49) = 0.18$, $p = 0.672$) or Montgomery-Åsberg Depression Rating Scale (MADRS) scores ($F(1,49) = 0.008$, $p = 0.929$).

The most sophisticated analysis was conducted by Zheng et al. [25], who used latent profile analysis to examine the association between vitamin D and depression severity in bipolar depression. The sample was stratified into three vitamin D profiles: low-level profile (32.9%),

medium-level profile (51.0%), and high-level profile (16.1%) based on baseline vitamin D concentrations. Depression severity was assessed using the Zung Self-Rating Depression Scale (SDS). The three profiles showed significant differences in both baseline vitamin D and post-treatment vitamin D levels ($p < 0.001$). Critically, higher SDS improvement over two weeks of treatment was associated with higher odds of belonging to the high-level vitamin D profile compared to the low-level profile (OR = 7.00; 95% CI: 1.23, 39.78; p-trend = 0.017). This suggests an association between higher baseline vitamin D levels and better treatment response in bipolar depression, though this finding requires replication.

The findings on vitamin D status in BD were inconsistent, with studies reporting lower, higher, or comparable levels relative to controls. In addition to that, reported associations between vitamin D levels and mood symptom scales were mixed, with different studies reporting both significant and non-significant findings.

As demonstrated in Table 1, these contradictory findings likely reflect substantial methodological heterogeneity, including varying vitamin D deficiency definitions (ranging from <25 to <50 nmol/L), different BD subtypes and mood states, seasonal timing variations, geographic differences, gender-specific effects, and the complex relationship between vitamin D status and mood symptom severity.

Table 1. Vitamin D Status and disease activity in bipolar disorder

Study	BD type/state	(BD/HC)	BD Vitamin D (nmol/L)	HC Vitamin D (nmol/L)	Deficiency Definition	Deficiency %	Main Finding	Associations/Correlations with clinical variables
Higher Vitamin D in BD								
Li et al., 2022	Drug-naive, mixed	100/50	46.10±20.15	40.95±11.30	<30 nmol/L	NR	BD > HC (p= .041, NS after correction)	No correlation with HAM-D, YMRS, HCL
Li et al., 2023	Mixed states	102/51	45.90±17.68	39.05±9.15	<30 nmol/L	NR	BD > HC (p= .043)	No correlation with HAM-D, YMRS
Lower Vitamin D in BD								
Altunsoy et al., 2018	Acute mania	26/26	37.90±18.70	55.78±22.00	<25 nmol/L	30.8%	BD < HC (p= .002)	YMRS: r=-0.641, p< .001; CGI-S: r=-0.559, p= .003
İmre et al., 2023	Acute mania	34/30	Pre-tx: 26.15±12.33; Post-tx: 39.88±14.25	41.08±13.20	<50 nmol/L	55.8%	BD < HC (p< .001); Improvement Post-tx (p<0.001)	NR
Astaneh et al., 2024	Mania/mixed	50/50	NR	NR	NR	NR	BD < HC (p< .05, males only)	CGI-S: r=-0.311, p= .028; YMRS: r=-0.464, p= .001; HAM-D: r=-0.393, p= .005
No Difference								
Leser et al., 2023	Euthymic	86/93	56.37±23.64	57.29±23.95	<50 nmol/L	40.7%	No difference (p> .05)	No correlations with mood clinical scales
Späth et al., 2023	Mixed	170/175	57.8±24.3	61.5±29.3	<50 nmol/L	9.6%	No difference (p> .05)	$24,25(OH)_2D$ vs YMRS: r=-0.154, p= .040; VMR vs YMRS: r=-0.238, p= .015
Van Rheenen et al., 2023	Mixed states	55/22	38.25±8.50	33.00±8.00	<50 nmol/L	~26%	No difference (p> .05)	YMRS: $F(1,49)=0.18$, p= .672; MADRS: $F(1,49)=0.008$, p= .929
Latent Profile Analysis								
Zheng et al., 2024	Bipolar depression	155/0	Low: 22.5±4.5; Medium: 37.8±6.0; High: 62.3±12.8	N/A	<50 nmol/L	32.9% (low profile)	Three vitamin D profiles identified	High vitamin D profile associated with better treatment response (OR=7.00, p= .017)

$24,25(OH)_2D$ - 24,25-dihydroxyvitamin D; BD - Bipolar Disorder; CGI-S - Clinical Global Impression Scale - Severity; HAM-D - Hamilton Depression Rating Scale; HC - Healthy Controls; HCL - Hypomania Check List; MADRS - Montgomery Åsberg Depression Rating Scale; OR - Odds Ratio; Pre-tx - Pre-Treatment; Post-tx - Post-Treatment; NR - Not Reported; NS - Not Significant; VMR - Vitamin D Metabolite Ratio; YMRS - Young Mania Rating Scale

Vitamin D and Cognitive Function

Four studies examined associations between vitamin D and cognitive performance, yielding inconsistent results (Table 2). Li et al. (2023) [20] reported negative correlations between vitamin D levels and memory performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in patients with BD, including total scores (r = -0.224, p = 0.023), immediate memory (r = -0.207, p = 0.037), and delayed memory (r = -0.281, p = 0.004). Paradoxically, this same study found that patients with BD had higher vitamin D levels than controls.

Chen et al. [26] found age-dependent effects in euthymic bipolar type I disorder (BD-I) patients using the Brief Assessment of Cognition in Affective Disorders (BAC-A). In older patients (46-65 years), vitamin D levels were positively associated with composite scores (β = 0.347, p = 0.020) and verbal fluency (β = 0.252, $p < 0.001$). However, in younger patients (20-45 years), these associations were negative (composite scores: β = -0.344, p = 0.040; verbal fluency: β = -0.230, $p < 0.001$).

Two studies found no significant associations. Leser et al. [22] reported no correlations between vitamin D metabolites and attention, memory, or executive function domains in BD patients or controls. Similarly, Van Rheenen et al. [23] found no association between vitamin D status and global cognitive performance on the MATRICS Consensus Cognitive Battery ($F(1,67) = 0.72$, p = 0.410).

The findings on vitamin D and cognitive function in BD were inconsistent, with studies reporting negative correlations with memory, age-dependent effects, or no associations.

As demonstrated in Table 2, the conflicting nature of these findings, combined with different cognitive assessment tools and age-related effects, precludes definitive conclusions about vitamin D's role in BD-related cognitive dysfunction.

Table 2. Studies examining vitamin D and cognitive function in bipolar disorder

Study	Population (n)	Design	Vitamin D Level (nmol/L)	Deficiency Definition	Cognitive Measure	Key Finding
Chen et al., 2022	BD: 100	Cross-sectional	41.15 (72% deficient)	<50 nmol/L	BAC-A	Age-dependent effects
Leser et al., 2023	BD: 86 HC: 93	Cross-sectional	BD: 56.37±23.64	<50 nmol/L	CVLT, SCWT, TMT	No associations
Li et al., 2023	BD: 102 HC: 51	Cross-sectional	BD: 45.90±17.68 (Higher than HC)	<30 nmol/L	RBANS	Negative correlation with memory
Van Rheenen et al., 2023	BD: 55 HC: 22	Cross-sectional	BD: 38.25±8.50	<50 nmol/L	MCCB	No associations

BAC-A - Brief Assessment of Cognition in Affective Disorders; BD - Bipolar Disorder; CVLT - California Verbal Learning Test; HC- Healthy Controls; MCCB - MATRICS Consensus Cognitive Battery; RBANS - Repeatable Battery for the Assessment of Neuropsychological Status; SCWT - Stroop Color and Word Test; TMT - Trail Making Test

Vitamin D Supplementation

Only two small studies examined vitamin D supplementation in bipolar spectrum disorders (BSD), yielding contradictory results (Table 3). Marsh et al. [27] conducted a randomized controlled trial in 33 adults with BSD experiencing depressive symptoms. The study found no significant differences in depression (MADRS), mania (YMRS), or anxiety (HAM-A) scores between vitamin D supplementation (5000 IU daily) and placebo groups over 12 weeks ($p = 0.89$, $p = 0.51$, $p = 0.89$, respectively). Only 25 of 33 participants completed the trial, and there was no correlation between vitamin D level changes and symptom improvement.

In contrast, Sikoglu et al. [28] reported positive findings in an open-label trial of 16 youth with BSD. After 8 weeks of vitamin D supplementation (2000 IU daily), significant

improvements were observed in YMRS scores (t = -3.66, p = 0.002) and Children's Depression Rating Scale scores (t = -2.93, p = 0.01), along with increased anterior cingulate cortex γ-aminobutyric acid (GABA) levels (t = 3.18, p = 0.007).

The limited reported data on vitamin D supplementation is inconclusive, with seemingly contradictory results.

As shown in Table 3, the conflicting results between these studies, differences in population (adults vs. youth), study design (randomized controlled vs. open-label), dosing regimens, and small sample sizes preclude any conclusions about vitamin D supplementation efficacy in BD.

Table 3. Vitamin D supplementation studies in bipolar spectrum disorders

Study	Population	Design	n	Intervention	Duration	Primary Outcome	Result
Marsh et al., 2017	BSD adults, depressed	RCT, double-blind	25 completed	5000 IU/day vs placebo	12 weeks	MADRS, YMRS, HAM-A	No significant differences
Sikoglu et al., 2015	BSD youth, manic	Open-label Trial	16	2000 IU/day	8 weeks	YMRS, CDRS	Significant improvement

BSD - Bipolar Spectrum Disorder; CDRS - Children's Depression Rating Scale; HAM-A - Hamilton Anxiety Rating Scale; IU - International Units; MADRS - Montgomery Åsberg Depression Rating Scale; RCT - Randomized Controlled Trial; YMRS - Young Mania Rating Scale

Parathyroid Hormone and Serum Calcium

Few studies examined PTH and serum calcium, with limited and inconsistent findings (Table 4). Two studies suggested associations between elevated PTH and illness characteristics. Steardo et al. [29] found that higher PTH levels were associated with younger age of onset (β = -0.289, p = 0.032), more hospitalizations (β = 0.160, p = 0.017), higher childhood trauma scores (β = 1.276, p = 0.001), and lithium treatment (β = 0.179, p = 0.013).

De Filippis et al. [30] reported the statistical mediation effect of PTH levels between evening chronotype and mood symptom severity, accounting for 25.5% of the effect on depression scores (indirect effect: -5.15, $p = 0.003$) and 27.5% of the effect on anxiety scores (indirect effect: -3.16, $p = 0.01$).

Serum calcium findings were inconsistent. Li et al. (2022, 2023) [20,21] reported significantly lower calcium levels in BD patients compared to controls, while Steardo et al. [29] found positive correlations between calcium levels and anxiety scores. However, İmre et al. [19] and Sikoglu et al. [28] found no significant differences in calcium levels between groups or over time.

Few studies have examined PTH and serum calcium in BD. Several studies reported higher PTH levels and associations with clinical variables. Lower serum calcium levels were reported in some studies, while others found no significant differences.

As demonstrated in Table 4, the sparse and contradictory nature of these findings, combined with the potential confounding effect of lithium treatment on calcium metabolism, limits interpretation of PTH and calcium roles in BD.

Table 4. Studies examining parathyroid hormone and serum calcium in bipolar disorder

Study	Population	n	PTH (pmol/L)	Calcium (mmol/L)	Key Finding
de Filippis et al., 2022	BD outpatients	100	Evening type: 6.59±1.34	Evening type: 2.38±0.13	PTH mediates chronotype-mood relationship
Li et al., 2022	Drug-naive BD	100	BD: 4.36±1.79 HC: 3.45±1.40	BD: 2.27±0.17 HC: 2.40±0.39	Higher PTH, lower calcium in BD
Li et al., 2023	BD mixed	102	NR	BD: 2.28±0.17 HC: 2.42±0.41	Lower calcium in BD (p= .002)
Steardo et al., 2020	BD mixed	199	4.83±2.29	2.36±0.19	Higher PTH → younger onset, more hospitalizations

BD - Bipolar Disorder; HC - Healthy Controls; NR - Not Reported; PTH - Parathyroid Hormone

Summary of Key Findings

The evidence base was characterized by substantial heterogeneity and contradictory findings. Vitamin D status comparisons between BD patients and controls showed inconsistent patterns, with some studies suggesting associations between vitamin D levels and mood symptom severity while others found no relationships. Cognitive function studies yielded highly inconsistent results with potential age-dependent effects. The limited evidence of supplementation was insufficient to support clinical recommendations, and PTH/calcium data were too sparse and inconsistent to draw meaningful conclusions. Gender-specific effects and methodological heterogeneity further complicated interpretation of findings.

Discussion

This scoping review examined calcium metabolism biomarkers in BD, revealing a complex and largely inconsistent evidence base that does not support definitive conclusions about their clinical utility. Contrary to our hypothesis that hypovitaminosis D, elevated PTH, and hypocalcemia would be consistently associated with greater symptom severity, the evidence demonstrates substantial contradictions and methodological limitations.

The most striking finding is the fundamental contradiction in vitamin D status between BD patients and healthy controls. While three studies reported lower vitamin D levels in BD patients [17-19], two studies by the same author found significantly higher levels [20,21], and three studies found no differences [22-24]. Contributing factors include heterogeneous vitamin D deficiency definitions ranging from <25 to <50 nmol/L, varied mood states at assessment, and lack of control for seasonal and geographic variations [31].

Several factors may contribute to these contradictory findings. Publication bias may favor studies showing significant associations while null results remain unpublished [32]. Medication effects, particularly mood stabilizers, may confound vitamin D metabolism through effects on cytochrome P450 enzymes [31, 33]. Additionally, timing of blood sampling relative to mood episodes and lifestyle factors including altered sunlight exposure and physical activity in BD patients may independently affect vitamin D status [3]. Sex-specific effects also complicate interpretation, as Astaneh et al. [18] found significant differences only in males, while Li et al. (2022) [21] reported higher vitamin D levels in BD males compared to females.

Cognitive function findings are similarly inconsistent. Li et al. (2023) [20] paradoxically reported both higher vitamin D levels in BD patients and negative correlations with cognitive performance, while Chen et al. [26] found opposite associations depending on age. Two other studies found no associations [22,23] with cognitive test levels. Despite vitamin D receptors being abundantly expressed in brain regions implicated in mood regulation and cognitive function [34], the relationship between peripheral vitamin D levels and central nervous system activity may be more complex than assumed.

The evidence for vitamin D supplementation is insufficient for clinical recommendations, contrasting with previous systematic review suggesting potential benefits [32]. Only two small studies with contradictory results in different populations using different designs are available [27,28]. The negative findings from the higher-quality randomized trial contrast with positive open-label findings in youth, but small sample sizes and methodological differences prevent meaningful conclusions. PTH and calcium findings are too sparse and inconsistent to inform practice, with potential lithium confounding inadequately addressed [33].

This review has several significant limitations. Our search was limited to PubMed, which may have resulted in an incomplete synthesis of evidence. The observed inconsistencies between studies may have been caused in part by the failure to include relevant studies published in journals that are indexed in other databases. The included studies had small sample sizes (median $n = 55$), predominantly cross-sectional designs, and varying methodological rigor. Heterogeneity in populations, methods, and assessments prevented meta-analysis. Many studies failed to control for seasonal variation, medications, and comorbidities that could influence calcium metabolism [5].

There was a significant methodological heterogeneity in the included studies. Vitamin D measurement methods varied across studies, including chemiluminescent immunoassays [18,19,26,27,29,30], electrochemiluminescence assays [17,20,21], enzyme-linked immunosorbent assays [23], and liquid chromatography–tandem mass spectrometry [22,24], while some studies did not report assay methods [25,28]. It should be noted that, Astaneh et al. [18] described their method as a "radioimmunoassay technique utilizing the Architect i2000 (Abbott Laboratories)". However, Architect i2000 operates on chemiluminescence and was therefore classified accordingly. Definitions of vitamin D deficiency differed substantially, ranging from <25 nmol/L [17,19] to <30 nmol/L [20, 27] and <50 nmol/L [22–26], with several studies not specifying a predefined threshold [18,21,28-30] . Exclusion or control of vitamin D supplementation was not explicitly stated by several studies [18,20,21,23,26,28,29]. While the exact definition of vitamin D supplementation as an exclusion criterion varied across the remaining studies. Lithium exposure differed across studies, with studies on drug-naïve BD patients [20,21] and studies including lithium treatment BD patients [29]. Study populations varied in mood states, including acute manic, depressive, mixed, and euthymic states, as well as in BD types (BD I, BD II, BD NOS, BSD). Clinical outcome measures were also varied, with

mood symptom severity and cognitive function evaluated with different tools, limiting direct comparability across studies. In addition to that, the included studies differed in age distribution and geographic origin. This methodological heterogeneity limits the direct comparison of studies and may influence the inconsistency in reported findings.

The observed inconsistencies may stem from both true biological heterogeneity and methodological artefacts. Biological heterogeneity may be influenced by BD subtype, mood states, illness duration or sex-specific differences. On the other hand, methodological artefacts may arise from the use of different vitamin D assays, varying thresholds for deficiency, geographical location, season and timing of sampling, lithium treatment. Clearly distinguishing between the biological and methodological influences requires further research.

Notably, lithium-related alterations in calcium metabolism require detailed attention in future research as it is known to influence calcium and PTH regulation. In addition to that, the potential influence of sex-specific differences in BD requires future research to be designed to compare not only the BD patients and healthy controls but also the subgroups within them based on sex.

Although findings from peripheral biomarker studies are inconsistent, calcium-related pathways have been implicated in BD research and therefore further methodologically rigorous research is needed to investigate potential clinical utility of peripheral calcium metabolism biomarkers in BD. Vitamin D receptors regulate over 1000 genes involved in neurotransmitter synthesis and immune function [6], while meta-analytic evidence shows elevated intracellular calcium in BD [9]. However, the findings in our review were heterogeneous and derived predominantly from cross-sectional studies, making it difficult to draw reliable conclusions and limiting the assessment of more complex patterns of

association. The sophisticated latent profile analysis by Zheng et al. [25] reported an association between higher vitamin D levels and a better treatment response in bipolar depression patients. However, the validity of this association needs to be replicated by further research to confirm its potential predictive value. The inconsistencies may also reflect BD's heterogeneous nature, as different subtypes and mood states may have varying relationships with calcium metabolism [2].

Based on current evidence, routine vitamin D screening as a disorder-specific biomarker for the management of BD cannot be recommended. However, this conclusion does not contradict general medical indications for vitamin D screening and supplementation. While vitamin D deficiency is common in psychiatric populations, our findings do not support its use as a BD biomarker or treatment predictor [3]. Similarly, vitamin D supplementation cannot be recommended as adjunctive BD treatment based on limited and contradictory evidence.

Future research requires large-scale, longitudinal studies with standardized assays, consistent deficiency definitions, and adequate confounder control. Studies should stratify by BD subtype and mood state while controlling for seasonal, geographic, and medication factors. Investigation of threshold effects and central nervous system vitamin D markers may provide insights beyond peripheral levels. Gender-specific analyses should be routinely conducted given emerging evidence of sex differences in vitamin D metabolism in BD.

In conclusion, current evidence does not support the clinical utility of vitamin D, PTH, or serum calcium as BD biomarkers. More rigorous, standardized research is required before clinical recommendations can be justified. Until then, clinicians should focus on evidence-

based BD treatments while considering vitamin D status only for general health maintenance.

Abbreviations

ACC - Anterior Cingulate Cortex

BAC-A - Brief Assessment of Cognition in Affective Disorders

BD - Bipolar Disorder

BSD - Bipolar Spectrum Disorder

CDRS - Children's Depression Rating Scale

CGI-S - Clinical Global Impression Scale - Severity

CVLT - California Verbal Learning Test

GABA - γ-aminobutyric acid

HAM-A - Hamilton Anxiety Rating Scale

HAM-D - Hamilton Depression Rating Scale

HC - Healthy Controls

IU - International Units

MADRS - Montgomery-Åsberg Depression Rating Scale

MCCB - MATRICS Consensus Cognitive Battery

NR - Not Reported

NS - Not Significant

OSF - Open Science Framework

PRISMA-ScR - Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

PTH - Parathyroid Hormone

RBANS - Repeatable Battery for the Assessment of Neuropsychological Status

RCT - Randomized Controlled Trial

SDS - Zung Self-Rating Depression Scale

SCWT - Stroop Color and Word Test

TMT - Trail Making Test

VDRs - Vitamin D Receptors

VMR - Vitamin D Metabolite Ratio

YMRS - Young Mania Rating Scale

1,25(OH)$_2$D - 1,25-dihydroxyvitamin D

24,25(OH)$_2$D - 24,25-dihydroxyvitamin D

25(OH)D - 25-hydroxyvitamin D

Ethics approval and consent to participate

This scoping review synthesizes data from previously published studies. No primary data were collected from human participants.

Consent to Publish declaration

Not applicable.

Consent to Participate declaration

Not applicable.

Data Availability Statement

No new data were generated or analyzed in this study. All data supporting the findings of this review are derived from previously published studies, which are cited in the reference list.

Conflict of Interest Declaration

The authors declare no conflicts of interest related to this work.

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References

1. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022;9(2):137–150. doi:10.1016/S2215-0366(21)00395-3

2. Rowland TA, Marwaha S. Epidemiology and risk factors for bipolar disorder. Ther Adv Psychopharmacol. 2018;8(9):251–269. doi:10.1177/2045125318769235

3. Cereda G, Enrico P, Ciappolino V, Delvecchio G, Brambilla P. The role of vitamin D in bipolar disorder: epidemiology and influence on disease activity. J Affect Disord. 2021;278:209–217. doi:10.1016/j.jad.2020.09.039

4. Peacock M. Calcium metabolism in health and disease. Clin J Am Soc Nephrol. 2010;5(Suppl 1):S23–S30. doi:10.2215/CJN.05910809

5. Bikle DD. Vitamin D: production, metabolism and mechanisms of action. In: Feingold KR, Ahmed SF, Anawalt B, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc.; 2021.

6. Lang F, Ma K, Leibrock CB. 1,25(OH)2D3 in brain function and neuropsychiatric disease. Neurosignals. 2019;27(1):40–49. doi:10.33594/000000182

7. Patrick RP, Ames BN. Vitamin D and the omega-3 fatty acids control serotonin synthesis and action, part 2: relevance for ADHD, bipolar disorder, schizophrenia, and impulsive behavior. FASEB J. 2015;29(6):2207–2222. doi:10.1096/fj.14-268342

8. Menéndez SG, Manucha W. Vitamin D as a modulator of neuroinflammation: implications for brain health. Curr Pharm Des. 2024;30(5):323–332. doi:10.2174/0113816128281314231219113942

9. Harrison PJ, Hall N, Mould A, Al-Juffali N, Tunbridge EM. Cellular calcium in bipolar disorder: systematic review and meta-analysis. Mol Psychiatry. 2021;26(8):4106–4116. doi:10.1038/s41380-019-0622-y

10. Smedler E, Abé C, Pålsson E, Ingvar M, Landén M. CACNA1C polymorphism and brain cortical structure in bipolar disorder. J Psychiatry Neurosci. 2020;45(3):182–187. doi:10.1503/jpn.190029

11. Chen HM, DeLong CJ, Bame M, Rajapakse I, Herron TJ, McInnis MG, O'Shea KS. Transcripts involved in calcium signaling and telencephalic neuronal fate are altered in induced pluripotent stem cells from bipolar disorder patients. Transl Psychiatry. 2014;4(3):e375. doi:10.1038/tp.2014.12

12. Moghaddam B, Bolinao ML, Stein-Behrens B, Sapolsky R. Glucocorticoids mediate the stress-induced extracellular accumulation of glutamate. Brain Res. 1994;655(1–2):251–254. doi:10.1016/0006-8993(94)91622-5

13. Berk M, Sanders KM, Pasco JA, Jacka FN, Williams LJ, Hayles AL, Dodd S. Vitamin D deficiency may play a role in depression. Med Hypotheses. 2007;69(6):1316–1319. doi:10.1016/j.mehy.2007.04.001

14. Laughlin GA, Kritz-Silverstein D, Bergstrom J, Reas ET, Jassal SK, Barrett-Connor E, McEvoy LK. Vitamin D insufficiency and cognitive function trajectories in older adults: the Rancho Bernardo Study. J Alzheimers Dis. 2017;58(3):871–883. doi:10.3233/JAD-161295

15. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018;169(7):467–473. doi:10.7326/M18-0850

16. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71

17. Altunsoy N, Yüksel RN, Cingi Yirun M, Kılıçarslan A, Aydemir Ç. Exploring the relationship between vitamin D and mania: correlations between serum vitamin D levels and disease activity in bipolar disorder. Nord J Psychiatry. 2018;72(3):221–225. doi:10.1080/08039488.2018.1424238

18. Astaneh AN, Jafari N, Sadighi G. Serum vitamin D, mania and depression-related scores: a comparison among mixed bipolar, mania, and healthy subjects. Iran J Psychiatry. 2024;19(3):265–273. doi:10.18502/ijps.v19i3.15803

19. İmre O, Karaağaç M, Caglayan C. Does decreased vitamin D level trigger bipolar manic attacks? Behav Sci (Basel). 2023;13(9):779. doi:10.3390/bs13090779

20. Li S, Xu X, Qiu Y, Teng Z, Liu J, Yuan H, et al. Alterations of vitamin D and cognitive function in first-diagnosed and drug-naïve BD patients: physical activity as a moderator. J Affect Disord. 2023;323:153–161. doi:10.1016/j.jad.2022.11.064

21. Li S, Qiu Y, Teng Z, Xu B, Tang H, Xiang H, et al. Research on biochemical indexes of bone metabolism in bipolar disorder: a cross-sectional study with newly diagnosed, drug-naïve patients. J Psychiatr Res. 2022;151:197–204. doi:10.1016/j.jpsychires.2022.04.015

22. Leser B, Dalkner N, Tmava-Berisha A, Fellendorf FT, Unterrainer HF, Stross T, et al. The influence of vitamin D status on cognitive ability in patients with bipolar disorder and healthy controls. Nutrients. 2023;15(19):4111. doi:10.3390/nu15194111

23. Van Rheenen TE, Ringin E, Karantonis JA, Furlong L, Bozaoglu K, Rossell SL, et al. A preliminary investigation of the clinical and cognitive correlates of circulating vitamin D in bipolar disorder. Psychiatry Res. 2023;320:115013. doi:10.1016/j.psychres.2022.115013

24. Späth Z, Tmava-Berisha A, Fellendorf FT, Stross T, Maget A, Platzer M, et al. Vitamin D status in bipolar disorder. Nutrients. 2023;15(22):4752. doi:10.3390/nu15224752

25. Zheng X, Neeraj D, Zhu Q, Zhang Y, Li T, Yang W, Guan N. Latent profile analysis of vitamin D and its association with depression severity of hospitalized patients with bipolar depression. Nutr Neurosci. 2024;27(12):1413–1421. doi:10.1080/1028415X.2024.2339739

26. Chen WY, Huang MC, Chiu CC, Cheng YC, Kuo CJ, Chen PY, Kuo PH. The interactions between vitamin D and neurofilament light chain levels on cognitive domains in bipolar disorder. BJPsych Open. 2022;8(6):e207. doi:10.1192/bjo.2022.608

27. Marsh WK, Penny JL, Rothschild AJ. Vitamin D supplementation in bipolar depression: a double-blind placebo-controlled trial. J Psychiatr Res. 2017;95:48–53. doi:10.1016/j.jpsychires.2017.07.021

28. Sikoglu EM, Navarro AA, Starr D, Dvir Y, Nwosu BU, Czerniak SM, et al. Vitamin D3 supplemental treatment for mania in youth with bipolar spectrum disorders. J Child Adolesc Psychopharmacol. 2015;25(5):415–424. doi:10.1089/cap.2014.0110

29. Steardo L Jr, Luciano M, Sampogna G, Carbone EA, Caivano V, Di Cerbo A, et al. Clinical severity and calcium metabolism in patients with bipolar disorder. Brain Sci. 2020;10(7):417. doi:10.3390/brainsci10070417

30. de Filippis R, D'Angelo M, Carbone EA, De Fazio P, Steardo L Jr. The mediation effect of peripheral biomarkers of calcium metabolism and chronotypes in bipolar disorder psychopathology. Metabolites. 2022;12(9):827. doi:10.3390/metabo12090827

31. Wakeman M. A literature review of the potential impact of medication on vitamin D status. Risk Manag Healthc Policy. 2021;14:3357–3381. doi:10.2147/RMHP.S316897

32. Spedding S. Vitamin D and depression: a systematic review and meta-analysis comparing studies with and without biological flaws. Nutrients. 2014;6(4):1501–1518. doi:10.3390/nu6041501

33. Kovacs Z, Vestergaard P, Licht RW, Straszek SPV, Hansen AS, Young AH, et al. Lithium induced hypercalcemia: an expert opinion and management algorithm. Int J Bipolar Disord. 2022;10(1):34. doi:10.1186/s40345-022-00283-3

34. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. J Chem Neuroanat. 2005;29(1):21–30. doi:10.1016/j.jchemneu.2004.08.006

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• OpenAI
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