

Serum C-Reactive Protein (CRP) Titres in Bipolar Disorder: Systematic Review

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Abstract:

Background: Bipolar disorder (BD) is a severe psychiatric illness linked to chronic inflammation, with elevated C-reactive protein (CRP) levels frequently reported, although findings across studies remain inconsistent. This systematic review synthesized evidence from 18 eligible studies, identified through a comprehensive search of Scopus, PubMed, and Web of Science (2010–2025), to evaluate CRP as a potential biomarker in BD and to explore its associations with disease phases, comorbidities, and other psychiatric disorders. The included cross-sectional, case-control, and cohort studies measured CRP in BD populations compared with healthy or psychiatric controls. Overall, CRP titers were consistently higher in BD than in healthy controls, with some studies indicating peak elevations during manic episodes. Comparisons with schizophrenia and depression yielded mixed findings, suggesting that inflammation may not be specific to BD. Methodological heterogeneity, inconsistent adjustment for confounding factors such as metabolic comorbidities and medication use, and a predominance of cross-sectional designs limited interpretability. Notably, only one large cohort study linked elevated CRP levels to subsequent BD onset, pointing to possible predictive value. These findings support the role of CRP in BD pathophysiology, yet its diagnostic or prognostic utility remains uncertain. Further longitudinal research using standardized methodologies is needed, and therapeutic strategies targeting inflammation may hold promise if confounding influences are adequately addressed.

Keywords: C - reactive protein, Bipolar Disorder, Schizophrenia.

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Introduction

Bipolar disorder (BD) is a chronic psychiatric illness affecting over 1% of the global population and is marked by recurrent episodes of mania and depression that disrupt daily functioning and impair quality of life ⁽¹⁾. Even during remission, subsyndromal mood symptoms often persist, contributing to cognitive deficits and reduced psychosocial performance ^(2, 3).

Mounting evidence suggests that chronic low-grade inflammation may play a key role in BD pathophysiology, potentially disrupting neurochemical pathways involved in mood regulation and cognition ⁽⁴⁾. Elevated levels of pro-inflammatory markers, particularly C-reactive protein (CRP), have been consistently reported in individuals with BD ⁽⁵⁾. CRP, an acute-phase protein produced by the liver, is a stable and routinely measured biomarker of systemic inflammation ^(6, 7). In healthy individuals, CRP levels are usually below 3 mg/L but can exceed 10 mg/L during inflammatory responses ⁽⁷⁾. In BD, increased CRP levels—especially during acute mood episodes—have been linked to greater symptom severity, cognitive impairments, and overall disease burden ^(5, 8).

Early-life inflammation has also been implicated in the development of psychiatric disorders, with elevated levels of pro-inflammatory cytokines, particularly interleukin-6 (IL-6), during childhood associated with a higher risk of later mood and psychotic disorders ⁽⁹⁾. Peripheral inflammatory signals can activate microglia and influence neuronal pathways, affecting neurotransmitter regulation, synaptic plasticity, and stress hormone (cortisol) activity, all of which are critical for mood regulation and cognitive functioning. These findings support the use of peripheral biomarkers such as CRP to capture the neuroimmune processes that may contribute to the onset and progression of BD ⁽¹⁰⁾.

Previous studies have linked elevated baseline CRP levels to an increased risk of developing psychiatric conditions such as schizophrenia (SCZ) and post-traumatic stress disorder (PTSD) ^(11,12). While these findings highlight the broader relevance of inflammation in mental health, most research to date has focused on SCZ and major depressive disorder (MDD). In contrast, the role of inflammatory markers like CRP in bipolar disorder (BD) remains less clearly synthesized and warrants a systematic review to clarify their potential contribution to the disorder's pathophysiology and clinical course ⁽¹³⁾.

1. Bipolar disorder

Bipolar disorder (BD) is a chronic, recurrent psychiatric illness characterized by alternating episodes of depression and mania or hypomania, leading to marked impairment in functioning and quality of life. It encompasses BD-I, BD-II, cyclothymic disorder, and other specified or unspecified bipolar-related disorders. The ICD-11 and DSM-5 both classify these conditions under “bipolar and related disorders,” promoting diagnostic consistency ^(14,15). Globally, BD affects an estimated 40 million people, with lifetime prevalence rates around 1% for BD-I and BD-II each ^(16–18).

❖ Etiopathogenesis

BD arises from complex interactions among genetic vulnerability, epigenetic modifications, neurobiological abnormalities, and environmental stressors. Familial aggregation is strong, and neuroimaging studies have shown structural and functional brain alterations, including reduced subcortical volumes, cortical thinning, and disrupted network connectivity. Dysregulation of neurotrophic factors (e.g., BDNF), mitochondrial dysfunction, oxidative stress, and HPA axis abnormalities have also been implicated. Increasing evidence supports a role for neuroinflammatory mechanisms: psychosocial stress can activate immune-inflammatory pathways, prompting the release of cytokines such as

TNF- α and IL-6, which may cross the blood–brain barrier and influence mood-related neural circuits^(19–22).

❖ **Clinical Features and Diagnosis**

BD usually begins before age 25 and follows a recurrent course of depressive and manic/hypomanic episodes. Depressive episodes often predominate and are the major source of disability, while manic episodes can be severe enough to require hospitalization. Diagnosis is clinical, based on DSM-5 criteria, and can be challenging due to overlapping symptoms with other disorders (e.g., unipolar depression, ADHD, borderline personality disorder, PTSD). Misdiagnosis and delayed recognition are common and contribute to poorer outcomes. BD is associated with high suicide risk and increased cardiovascular morbidity, partly related to systemic inflammation and medication side effects^(23–26).

❖ **Management**

Management of bipolar disorder (BD) typically involves mood stabilizers (e.g., lithium, valproate, lamotrigine), second-generation antipsychotics (e.g., quetiapine, olanzapine, lurasidone), and adjunctive psychotherapies such as psychoeducation, cognitive-behavioral therapy, and interpersonal and social rhythm therapy to improve adherence and reduce relapse⁽²³⁾. While treatment details are beyond the scope of this review, it is important to note that several widely used psychotropic medications can influence systemic inflammation and metabolic health—particularly antipsychotics and mood stabilizers, which may contribute to weight gain, insulin resistance, and cardiovascular risk. These medication-related effects should be considered when interpreting inflammatory biomarker findings in BD^(27–29).

2. CRP

CRP is a pentameric acute-phase protein predominantly synthesized by the liver in response to pro-inflammatory cytokines, especially interleukin-6 (IL-6). Initially

identified for its ability to bind the “C” polysaccharide of the pneumococcal capsule, CRP has become a widely used marker of systemic inflammation, with serum levels rising rapidly and markedly during inflammatory episodes. Its biological half-life is stable (approximately 19 hours), and circulating concentrations are determined almost entirely by synthesis rate, making it a reliable and reproducible measure of inflammatory activity. Because CRP can be measured quickly, inexpensively, and accurately using standardized assays routinely available in clinical laboratories, it is one of the most accessible and scalable inflammatory biomarkers⁽³⁰⁾.

Importantly, high-sensitivity CRP (hs-CRP) assays can detect subtle, low-grade inflammation at levels well below those seen in overt infection or injury. This sensitivity is especially valuable in psychiatric research, where inflammatory activation is often mild and chronic rather than acute. Unlike many cytokines, which show high intraindividual variability and require specialized handling, CRP remains stable in stored samples and exhibits low diurnal variation, further supporting its use in large epidemiological and longitudinal studies. These methodological advantages, combined with its responsiveness to IL-6-driven inflammatory pathways, make CRP a practical and informative biomarker for investigating the role of inflammation in psychiatric disorders, including BD⁽³¹⁾.

❖ **C-Reactive Protein in Bipolar Disorder**

BD is a chronic, disabling psychiatric condition that typically begins in adolescence or early adulthood, with nearly 60% of affected individuals experiencing their first mood episode during these early life stages. For many, BD persists across the lifespan, underscoring the need for early detection and prognostic markers. In this context, there is growing interest in inflammatory biomarkers such as CRP, given mounting evidence that immune dysregulation

contributes to BD pathophysiology and clinical presentation⁽³²⁾. Beyond psychiatric symptoms, BD is frequently associated with cardiovascular and metabolic comorbidities, conditions strongly linked to chronic low-grade inflammation and often exacerbated by lifestyle factors and certain psychotropic medications⁽³³⁾. Dysregulation of the autonomic nervous system, manifesting as HPA axis hyperactivity, sympathetic overdrive, and reduced heart rate variability, may interact with immune pathways to sustain this pro-inflammatory state, which contributes to both psychiatric symptoms and physical health burden in BD^(34,35). These findings highlight CRP as a strategically useful biomarker to explore inflammatory processes that bridge mental and physical health outcomes in BD.

Methods

A comprehensive and methodologically rigorous literature search was undertaken using three major scientific databases: PubMed, Scopus, and Web of Science. The search encompassed studies published between 2010 and July 2025. A strategic combination of keywords was employed, including “C-reactive protein,” “CRP,” or “hs-CRP” in conjunction with “bipolar disorder,” “BD,” or “mania.” All retrieved bibliographic records were exported into a reference management tool for initial screening, which was based on the evaluation of titles and abstracts. Furthermore, the reference lists of all eligible articles were manually examined to identify any additional relevant studies potentially overlooked in the electronic search.

Inclusion criteria were clearly defined and applied as follows: (1) studies involving human participants with a confirmed clinical diagnosis of bipolar disorder; (2) investigations reporting serum or plasma CRP levels; (3) observational (cross-sectional, cohort, or case-control) or interventional clinical designs; and (4) inclusion of at least one comparator group,

such as healthy individuals or patients diagnosed with alternative psychiatric conditions.

Studies were excluded if they met any of the following criteria: (1) non-original works including case reports, narrative reviews, editorials, or expert commentaries; (2) lack of specific CRP data; (3) publications not written in English; or (4) research conducted in animal models or in vitro environments.

For each study that met the inclusion criteria, essential data were systematically extracted. These included authorship, year of publication, study design, total sample size, and detailed information about diagnostic categories. The extracted data were organized into a structured review matrix to support qualitative synthesis and facilitate comparative analysis across the included studies.

The selection process adhered strictly to the PRISMA 2020 guidelines. A total of 414 citations were initially retrieved from the database search: PubMed (n=32), Scopus (n=270), and Web of Science (n=112). Following the removal of 138 duplicate records and 17 entries excluded for other reasons (e.g., incomplete bibliographic information or non-English language), a total of 259 unique records remained for title and abstract screening (**Figure 1**).

During this initial screening phase, 181 articles were excluded for failing to meet the preliminary inclusion criteria, most commonly due to irrelevant focus (e.g., unrelated to BD or CRP), use of animal models, or being review articles lacking original empirical data. The remaining 78 articles were selected for full-text assessment.

Following full-text review, 38 studies were excluded for not meeting the key inclusion parameters, such as failure to report CRP levels, absence of a comparator group, or insufficient diagnostic clarity for bipolar disorder. An additional 22 studies were eliminated due to inadequate data reporting or methodological limitations

that precluded reliable data extraction and quality evaluation.

Ultimately, 18 studies satisfied all predefined inclusion criteria and were incorporated into the qualitative synthesis.

These studies collectively underpin the comparative evaluation of serum CRP titres in individuals with BD across diverse clinical and research contexts (**Table 1**).

Table 1: Studies on CRP in Bipolar Disorder

Author(s)	Year	Study Design	Sample Size & Groups
Aksoy and co-authors ⁽³⁶⁾	2010	Cross-sectional study	BD+ADHD: 30; BD: 30; Healthy controls: 30
Vuksan-Cusa co-authors ⁽³⁷⁾	2010	Cross-sectional study	BD: 60; Schizophrenia: 63
Goldstein co-authors ⁽³⁸⁾	2011	Cross-sectional study	BD (adolescents): 30
Hope co-authors ⁽³⁹⁾	2011	Cross-sectional study	BD: 112; Schizophrenia: 153; Healthy controls: 239
Goldstein co-authors ⁽⁴⁰⁾	2015	Retrospective cohort study	BD: 123
Wysockiński co-authors ⁽⁴¹⁾	2015	Cross-sectional study	BD: 146; Schizophrenia: 485; Depression: 319
Wium-Andersen co-authors ⁽⁴²⁾	2016	Population-based cohort	General population (N=78,809)
Wang co-authors ⁽⁴³⁾	2016	Cross-sectional study	BD I: 234; BD II: 260; Other BD: 243; Healthy controls: 140
Tanaka co-authors ⁽⁴⁴⁾	2017	Case-control study	BD: 25; Healthy controls: 25
Lee co-authors ⁽⁴⁵⁾	2018	Prospective cohort study	BD: 541
Frye co-authors ⁽⁴⁶⁾	2019	Case-control study	BD: 1207; Healthy controls: 745
Evers co-authors ⁽⁴⁷⁾	2019	Cross-sectional study	BD: 221
Lyu co-authors ⁽⁴⁸⁾	2021	Cross-sectional study	BD: 1901; Schizophrenia: 1659; Depression: 1521
Zou co-authors ⁽⁴⁹⁾	2022	Cross-sectional study	BD (asymptomatic): 48; BD (symptomatic): 39; Healthy controls: 67
Huang co-authors ⁽⁵⁰⁾	2022	Case-control study	BD: 77; Healthy controls: 61
Chen co-authors ⁽⁵¹⁾	2023	Cross-sectional study	BD: 35; Schizophrenia: 26; Depression: 29; Healthy controls: 22
Aytekin co-authors ⁽⁵²⁾	2024	Case-control study	BD: 36; Healthy controls: 41
Petrovic co-authors ⁽⁵³⁾	2025	Cross-sectional study	BD: 93; Healthy controls: 84

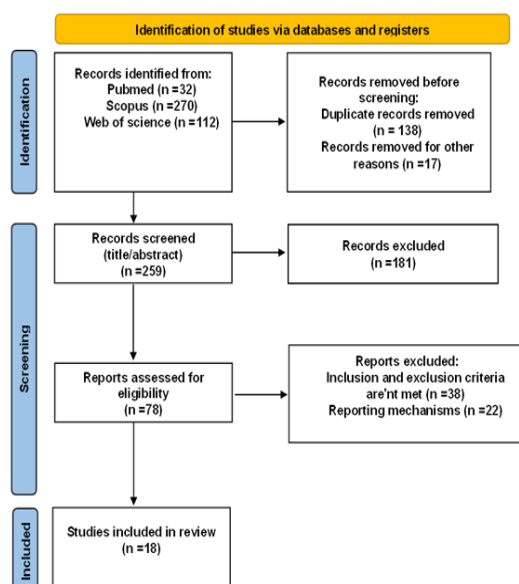


Figure 1: PRISMA Flowchart of the Studies on CRP in Bipolar Disorder

Results

The initial database search resulted in 414 records: 32 from PubMed, 270 from Scopus, and 112 from Web of Science. After removing 138 duplicate entries and excluding 17 additional records due to administrative or technical discrepancies, a total of 259 unique records remained for the screening of titles and abstracts. Of these, 181 studies were excluded based on irrelevance or insufficient alignment with the established inclusion criteria. Full-text review was then conducted for 78 articles. Following this phase, 38 studies were excluded for failing to meet eligibility standards, while an additional 22 were excluded due to inadequate or incomplete reporting of CRP data. Ultimately, 18 studies fulfilled all criteria and were included in the final qualitative synthesis.

These 18 studies, published between 2010 and 2025, represented a spectrum of methodological approaches. Thirteen utilized a cross-sectional design, four employed a case-control framework, and one adopted a retrospective cohort design based on large-scale population data. Sample sizes ranged from fewer than 100 participants in smaller clinical studies to over 78,000 individuals in large epidemiological cohorts.

Findings were summarized qualitatively and grouped by comparison categories, including BD versus healthy controls, BD versus other psychiatric disorders, and within-BD comparisons across mood states. Most studies enrolled adults with a confirmed BD diagnosis, although some also included adolescent populations. Comparator groups varied considerably, encompassing healthy controls, individuals with schizophrenia, major depressive disorder (MDD), and other psychiatric conditions. Several studies incorporated multiple diagnostic categories, enabling cross-disorder comparisons of CRP titres. Nearly all included studies reported significantly elevated serum CRP titres in individuals with BD compared to healthy

controls. This elevation was observed across different phases of the illness, although not all studies stratified participants by mood state (i.e., manic, depressive, or euthymic). Where stratification was performed, CRP titres tended to be highest during manic episodes; however, this finding was not consistently replicated.

Eight studies incorporated additional psychiatric comparator groups, such as individuals with schizophrenia or MDD. The findings from these comparisons were heterogeneous. Some investigations ⁽⁴¹⁾; ⁽⁴⁸⁾ identified higher CRP titres in participants with BD compared to those with schizophrenia or depression. Conversely, other studies found no significant differences in CRP titres between groups, suggesting that systemic inflammation, as reflected by CRP titres, may represent a shared biological process among several forms of severe mental illness rather than a biomarker specific to bipolar disorder.

Discussion

This systematic review synthesizes evidence from 18 studies published between 2010 and 2025 examining circulating CRP titres in subjects with BD. The collective findings indicate that CRP is consistently elevated in subjects with BD as opposed to healthy controls, lending support to the growing body of evidence implicating systemic inflammation in the pathophysiology of BD.

Despite methodological heterogeneity across studies, the consistent elevation of CRP, observed even in euthymic or treatment-stable subjects, suggests a possible trait-like inflammatory state in BD, rather than a state-limited biomarker confined to acute mood episodes. These findings align with the broader inflammatory hypothesis of BD and may offer insights into mechanisms underlying chronicity and episode recurrence.

However, the predominance of cross-sectional designs among the included

studies restricts the ability to infer causality or temporal relationships. Whether elevated CRP represents a causal factor, a consequence of illness activity, or a marker of underlying metabolic burden remains to be clarified. Only one large-scale cohort study ⁽⁸⁾ provided evidence suggesting that elevated baseline CRP may precede and predict the onset of BD, pointing to its potential role as a risk biomarker.

Comparative findings involving other psychiatric populations, particularly subjects with schizophrenia or major depressive disorder, were mixed. Some studies reported a distinct inflammatory profile in BD, while others found comparable CRP titres across disorders. These inconsistencies may reflect variations in sample composition (e.g., age distribution, presence of metabolic comorbidities), diagnostic heterogeneity, degree of symptom control, or differences in assay methodologies and sensitivity. Additionally, inadequate control of confounding factors like body mass index (BMI), smoking, and medication use may have influenced observed CRP levels.

Strengths and Limitations

The strengths of the current body of evidence include the inclusion of both clinical and population-based samples, the use of standardized psychiatric diagnostic criteria, and the measurement of objective, quantifiable inflammatory markers. However, several limitations warrant consideration. First, the heterogeneity in study design, CRP assay type (standard vs. high-sensitivity), and inconsistent reporting of mood states at the time of blood sampling limit comparability across studies. Second, few studies accounted for major confounding variables, like obesity, smoking, or use of psychotropic medications known to impact inflammatory status. Finally, the cross-sectional nature of most studies limits the interpretation of CRP as a dynamic marker responsive to clinical state or treatment.

Future Directions

Future research should prioritize longitudinal study designs that repeatedly measure CRP across different mood states within the same individuals, to determine whether CRP variations track illness activity or reflect a stable trait marker. Large-scale prospective cohorts are also needed to establish whether elevated baseline CRP predicts illness onset, course, or treatment response. Importantly, future work must rigorously control for key confounding factors such as BMI, smoking, alcohol consumption, metabolic comorbidities, and psychotropic medication use. Mechanistic studies should also explore why CRP is elevated in BD, examining pathways such as hypothalamic–pituitary–adrenal (HPA) axis dysregulation, unhealthy lifestyle behaviors, genetic predispositions, and autoimmune mechanisms. Such integrative work will clarify whether inflammation represents a causal pathway or an epiphenomenon in BD.

Clinical Implications

From a clinical standpoint, CRP holds promise as part of a multimodal biomarker panel for BD. Identifying patients with persistently elevated CRP may help define a biologically distinct “inflammatory subtype” of BD, which could be targeted with adjunctive anti-inflammatory or immunomodulatory interventions. Incorporating CRP measurement into routine clinical monitoring, alongside metabolic and psychiatric assessments, may eventually guide personalized treatment strategies. Finally, interventional trials testing whether pharmacological (e.g., anti-inflammatory agents) or lifestyle-based strategies (e.g., weight management, sleep regulation, exercise) that reduce systemic inflammation also improve mood stability will be essential for translating biomarker findings into precision psychiatry.

Conclusion

Serum CRP is a reproducibly elevated biomarker in bipolar disorder, with

potential applications in risk stratification and treatment monitoring. Standardized, prospective studies are needed to establish its diagnostic and prognostic utility.

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