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Serum BDNF levels in children and adolescents with bipolar disorder: a systematic review and meta-analysis

Short Title: Serum levels of bdnf in pediatric bipolar disorder

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ABSTRACT

Introduction: Recent evidence suggests that reduced peripheral levels of brain-derived neurotrophic factor (BDNF) may be involved in the pathophysiology of bipolar disorder (BD), although its relevance in young populations remains uncertain. This systematic review synthesized studies that evaluated serum BDNF levels in children and adolescents with BD, examining its potential as a risk marker.

Methods: Following PRISMA 2020 guidelines and a protocol registered in PROSPERO, searches were conducted in the Cochrane, MEDLINE, SciELO, and Scopus databases. Studies including participants aged 0–19 years diagnosed with BD according to DSM criteria were included. Studies with mixed samples (adults, children and adolescents) without separate age-group analyses were excluded.

Results: After screening and eligibility assessment, seven studies were included. Five of them included a control group, from which a meta-analysis was performed. Moderate methodological heterogeneity was observed and corrected after sensitivity analysis, reinforcing the robustness of the findings, although no statistically significant difference in serum BDNF levels was found between patients with bipolar disorder and controls.

Conclusion: Current evidence does not support BDNF as a diagnostic biomarker for pediatric BD. Future studies with greater sample power and methodological standardization are needed to clarify its role in the risk and course of early-onset bipolar disorder.

Keywords: Bipolar disorder; BDNF; child; adolescent.

1 INTRODUCTION

Bipolar disorder (BD) in childhood and adolescence has been less studied compared to adults and was significantly underdiagnosed for much of the 20th century [1]. However, early-onset BD is increasingly recognized as a serious public health problem, associated with disruption of the family environment, social impairment, poor academic performance, psychotic symptoms, substance use disorders, hospitalizations, and suicide attempts—or even suicide itself [1,2]. It is known that BD is the fourth leading cause of disability among adolescents [3], and family history is recognized as the best predictor of risk for the disorder in the pediatric population [2,4]. Undiagnosed children and adolescents with BD incur higher treatment costs compared to those correctly diagnosed. Due to the high rates of morbidity and mortality and the chronic nature of the disorder, early diagnosis and treatment are essential [1].

Recurrent episodes of hypomania or mania and depression, alternating with periods of euthymia, constitute one of the diagnostic criteria for the disorder [1]. It is a complex condition that can affect individuals of all ages but manifests differently in children and adults. Pediatric BD presents specific characteristics, such as longer episodes, a higher frequency of mixed states, marked irritability, and high rates of comorbidities with other disorders, including oppositional defiant disorder, attention-deficit/hyperactivity disorder, and substance use disorders [5,6].

Recent research suggests that BD is associated with alterations in neuroplasticity and cellular resilience, particularly in brain areas responsible for mood regulation [7]. Evidence points to inflammatory and immunological changes in both the brain and periphery. Brain-derived neurotrophic factor (BDNF) plays a fundamental role in this process, being essential for neuronal communication, brain connectivity, synaptic plasticity, neurogenesis, and dendritic growth. BDNF is found in high concentrations in the cerebral cortex and hippocampus—structures crucial for memory and emotional regulation. Furthermore, it can cross the blood-brain barrier, allowing its serum levels to reflect changes occurring in the brain [7,8].

Several studies in adult populations indicate that BDNF levels fluctuate according to mood polarity in BD. During manic or depressive episodes, a significant reduction in peripheral BDNF levels is observed, while in euthymia, there tends to be partial normalization. Patients in more advanced stages of the disease—marked by a greater number of episodes and functional impairment—exhibit persistently low BDNF levels, suggesting a neuroprogressive process associated with loss of plasticity over time [7,8,9]. Although this evidence predominantly derives from studies in adults, it is essential to determine whether similar patterns occur in children and adolescents, who have a shorter duration of illness, less exposure to stressors, and less use of medications [4].

BDNF has been associated with a wide range of neuropsychiatric and neurodegenerative disorders, and numerous meta-analyses have revealed reduced BDNF levels in mood disorders [10,11].

In contrast to research in adults, little is known about the relationship between BDNF and BD in pediatric populations. The utility of serum BDNF levels as a biological marker may differ between adults, children, and adolescents due to distinct neurobiological and developmental characteristics, as well as differences in clinical presentation [4,11].

Therefore, our objective is to contribute to the medical literature by specifically exploring the relationship between BDNF and bipolar disorder in children and adolescents. In this systematic review, we aim to answer the following question: Can BDNF act as a risk marker for BD in children and adolescents?

2 METHODS

2.1 Protocol and Guidelines

This systematic review was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)[12]. The complete PRISMA checklist was considered in the design, analysis, and reporting of the results. The protocol for this review was prospectively registered in PROSPERO (ID: CRD420251170347), which corresponds to the active and current registration governing the present systematic review and meta-analysis.

2.2 Research Question and PICO Framework

The research question was formulated according to the PICO acronym, which guided the definition of the main components of the review. P (Population): Children and adolescents (≤ 19 years) diagnosed with bipolar disorder according to DSM-IV or DSM-5 criteria, confirmed by structured interviews (K-SADS-PL and/or WASH-U-K- SADS). I (Intervention/Exposure): Presence of bipolar disorder. C (Comparison): Healthy control group, when available. O (Outcome): Serum levels of brain-derived neurotrophic factor (BDNF) measured by immunoassay (ELISA).

The primary outcome was the quantification of serum BDNF levels. The absence of a control group was not considered an exclusion criterion, as the main objective was to map and synthesize all available evidence on serum BDNF levels in pediatric populations with BD, given the scarcity of studies in the area. This decision was pre- specified in the protocol.

2.3 Search Strategy

Searches were conducted in the PubMed/MEDLINE, Scopus, SciELO, and Cochrane Library databases, without language restrictions, from the inception of the databases until April 8, 2024, and were subsequently updated on October 14, 2025, according to the optimized strategy described below. No filters (by study type, date, or language) or specific field codes (e.g., title or abstract) were applied, ensuring maximum search coverage. The strategy combined terms

related to three domains, using Boolean operators (AND, OR) and truncations () to increase sensitivity:

1. Population: ("child" OR "adolescen*" OR "teen*" OR "juvenil*" OR "young" OR "offspring*" OR "descend*" OR "kid*" OR "son*" OR "brood*")
2. Disorder: ("bipolar disorder*" OR "mood disorder*" OR "affective disorder*")
3. Biomarker: ("BDNF" OR "brain-derived neurotrophic factor" OR "neurotrophin*" OR "neurotrophic factor*")

The three sets were combined: (1) AND (2) AND (3).

2.4 Management of Records and Removal of Duplicates

All identified records were exported in .TXT, .CSV, or .BIB formats and imported into Rayyan (Qatar Computing Research Institute) for screening and reference management. Duplicate detection was performed automatically by Rayyan's internal algorithm, followed by independent manual verification by two reviewers. Disagreements were resolved with the assistance of a third senior reviewer.

The search was initially conducted on April 8, 2024, and subsequently updated on October 14, 2025, using the same optimized strategy. In total, 1,186 records were identified across both searches. Of these, 317 were recognized as duplicates (316 automatically and 1 manually) and removed, leaving 869 unique records for title and abstract screening.

During the updated search, one additional study was assessed at the full-text level but excluded for including mixed samples of adolescents and young adults without stratified age analysis (≤ 19 years). The updated search did not yield any additional eligible studies.

The updated search was conducted as a surveillance search aimed at identifying newly published studies after the initial comprehensive search and was not intended to replicate the original identification process. Therefore, the PRISMA 2020 flowchart represents the final study selection after both searches, in accordance with PRISMA 2020 recommendations (Figure 1).

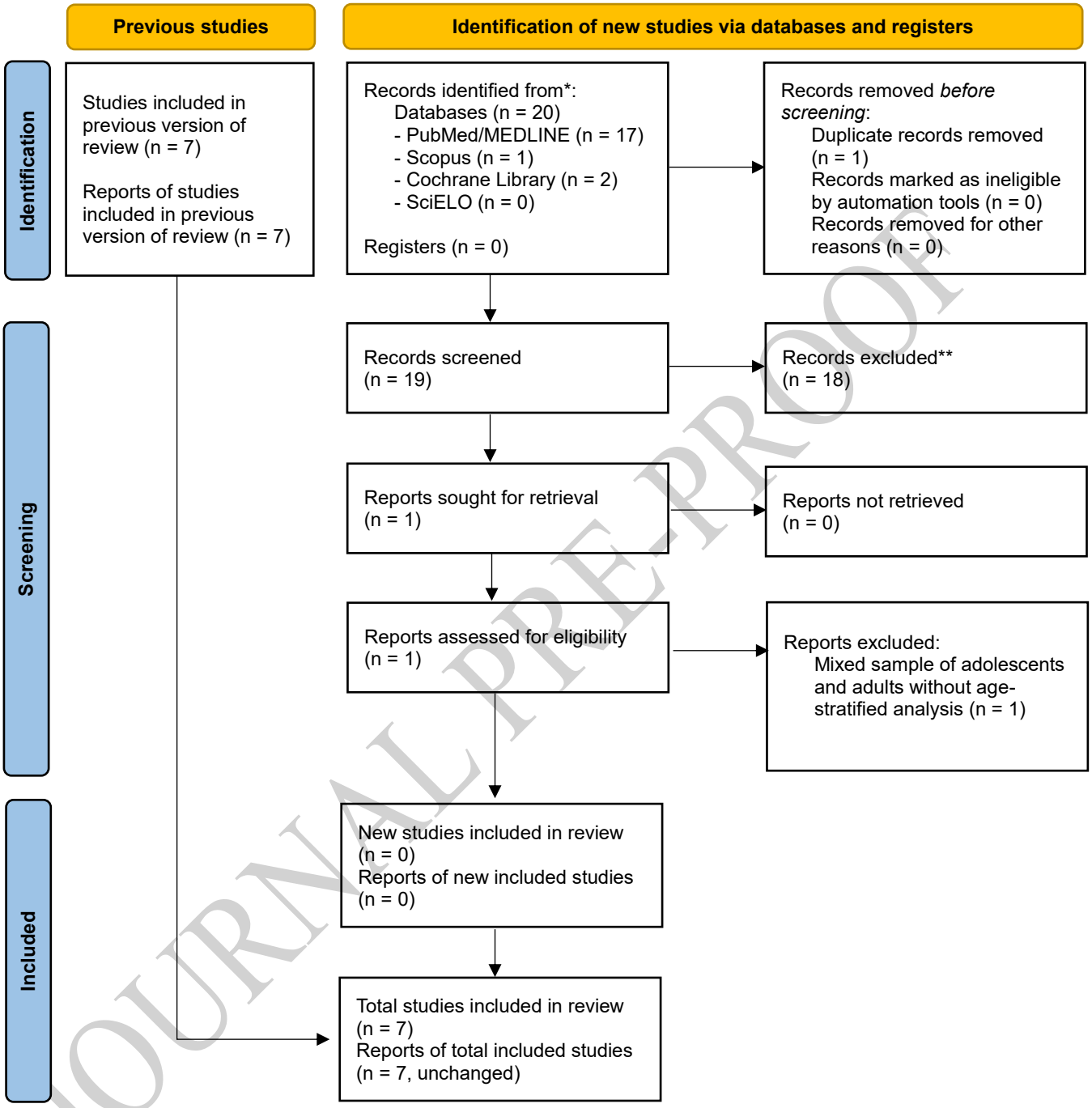

Figure 1. Flowchart illustrating the study selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020). This flowchart represents the updated surveillance search conducted on October 14, 2025, following an initial comprehensive search performed on April 8, 2024. The updated search did not identify additional eligible studies, and the total number of included studies remained unchanged (n = 7).

2.5 Screening and Eligibility

Screening was conducted in two sequential phases: (1) reading of title and abstract, followed by (2) full-text evaluation for final eligibility. Both stages were performed by two independent reviewers; in case of disagreement, a third senior reviewer was consulted, and consensus was reached through discussion.

2.6 Inclusion Criteria

Studies were included that:

• Had an observational design (cross-sectional, case-control, or longitudinal);

• Assessed serum BDNF levels in children and/or adolescents with BD;

• Used DSM-IV or DSM-5 criteria confirmed by structured instruments (K-SADS-PL, WASH-U-K-SADS);

• Measured BDNF by ELISA (expressed in pg/mL or ng/mL);

• Provided quantitative data (mean ± SD, standard error, or median ± interquartile range) or extractable values from figures;

• Had a sample with a maximum age of ≤ 19 years;

• Included or did not include a healthy control group.

2.7 Exclusion Criteria

Studies were excluded that:

• Measured BDNF in plasma, platelets, or cerebrospinal fluid without serum data;

• Did not provide numerical or extractable graphical data;

• Involved mixed samples (adults + children/adolescents) without separate age-group analysis;

• Included only at-risk populations (offspring of patients with BD without confirmed diagnosis);

• Were reviews, case reports, editorials, letters, protocols, or conference abstracts;

• Duplicated publications from the same sample—retaining only the most complete one.

2.8 Data Extraction

Data extraction was conducted by two independent reviewers using a standardized spreadsheet. The following were collected: lead author, year, country, study design, total and group-specific sample size (BD and controls), mean age ± SD, sex distribution, diagnostic instrument, mean age of onset, clinical phase at the time of collection (euthymia, mania, depression), medication use, type of biological sample, BDNF assay method, unit of measurement, and quantitative results. When values were only available in figures, they were extracted digitally using WebPlotDigitizer (v 4.6) with calibration based on axes and units. Means and SDs were converted from medians and interquartile ranges according to Wan et al. (2014) and Luo et al. (2018) [13],[14]—a widely validated method in meta-analyses, with an average error of < 5%.

2.9 Assessment of Methodological Quality

The quality of the studies was assessed using the Newcastle–Ottawa Scale (NOS), considering three domains: selection, comparability, and outcome assessment. NOS scores were not used as an exclusion criterion but were considered in the interpretation of results. Individual scores are presented in Table S1.

2.10 Missing Data and Author Contact

When essential information (e.g., mean or SD) was unavailable, or when the full text could not be obtained, corresponding authors were contacted by email. In the absence of a response within four weeks, the study was classified as unrecoverable and excluded, with the reason indicated in the PRISMA flowchart.

2.11 Data Synthesis

Given the methodological heterogeneity (presence of a control group, clinical phase, medication use), the results were synthesized in two complementary ways: Qualitative synthesis (descriptive): Included the seven eligible studies. Quantitative synthesis (meta-analysis): Restricted to the five studies with a control group, allowing the calculation of the standardized mean difference

(Hedges' g, with correction for small samples) between the BD and control groups.

When studies reported medians and interquartile ranges, values were converted to means and SDs according to Wan et al. (2014) and Luo et al. (2018) [13,14]. All BDNF values were standardized to pg/mL (1 ng/mL = 1,000 pg/mL). Meta-analyses used a random-effects model with the REML estimator for τ^2. Heterogeneity was quantified by Q, τ^2, and I^2. Uncertainty was expressed as 95% CI and two-tailed p-values. Sensitivity analyses included (i) one-by-one removal (leave-one-out) and (ii) targeted exclusion of Baykara 2020 (due to the 1:50 dilution protocol in ELISA). Forest plots were generated in Python (matplotlib). The significance level adopted was $\alpha = 0.05$. Due to the small number of studies ($k < 10$), publication bias was not assessed using a funnel plot.

3 RESULTS

A total of 340 participants (217 patients with bipolar disorder and 123 healthy controls) were included in this systematic review. One study presented two cohorts with overlapping samples; therefore, only the publication with more complete BDNF data was retained [15]. Table 1 presents the general characteristics of the included studies. Six studies used a cross-sectional/case-control design (Cevher Binici 2016; İnal-Emiroğlu 2015; İnal 2023; Baykara 2020; Peruzzolo 2015; Goldstein 2011), and one study had a longitudinal repeated-measures design [16]. All measured serum BDNF by ELISA, with units standardized to pg/mL. The only exception was Peruzzolo et al. (2015), which expressed BDNF in pg/μg of protein, not directly comparable to the other concentrations.

3.1 Sample and Clinical Characteristics

Sample sizes ranged from 27 to 79 participants. All studies included children and adolescents ≤ 19 years, and five included a healthy control group. The diagnosis of BD was predominantly confirmed by K-SADS-PL (or WASH-U-K-SADS) according to DSM-IV or DSM-5 criteria. In all controlled studies, a portion of the patients was using psychotropic medications (77%–97%), mainly lithium, valproate, and second- generation antipsychotics. The timing of BDNF

collection varied between studies. Two studies collected samples during symptomatic periods: Karthikeyan et al. (2022) analyzed the “most severe symptomatic interval,” and Goldstein et al. (2011) evaluated participants in different mood polarities (mania/hypomania, depression, mixed state, or euthymia). In the other case-control studies (İnal 2023; Baykara 2020; Cevher Binici 2016; İnal-Emiroğlu 2015) and the case series study (Peruzzolo 2015), collection occurred during euthymia. The mean age of participants ranged from 13.9 ± 3.0 to 17.3 ± 1.5 years. The demographic and clinical characteristics of each study are detailed in Table 1.

3.2 Serum BDNF Levels (Descriptive Synthesis)

Five studies provided means and standard deviations of BDNF in BD patients and controls, allowing meta-analysis. Mean serum BDNF values varied widely, reflecting methodological heterogeneity (differences in ELISA kits, dilution protocols, and clinical phases):

• Baykara 2020: 18,000 ± 8,000 pg/mL (BD) vs 28,000 ± 12,000 pg/mL (controls)
• İnal-Emiroğlu 2015: 1,735 ± 899 pg/mL (BD) vs 2,000 ± 1,160 pg/mL (controls)
• İnal 2023: 1,724 ± 1,316 pg/mL (BD) vs 2,267 ± 1,603 pg/mL (controls)
• Cevher Binici 2016: 1,156 ± 245 pg/mL (in both groups)
• Karthikeyan 2022: 247 ± 153 pg/mL (BD) vs 252 ± 145 pg/mL (controls).

In the two studies without a control group, Goldstein 2011 reported a mean of 25,800 ± 5,800 pg/mL (varying by mood phase), and Peruzzolo 2015 reported 19.6 ± 6.3 pg/µg of protein, not comparable after standardization.

3.3 Methodological Quality (NOS)

Assessment using the Newcastle–Ottawa Scale (NOS) indicated moderate to high quality, with scores ranging from 4 to 7 (maximum 9). Assessments by domain (selection, comparability, and outcome) are presented in Table S1. No study presented a critical risk of bias that justified exclusion.

3.4 Quantitative Synthesis (Meta-Analysis)

The meta-analysis combined five studies with a control group (total = 282 participants; BD = 155; control = 127). Using a random-effects model (REML)

and standardized mean difference (Hedges' g), no significant difference in serum BDNF levels was found between BD and controls (Hedges' g = −0.34; 95% CI −0.71 to 0.04; p > 0.05). Heterogeneity was moderate (I^2 = 58.7%, τ^2 = 0.10478) (Figure 2). To test robustness, a sensitivity analysis was performed excluding Baykara et al. (2020)— which used a 1:50 dilution protocol in ELISA and discrepant values. After exclusion, the pooled effect remained non-significant (Hedges' g = −0.15; 95% CI −0.42 to 0.12), with no heterogeneity (I^2 = 0%, τ^2 = 0) (Figure 3). This indicates that the observed heterogeneity mainly resulted from methodological differences in that study, keeping the overall conclusion stable. Individual effects were:

• İnal-Emiroğlu 2015: g = −0.26 (95% CI −0.79; 0.28)
• Cevher Binici 2016: g = 0.00 (95% CI −0.60; 0.60)
• Baykara 2020: g = −1.00 (95% CI −1.50; −0.50)
• Karthikeyan 2022: g = −0.03 (95% CI −0.49; 0.42)
• İnal 2023: g = −0.37 (95% CI −0.99; 0.25).

The leave-one-out analysis did not alter the direction or significance of the overall effect, reinforcing the consistency of the findings.

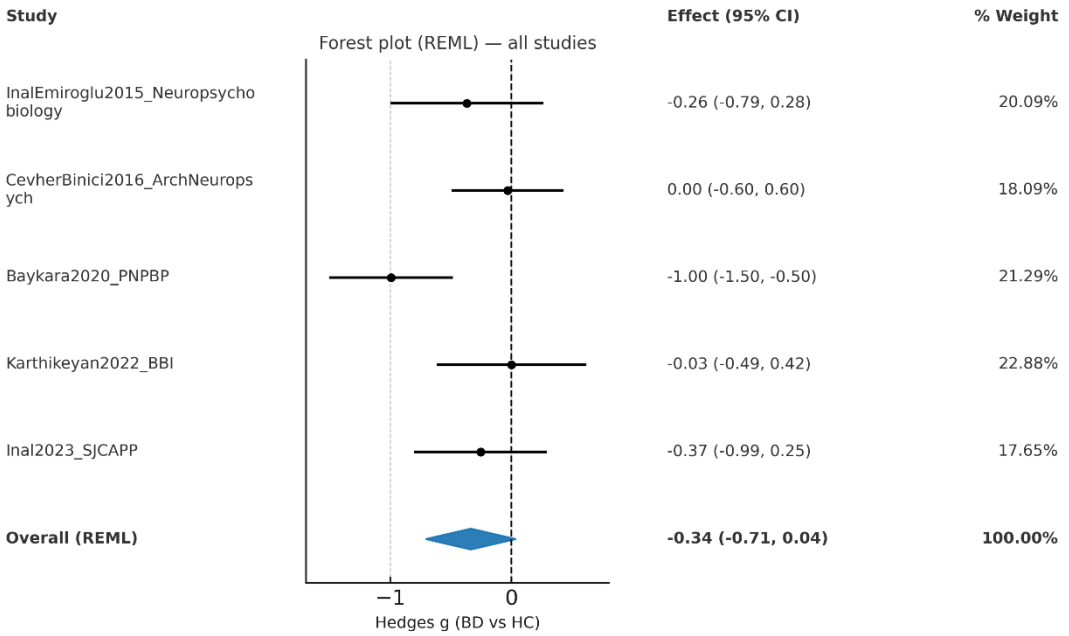

Figure 2 -

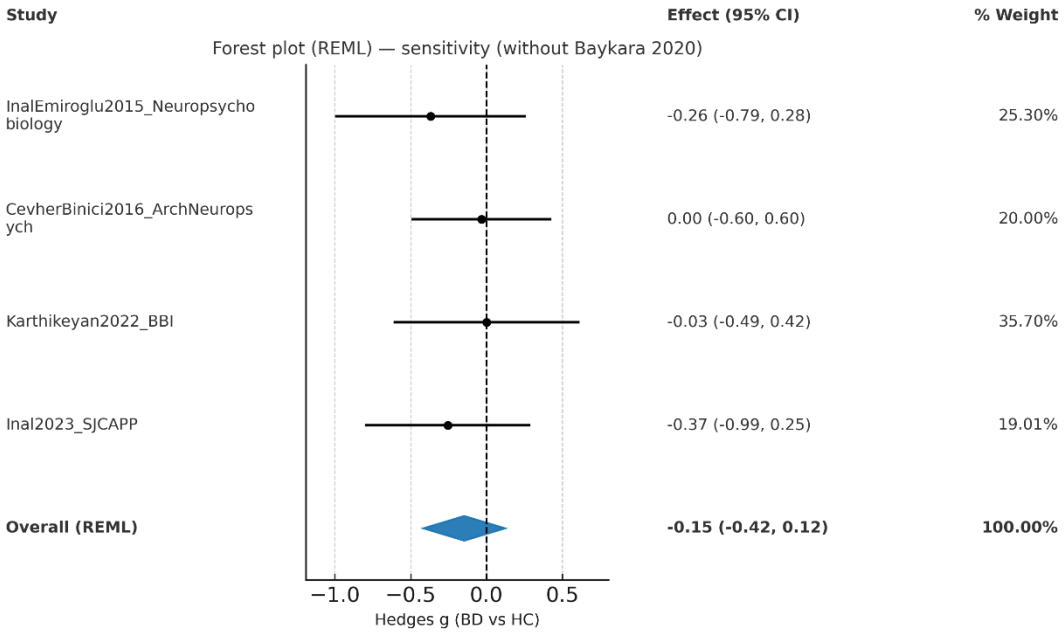

Figure 3 -

3.5 General Synthesis of Findings

The results suggest no significant difference in serum BDNF levels between adolescents with BD and healthy controls. The trend toward lower values in patients—especially in euthymic samples—may reflect subtle neuroplasticity alterations associated with the disorder. Moderate heterogeneity underscores the importance of standardizing laboratory protocols and controlling for medication use and disease phase in future studies.

4 DISCUSSION

To our knowledge, this is the first systematic review with meta-analysis to exclusively evaluate serum BDNF levels in children and adolescents with bipolar disorder (BD). Despite the limited number of available studies, synthesizing these findings is essential for delineating the initial neurobiological characteristics of BD and guiding the design of future research in the pediatric population. Far from being a limitation, the scarcity of data underscores the need for systematic efforts like this one, which allow the identification of

methodological gaps and the establishment of guidelines for subsequent studies.

Interpretation of Main Findings and Potential Biases

This meta-analysis, which combined five studies with a control group, found no statistically significant differences in serum BDNF levels between bipolar patients and controls (Hedges' g = −0.34; 95% CI −0.71 to 0.04). However, the trend toward lower BDNF levels among patients—especially in euthymic samples—is consistent with the hypothesis of subtle neurotrophic dysfunction even in the early stages of the disorder[10,18,7,8].

The moderate heterogeneity observed (I^2 = 58.7%) appears to stem mainly from methodological discrepancies between studies. After excluding Baykara et al. (2020)—which used a 1:50 dilution protocol in ELISA—the combined effect became homogeneous (I^2 = 0%), without altering the direction of the results. This sensitivity analysis reinforces the robustness of the findings and highlights the importance of laboratory standardization in future research.

The Baykara et al. study warrants attention due to its atypical dilution protocol, which likely contributed to the observed heterogeneity. Similar inconsistencies—such as variations in sample handling, storage time, and assay calibration—have been associated with large fluctuations in BDNF concentrations and may explain divergent findings between studies [19].

Another potential bias is related to medication use, particularly lithium. Although Cevher Binici et al. (2016) reported lower serum BDNF levels among patients using lithium, this finding contrasts with most of the literature, which points to a neurotrophic effect and increased BDNF expression induced by lithium [20–24]. Lithium increases BDNF expression by inhibiting GSK-3β and activating the CREB–BDNF pathway, promoting neuroplasticity and neuroprotection. Thus, the paradoxical reduction observed may reflect small sample size, concomitant use of other medications, or the predominance of euthymic samples, as BDNF levels tend to normalize outside acute episodes [10].

Another methodological limitation should be acknowledged. Although PRISMA 2020 emphasizes reporting reasons for exclusion primarily at the full-text screening stage to enhance transparency and reproducibility, exclusion reasons

at the title and abstract screening stage were not categorized in the present study.

BDNF in Pediatric vs. Adult Populations

In adults, several meta-analyses have demonstrated reduced peripheral BDNF levels during depressive and manic episodes, with an inverse correlation with symptom severity and partial normalization during euthymia[10,11,27]. These findings have been interpreted within a neuroprogressive model of the disorder, in which repeated mood episodes, cumulative psychosocial stress, inflammatory activation, and oxidative imbalance contribute to the progressive loss of neurotrophic support mechanisms[7,8,22,23]. In contrast, the absence of significant differences in pediatric samples may reflect distinct neurobiological and developmental processes. Childhood and adolescence are characterized by ongoing brain maturation, pronounced synaptic remodeling, and greater activity-dependent neuroplasticity, processes in which BDNF–TrkB signaling plays a central role[7,23]. This heightened neuroplastic state, together with shorter illness duration and a lower cumulative neuroprogressive burden, may attenuate detectable peripheral alterations in BDNF levels during the early phases of bipolar disorder[8,9,22].

Nevertheless, evidence from high-risk populations adds important nuance to this interpretation. Prospective studies in offspring of parents with bipolar disorder have reported lower baseline serum BDNF levels compared with controls, even before the clinical onset of mood symptoms[28,29]. These findings support the hypothesis that subtle neurotrophic alterations may precede symptomatic manifestation and interact with neurodevelopmental trajectories, in line with neurodevelopmental models of bipolar disorder.

From a biological and regulatory perspective, it is also important to note that peripheral BDNF levels are influenced by a complex interplay of transcriptional regulation, intracellular signaling pathways, and systemic physiological factors. BDNF is synthesized as a precursor (proBDNF) and subsequently cleaved into its mature form, exerting distinct biological effects mediated by differential receptor binding, particularly to TrkB and p75NTR. Activation of the BDNF–TrkB pathway triggers downstream intracellular signaling cascades, including the MAPK/ERK, PI3K/Akt, and PLCγ pathways, which are critically involved in

synaptic plasticity, neuronal survival, and activity-dependent remodeling. Dysregulation of these pathways has been implicated in bipolar disorder and may underlie the neuroplasticity deficits observed in this condition[30].

Broader Determinants of BDNF Levels and Future Perspectives

In addition to diagnosis and medication use, several factors influence serum BDNF concentrations, such as physical activity, body mass index, smoking, circadian rhythm, and inflammatory state [31,32]. Most pediatric studies did not control for these variables, which may mask subtle differences between groups. Future research should control for these factors and conduct phase-specific analyses (mania, depression, euthymia), ideally with longitudinal designs capable of capturing the individual dynamics of BDNF over time.

Despite methodological heterogeneity, this review reinforces that BDNF remains a potentially relevant biomarker of neuroplasticity in pediatric BD. Progress in this field depends on new studies that: employ standardized and detailed ELISA protocols; control for medication exposure and physical activity levels; stratify by mood phase and disease duration; and investigate genetic and epigenetic regulation of BDNF. It is highlighted as one of the most promising biomarkers in BD, although its clinical applicability is still limited by study heterogeneity and the scarcity of pediatric research[30].

In this sense, our systematic review partially fills this gap, synthesizing the available evidence on serum BDNF levels in children and adolescents with BD—a field still in its infancy but of great relevance for understanding brain plasticity. This review provides a foundation for future advances, highlighting the urgency of longitudinal studies with larger samples and methodological alignment to investigate developmental dynamics and possible early alterations associated with BD.

5 CONCLUSION

In summary, our findings suggest that additional studies in this specific population are needed to evaluate BDNF as a potential neurodevelopmental biomarker across the lifespan. The quantification of serum BDNF levels in cases of bipolar disorder in childhood and adolescence may represent a promising approach for future dimensional diagnostic strategies, especially if

conducted in larger and methodologically standardized samples. Longitudinal investigations that consider the different phases of the disorder, medication use, and environmental factors modulating BDNF expression are essential to elucidate its role in the trajectory of neuroplasticity and the clinical course of bipolar disorder. Thus, understanding the dynamics of BDNF from early stages may not only contribute to understanding pathophysiological mechanisms but also guide preventive and personalized interventions in developmental psychiatry.

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Supplementary Material

Table S1. Methodological quality assessment according to the Newcastle–Ottawa Scale (NOS)

Study ID	Country	Design	S1	S2	S3	S4	C1	C2	E1	E2	E3	Total (Stars)	Quality Level
Inal 2023 (SJCAPP)	Turkey	Case-control	★	★	★	★	★	-	★	★	-	7 / 9	Good Quality (Low Risk of Bias)
Karthikeyan 2022 (BBI)	Canada	Longitudinal (case-control)	★	★	★	-	★	-	★	★	-	6 / 9	Moderate Quality (Low–Moderate Risk of Bias)
Baykara 2020 (PNPBP)	Turkey	Case-control	★	★	★	-	★	-	★	★	-	6 / 9	Moderate Quality (Low–Moderate Risk of Bias)
Cevher Binici 2016 (Arch Neuropsych)	Turkey	Case-control	★	★	★	-	★	-	★	★	-	6 / 9	Moderate Quality (Low–Moderate Risk of Bias)
Inal-Emiroglu 2015 (Neuropsychobiology)	Turkey	Case-control	★	★	★	-	★	-	★	★	-	6 / 9	Moderate Quality (Low–Moderate Risk of Bias)
Peruzzolo 2015 (Neural Plasticity)	Brazil	Case series (NOS adapted)	★	★	N/A	N/A	N/A	-	★	N/A	★	4 / 9	Limited Quality (Moderate Risk of Bias)
Goldstein 2011 (J Child Adolesc Psychopharmacol)	USA/Canada	Cross-sectional (NOS adapted)	★	★	N/A	N/A	N/A	-	★	N/A	★	4 / 9	Limited Quality (Moderate Risk of Bias)

Note: Adapted NOS applied for studies without a control group (Peruzzolo 2015, Goldstein 2011). Items dependent on comparators (control selection/definition, group comparability, and non-response rate) were marked as N/A.