C-Reactive Protein Alterations in Bipolar Disorder: A Meta-Analysis

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ABSTRACT

Objective: There is growing evidence that bipolar disorder (BD) is associated with inflammation, including abnormal levels of acute-phase C-reactive protein (CRP). Our meta-analysis was conducted to estimate the size of the association between CRP levels and BD, accounting also for subgroup differences (mood phases and treatment).

Data Sources: MEDLINE, EMBASE, PsycINFO, and ISI Web of Science and references of identified articles were searched up to June 2013 using the keywords (*bipolar disorder*) AND (*C-reactive protein* OR *CRP*).

Study Selection: English language studies measuring blood levels of CRP in patients with BD and control subjects were selected, 136 abstracts were reviewed, 20 articles retrieved, and 11 studies included.

Data Extraction: Two independent reviewers extracted data. All studies were included in the primary analyses, and between-group differences for subanalyses were also reported. This meta-analysis was performed using random-effects models.

Results: Eleven studies comprising 1,618 subjects were eligible for inclusion. Overall, CRP levels were significantly elevated in patients with BD versus controls (standardized mean difference [SMD] = 0.39; 95% CI, 0.24 to 0.55; $P < .0001$). CRP levels were significantly higher in manic (SMD = 0.73; 95% CI, 0.44 to 1.02; $P < .001$) and euthymic (SMD = 0.26; 95% CI, 0.01 to 0.51; $P = .04$), but not in depressed (SMD = 0.28; 95% CI, –0.17 to 0.73; $P = .22$) patients with BD compared to controls. CRP levels were unrelated to use of lithium or antipsychotic medication.

Conclusions: This meta-analysis supports an association between increased CRP levels and BD. Given that an elevated level of CRP is a marker of low-grade inflammation and a risk factor for cardiovascular and malignant diseases, measurement of CRP level might be relevant to the clinical care of bipolar patients.

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Individuals suffering from severe infections and autoimmune diseases have acute or persistently increased levels of markers of inflammation in their blood,[1] and such individuals are found to have an increased risk of developing mood disorders, including bipolar disorder (BD).[2] Recently, 2 meta-analyses confirmed that patients with BD, across the different mood phases of the disease, have abnormal blood levels of several inflammatory markers, including cytokines.[3,4] Cytokines are multifunctional signaling molecules of the immune system that act as key mediators in both central and peripheral inflammation.[5] Proinflammatory cytokines, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and particularly interleukin-6 (IL-6), are the chief inducers of acute-phase proteins, including haptoglobin, fibrinogen, and C-reactive protein (CRP),[1] which are associated with BD.[6] These findings indicate that inflammation may be involved in the pathophysiologic mechanisms of BD.[7]

C-reactive protein, which is synthesized by hepatocytes, is a classic acute-phase protein[1] and one of the most commonly used markers of inflammation. Normal levels of CRP are < 3 mg/L, and the high-sensitivity CRP (hsCRP) assay has a lower limit of detection < 0.1 mg/L.[8] During acute inflammatory processes (eg, bacterial infection), circulating blood levels of CRP can increase up to 1,000-fold.[9] Subjects who are apparently healthy have CRP levels that are usually below 3 mg/L, but such levels can be up to 10 mg/L.[9] Levels of CRP that are slightly elevated (> 3 mg/L to < 10 mg/L) reflect low-grade inflammation,[1] which has been linked with a range of conditions, including vascular and malignant diseases,[10] as well as autism[11] and depression.[12] Furthermore, prospective studies have recently demonstrated an association between elevated levels of CRP and increased risk of late-onset schizophrenia[13] and anxiety disorder.[14]

Growing evidence has been reported that BD is consistently associated with clinical comorbidities[15] in which cardiovascular illness and metabolic syndrome are highly prevalent.[16] Of note, elevated levels of CRP can independently predict several conditions, such as cancers[17] and respiratory illnesses, as well as cardiovascular diseases,[18] which are known to be the leading cause of excess mortality in BD.[19] Although cardiometabolic conditions in BD have been considered as a consequence of an unhealthy lifestyle and/or of psychotropic medications, the systemic mechanisms underlying this relationship are still unclear, and inflammation might be implicated.[7,20]

Several studies have reported an association between elevated levels of CRP and BD,[21–34] however, they have frequently been limited to small[21,25,27,34] and/or heterogeneous samples[24,26,33,34] and have failed to control for relevant confounding factors.[22,25,31,32] Moreover, previous studies were inadequately powered to assess the size of association between CRP levels and the different mood phases of BD (mania, depression, and euthymia).[22,25,30] Therefore, we conducted a meta-analysis to estimate the overall effect size of the association between CRP levels and BD. We also examined the influence of BD phases (mania, depression, or euthymia) and of medication (antipsychotics and lithium)

on the levels of CRP in patients with BD and whether the findings corroborate the inflammation hypothesis in BD, including CRP as a biomarker.

- Increased levels of C-reactive protein (CRP), a marker of systemic inflammation and an established risk factor for cardiovascular disease, appear to be associated with bipolar disorder.
- Inflammation may be implicated in the pathophysiology of bipolar disorder; thus, healthy lifestyle interventions (smoking cessation, dietary measures, and physical activity), which appear to reduce levels of proinflammatory markers (eg, CRP), might help to assuage severity of bipolar disorder.
- Measurement of CRP levels in patients with bipolar disorder should be considered as a possible strategy to motivate them toward healthy body-brain interventions.

Clinical Points

METHOD

Data Source and Study Selection

To identify relevant studies, we searched MEDLINE, EMBASE, PsycINFO, and ISI Web of Science from their inception to June 2013. Keywords utilized included (*C-reactive protein* OR *CRP)* AND (*bipolar disorder* OR *bipolar illness* OR *manic depression* OR *manic-depression* OR *manic-depressive illness* OR *bipolar depression* OR *mania* OR *manic episode* OR *hypomania* OR *bipolar affective disorder* OR *bipolar psychosis* OR *manic disorder* OR *manic psychosis* OR *dysphoric mania* OR *hypomanic* OR *mixed mania* OR *cyclothymic disorder* OR *cyclothymia)*. The reference lists from identified studies were also hand searched for any additional studies.

A priori criteria for inclusion in the meta-analysis were (1) cross-sectional studies comparing blood levels of CRP in adult BD patients (aged > 18 years) and healthy controls (psychiatrically healthy subjects), (2) diagnosis of BD with well-validated diagnostic criteria, and (3) studies published in English. Exclusion criteria were (1) studies without a control group (ie, not comparing BD patients with control subjects), (2) studies in which CRP levels were not detectable for > 50% of subjects, and (3) unavailability of mean and standard deviation (SD) for CRP levels in the article.

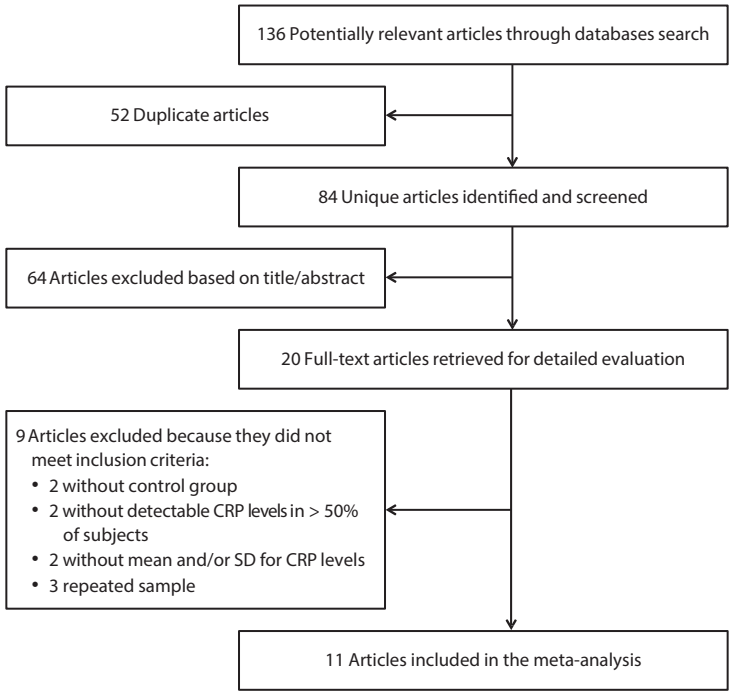
Data Extraction and Meta-Analysis

Two independent authors (A.A.D. and O.G.) screened articles by their titles and abstracts, and those eligible were retrieved. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[35] checklists were used to create the data extraction forms, which were completed for each eligible study. Any difference in abstracted content was discussed with a third author (M.L.) and was resolved by consensus. Extracted data included source (author names, year of publication, and country), study design, participants (sample, control, demographic, and clinical characteristics), assay methods (CRP or hsCRP), and inclusion/exclusion criteria. We also extracted mean and SD for CRP levels in each study. Requests for additional data were sent to authors for original studies, and, of the 9 contacted, a reply was received from 1 author.

For cases in which a sample was repeated (partially or totally) in more than 1 publication, the data from the study with more details on the subgroup of patients (or, if not applicable, the study with larger sample size) were included in the analysis. A study that evaluated symptom severity of BD in outpatients, using the score of Young Mania Rating Scale (YMRS) ≤ 6 versus YMRS > 6 to categorize manic versus euthymic patients, was included.[23] This cutoff is a standard one that has been used in studies of outpatients with BD to distinguish between patients who are euthymic and those who have manic symptoms.[36] For a study that measured CRP levels in psychiatric outpatients in remission (potentially having subsyndromal conditions), the BD population was included in the analysis as euthymic patients.[24] Lastly, in a study including patients in an *elevated* and a *depressed* state, not stating whether these patients fulfilled diagnostic criteria for mood episodes, the symptom rating scale results provided were estimated to fulfill criteria, and the study was included.[26] Considering there were different classifications for euthymic phase and remission (including subsyndromal conditions) among the studies included, we grouped these definitions together under "euthymia" subgroup to avoid increase in the number of subgroups.

To combine studies, the DerSimonian and Laird random-effects model[37] was used in all cases to calculate effect size estimates, considering that individuals in this meta-analytic study tended to be heterogeneous and methodological differences (eg, different assays employed) across studies could generate effect size differences. Since it was considered likely a priori that not all trials would produce exactly equal underlying effect sizes, a random-effects model was considered preferable to a fixed-effects model. The random-effects model includes both within-study and between-study variance and is usually more realistic and conservative than the fixed-effects model.[37] The results are presented as standardized mean difference (SMD) and 95% confidence intervals (CIs). This association measure (SMD) is a useful method that allows the pooling of data measured with different techniques (eg, different CRP assays). An effect size < 0.3 is considered small; from 0.3 to 0.8, medium; and > 0.8, large.[37] We quantified between-study heterogeneity using Cochran Q and the I^2 statistic.[38] I^2 can be interpreted as the proportion of the total variance due to heterogeneity between studies and may be categorized as a low ($I^2 = 25\%$), moderate ($I^2 = 50\%$), or high ($I^2 = 75\%$) degree of heterogeneity.[39] Additionally, we conducted subgroup analyses to assess the influence of BD phases (mania, depression, or euthymia), as well as of medication use (antipsychotics or lithium) on the levels of CRP in patients with BD. We visually inspected funnel plots portraying estimates of SMD from individual studies against their standard error to assess for potential publication bias using Egger regression-based test.[40] Given that statistically nonsignificant findings may have a lower probability of being published, which could lead to an

Figure 1. Flowchart of Study Selection Process



Abbreviations: CRP = C-reactive protein, SD = standard deviation.

overestimation of the effect size, we used the trim-and-fill method that estimates corrected effect sizes after imputing possible lacking effect sizes.[41] Statistical analyses were performed with the metaphor package in R (2.11.1).[42]

RESULTS

Search and Study Characteristics

The computerized search yielded 84 references after 52 duplicates were removed. We excluded 64 studies on the basis of title and abstract review. Of the remaining 20 studies, 9 additional articles were excluded after full-text review (2 studies that had no control group or did not compare BD patients with control subjects,[33,43] 2 studies in which CRP levels were not detectable in > 50% of subjects,[44,45] 2 studies without available mean and SD values of CRP levels in the article,[32,46] and 3 studies that reported results of CRP levels from the same population[47–49]). In total, we included 11 articles[21–31] in the meta-analysis (Figure 1).

Overall, 3 studies were conducted in Taiwan[27–29]; 2 studies each in the United States[23,24] and Brazil[22,25]; and 1 each in Croatia,[30] Norway,[26] South Africa,[31] and Turkey.[21] The available data were too limited to include analysis on ethnicity or geographical differences. The data set comprised 1,618 individuals (730 patients with BD and 888 control subjects), and the studies included in this meta-analysis involved sample sizes that ranged from 13 to 192 bipolar patients, of which 56.7% were female (n = 414; 9 studies). All of the studies included were published between 2007 and 2013 and used *DSM-IV*[50] diagnostic criteria for BD, and most of those used *DSM-IV* criteria to define manic and/or depressive episodes.[22,25,27–31]

Nine studies reported using a clinical protocol to screen control subjects,[22–30] 5 of those used the Structured Clinical Interview for *DSM-IV* Axis I Disorders–Non-Patient Edition.[22–24,27,30] Of the 11 studies included, 5 were conducted among inpatients (n = 166),[27–31] 4 were conducted in outpatient settings (n = 372),[21,23–25] and 2 were conducted in mixed samples (n = 192).[22,26] To avoid multiple hypothesis testing, we decided not to perform a subgroup analysis based on type of setting (inpatient or outpatient). However, we performed subgroup analysis stratified by phases of BD and medication use (antipsychotics and lithium) related to CRP levels that might be more relevant in this clinical context. Seven studies[22–26,29,30] provided data on medication status, although none of them reported CRP levels stratified by type of treatment. The majority of studies measured morning-drawn serum or plasma levels of hsCRP.[21,22,24–29] In fact, low heterogeneity was observed when pooling studies that used different CRP assays (CRP and hsCRP). Overall, the studies included in the meta-analysis reported excluding participants with clinically significant medical disorders, such as neurologic, infectious, and autoimmune diseases. Only 4 studies,[21,25,27,31] however, reported exclusion of individuals with a wide range of medical comorbidities, including metabolic and cardiovascular disorders. Six studies reported controlling for potential confounding factors of CRP levels, such as age, gender, and body mass index.[24,26–30] Three studies were adjusted for age, gender, and smoking[21,24,26]; and 2 of these also accounted for other relevant confounding factors (ie, race, educational level, use of antipsychotics, and alcohol/substance abuse).[24,26] Two studies, however, did not report clearly controlling for any potential confounders related to CRP levels.[25,31] A summary of included studies is shown in Table 1.

CRP Levels

There were significantly higher levels of CRP in BD patients compared with control subjects, with an overall effect size of 0.39 (SMD = 0.39; 95% CI, 0.24 to 0.55; $P < .0001$) (Figure 2). Overall, between-study heterogeneity was moderate ($I^2 = 47.6\%$; $P < .039$).

In the subgroup analysis based on different mood phases of BD, CRP levels were extracted from 7 studies that included 188 manic BD patients and 557 control subjects. Manic bipolar patients had significantly higher levels of CRP compared with control subjects, with a large effect size of 0.73 (SMD = 0.73; 95% CI, 0.44 to 1.02; $P < .001$) (Figure 3A).

There were 399 BD patients in euthymic phase and 735 control subjects from 6 studies for which CRP was measured. CRP levels were significantly increased in euthymic bipolar, albeit with a slight statistical difference (SMD = 0.26; 95% CI, 0.01 to 0.51; $P < .04$) (Figure 3B). Four studies measured CRP levels in depressed bipolar patients (n = 107) and control

Table 1. Characteristics of Studies Included in the Meta-Analysis

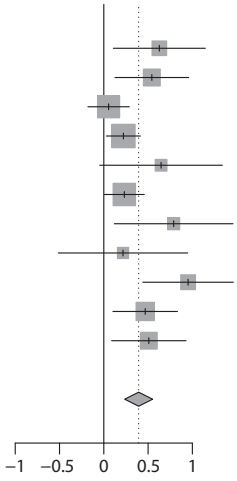
Study,Year Country	N BD/C[a]	Age, y, Mean (SD) BD/C[a]	Female, % BD/C[a]	Illness Duration, y/ Age-at-Onset,[c] y	Current Smoker, % BD/C[a]	BMI (kg/m^2), Mean (SD) BD/C[a]	CRP Assay	Antipsychotic Use,[c] % Any/Typical/ Atypical	Antidepressant Use,[c] %	Lithium Use,[c] %
Aksoy et al, 2010 Turkey[21]	30/30	32.8 (7.55)/ 34.2 (10.29)	60/56.7	NA/25.4 (7.55)	26.7/16.7[b]	NA/NA	hsCRP	NA/NA/NA	NA	NA
Cunha et al, 2008 Brazil[22]	80[d]/32	40.3 (11.26)/ 40.6 (12.12)	57.5/65.6	16.1 (11.90)/ 24.1 (11.97)	NA/NA	NA/NA	hsCRP	NA/NA/NA	63.7	NA
Dickerson et al, 2007 USA[23]	122/165	40.7 (12.34)/ 34.3 (12)	71.3/74	21.1 (12.6)/ 19.8 (9.2)	NA/NA	NA/NA	CRP	49/NA/49	NA	29
Dickerson et al, 2013 USA[24]	192/228	34.8 (13)/ 32.2 (11.4)	71/63	17.2 (12.9)/ 17.2 (8.9)	36/16	28.3 (7.8)/ 27.8 (6.8)	hsCRP	NA/NA/71	40	34
Fontoura et al, 2012 Brazil[25]	28/12	38.67 (7.22)/ 37 (10.39)	78.5/50	NA/NA	NA/NA	NA/NA	hsCRP	73/40/33	NA	83
Hope et al, 2011 Norway[26]	112/239	36.2 (12)/ 36 (10)	60/56	NA/NA	53/20[e]	25.7 (5)/ 24.3 (3)[f]	hsCRP	45/NA/NA	41	60
Huang et al, 2007 Taiwan[27]	13/31	36.9 (10.1)/ 30.5 (3.9)	38.4/42	NA/NA	NA/NA	25.9 (3.0)/ 22.6 (3.7)	hsCRP	NA/NA/NA	NA	NA
Hung et al, 2007 Taiwan[28]	15/14	23.8 (2.71)/ 23.8 (2.24)	NA/NA	NA/NA	NA/NA	22.2 (1.93)/ 22.7 (3)	hsCRP	NA/NA/NA	NA	NA
Tsai et al, 2012 Taiwan[29]	33/33	31.6 (6)/ 28.9 (3.9)	36.4/NA	NA/23.2 (7.0)	36.4/12.1	24.9 (3.9)/ 23.5 (4.4)	hsCRP	48.5/30.3/18.2	NA	33.3
Vuksan-Cusa et al, 2013 Croatia[30]	60/59	44.4 (15.8)/ 42.2 (8.7)	NA/NA	10.9 (9.47)/NA	NA/NA	27.3 (5.0)/ 24.9 (3.3)	CRP	100/NA/100	NA	NA
Wadee et al, 2002 South Africa[31]	45/45	32.7/31.2[g]	46.6/46.6	NA/NA	NA/NA	NA/NA	CRP	NA/NA/NA	NA	NA

[a]Patients without any psychiatric disorder.
[b]Total sample.
[c]Patients with bipolar disorder.
[d]30 euthymic patients, 30 manic patients, 20 depressed patients.
[e]n = 162 C nonsmokers (N = 239).
[f]n = 168 C nonsmokers (N = 239).
[g]SD values unavailable.
Abbreviations: BD = bipolar disorder, BMI = body mass index, C = control subjects, CRP = C-reactive protein, hsCRP = high-sensitivity C-reactive protein, NA = not available, SD = standard deviation.

Figure 2. Meta-Analysis of C-Reactive Protein Levels in Bipolar Disorder

Study	Bipolar Disorder Total	Mean	SD	Control Total	Mean	SD	SMD	95% CI	Weight
Aksoy et al, 2010[21]	30	3.74000	2.70000	30	2.4300	1.10000	0.63	0.11 to 1.15	6.5%
Cunha et al, 2008[22]	80	5.81000	8.99000	32	1.6000	2.24000	0.54	0.13 to 0.96	8.7%
Dickerson et al, 2007[23]	122	4.80000	6.97000	165	4.4000	7.70000	0.05	−0.18 to 0.29	14.9%
Dickerson et al, 2013[24]	192	1.32000	1.80000	228	0.9910	1.15000	0.22	0.03 to 0.41	16.7%
Fontoura et al, 2012[25]	28	0.35700	0.46000	12	0.1000	0.07000	0.65	−0.05 to 1.34	4.2%
Hope et al, 2011[26]	112	1.20000	2.50000	239	0.8000	1.20000	0.23	0.01 to 0.46	15.3%
Huang et al, 2007[27]	13	5.80000	9.60000	31	1.5000	1.80000	0.79	0.12 to 1.46	4.4%
Hung et al, 2007[28]	15	0.50000	0.70000	14	0.3820	0.23000	0.22	−0.51 to 0.95	3.8%
Tsai et al, 2012[29]	33	0.00358	0.00298	33	0.0014	0.00117	0.95	0.44 to 1.46	6.7%
Vuksan-Cusa et al, 2013[30]	60	4.24000	4.09000	59	2.5900	2.79000	0.47	0.10 to 0.83	10.2%
Wadee et al, 2002[31]	45	11.42200	18.24000	45	4.6780	3.67000	0.51	0.09 to 0.93	8.6%
Overall effect	**730**			**888**			**0.39**	**0.24 to 0.55**	**100%**

P = .0001
Heterogeneity: I^2 = 47.6%, tau^2 = 0.0291, *P* = .0394



Abbreviations: CI = confidence interval, SD = standard deviation, SMD = standardized mean difference.

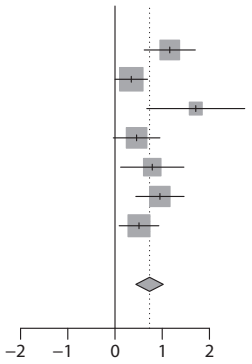
subjects (n = 297), and CRP levels did not differ significantly between such groups (SMD = 0.28; 95% CI, −0.17 to 0.73; *P* = .227) (Figure 3C). However, it is worth mentioning that the SMD was greater in BD depressed patients than in BD euthymic patients (0.28 vs 0.26, respectively), suggesting that the lack of statistical significance for CRP levels may be explained by the smaller sample size in the BD depression group. In the meta-regression to evaluate the influence of use of antipsychotic (any or atypical) or lithium on the CRP levels, no significant associations were identified (data not shown). Nevertheless, the small number of studies that provided data on use of antipsychotic or lithium has potentially limited the analysis. It is important to mention that larger effect sizes were observed in smaller studies with significant asymmetry

Figure 3. Subgroup Analysis of CRP Levels According to Phases of Bipolar Disorder

A. Mania

Study	Bipolar Disorder Total	Mean	SD	Control Total	Mean	SD	SMD	95% CI	Weight
Cunha et al, 2008[22]	30	11.81000	12.29000	32	1.6000	2.24000	1.16	0.62 to 1.70	14.2%
Dickerson et al, 2007[23]	41	7.20000	9.50000	165	4.4000	7.70000	0.35	0.00 to 0.69	20.2%
Fontoura et al, 2012[25]	9	0.80000	0.60000	12	0.1000	0.06920	1.71	0.67 to 2.75	6.1%
Hope et al, 2011[26]	17	1.40000	2.40000	239	0.8000	1.20000	0.46	−0.04 to 0.95	15.5%
Huang et al, 2007[27]	13	5.80000	9.60000	31	1.5000	1.80000	0.79	0.12 to 1.46	11.2%
Tsai et al, 2002[29]	33	0.00358	0.00298	33	0.0014	0.00117	0.95	0.44 to 1.46	15.0%
Wadee et al, 2002[31]	45	11.42200	18.24000	45	4.6780	3.67000	0.51	0.09 to 0.93	17.7%
Overall	**188**			**557**			**0.73**	**0.44 to 1.02**	**100%**

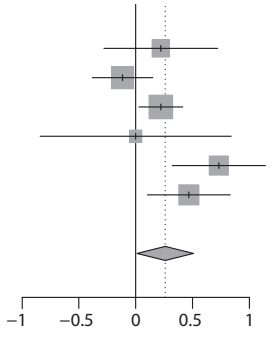
$P < .001$
Heterogeneity: $I^2 = 53.8\%$, $tau^2 = 0.0779$, $P = .0434$



B. Euthymia

Study	Bipolar Disorder Total	Mean	SD	Control Total	Mean	SD	SMD	95% CI	Weight
Cunha et al, 2008[22]	30	2.14	2.580	32	1.600	2.2400	0.22	−0.28 to 0.72	13.3%
Dickerson et al, 2007[23]	81	3.60	4.900	165	4.400	7.7000	−0.12	−0.38 to 0.15	21.6%
Dickerson et al, 2013[24]	192	1.32	1.800	228	0.991	1.1500	0.22	0.03 to 0.41	24.5%
Fontoura et al, 2012[25]	10	0.10	0.126	12	0.100	0.0692	0.00	−0.84 to 0.84	6.7%
Hope et al, 2011[26]	26	2.10	4.400	239	0.800	1.2000	0.73	0.32 to 1.14	16.1%
Vuksan-Cusa et al, 2013[30]	60	4.24	4.090	59	2.590	2.7900	0.47	0.10 to 0.83	17.8%
Overall	**399**			**735**			**0.26**	**0.01 to 0.51**	**100%**

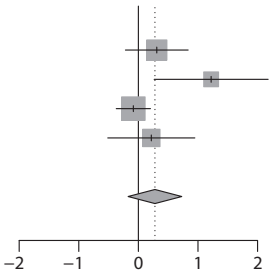
$P < .04$
Heterogeneity: $I^2 = 64.6\%$, $tau^2 = 0.0556$, $P = .0148$



C. Depression

Study	Bipolar Disorder Total	Mean	SD	Control Total	Mean	SD	SMD	95% CI	Weight
Cunha et al, 2008[22]	25	2.3	2.23	32	1.600	2.2400	0.31	−0.22 to 0.84	27.5%
Fontoura et al, 2012[25]	9	0.2	0.09	12	0.100	0.0692	1.22	0.26 to 2.18	14.8%
Hope et al, 2011[26]	58	0.7	1.10	239	0.800	1.2000	−0.08	−0.37 to 0.20	37.3%
Hung et al, 2007[28]	15	0.5	0.70	14	0.382	0.2300	0.22	−0.51 to 0.95	20.4%
Overall	**107**			**297**			**0.28**	**−0.17 to 0.73**	**100%**

$P = .227$
Heterogeneity: $I^2 = 60.3\%$, $tau^2 = 0.1201$, $P = .0559$



Abbreviations: CI = confidence interval, SD = standard deviation, SMD = standardized mean difference.

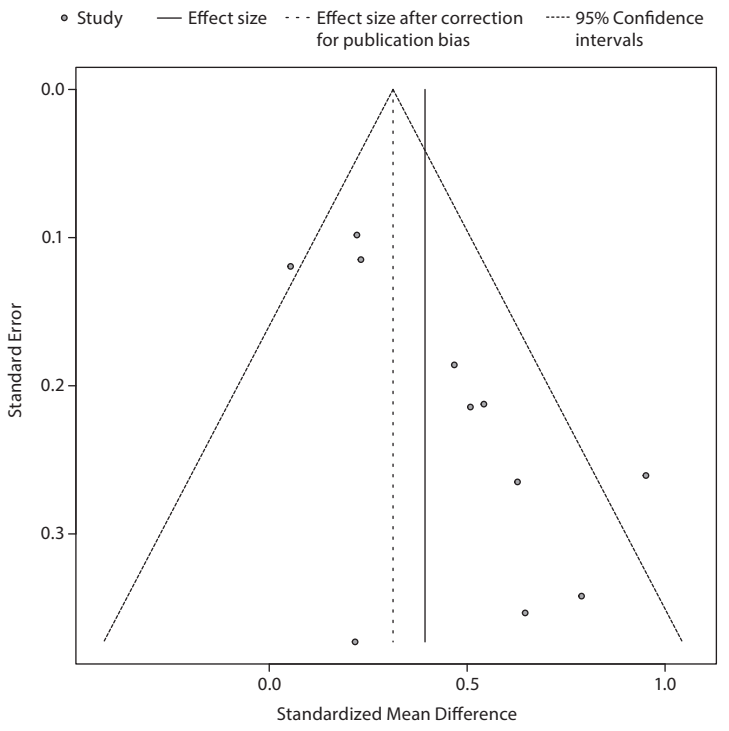
in the funnel plot test ($P < .006$), thus indicating a high probability of publication bias (Figure 4). After adjustment for publication bias, the association between elevated CRP levels in BD patients remained statistically significant with only a slight reduction in the effect size (SMD = 0.28; 95% CI, 0.11 to 0.44; $P = .001$), which reinforces the study findings.

DISCUSSION

We found a significant elevation in CRP levels in patients with BD compared to control subjects, with a small-to-moderate effect size of 0.39. This meta-analytic finding strengthens the evidence that BD is associated with inflammation. However, the mechanisms underlying the relationship between BD and inflammation are still unknown.[20] Consistent evidence has demonstrated elevated levels of cytokines, including IL-1β, IL-6, and TNF-α, in the serum of BD patients.[3,4] As these proinflammatory cytokines are known inducers of CRP,[1] it is reasonable to hypothesize that CRP levels would also be increased in BD patients. Three studies included in this meta-analysis simultaneously measured blood levels of CRP and cytokines.[26,28,29] Altogether, these data reinforce the hypothesis of peripheral inflammation in BD.[51]

Furthermore, a recent study reported the involvement of central inflammation in BD by demonstrating that markers of neuroinflammation are significantly increased in postmortem frontal cortex from BD patients.[52] In particular, this study found an important activation of the IL-1 receptor cascade,[52] which is involved in several regulatory process of inflammation.[52] Importantly, CRP itself seems to play a causal role in neuroinflammation. Elevated levels of CRP may induce a disruptive effect in the blood-brain-barrier,

Figure 4. Publication Bias Assessment for Studies of C-Reactive Protein Levels in Bipolar Disorder



as shown in animals.[53] This barrier-disrupting effect of CRP may increase the permeability of the blood-brain-barrier, making the brain susceptible to the effects of proinflammatory cytokines and/or autoantibodies, both of which are associated with BD.[2] Although the interrelationship between different inflammatory markers is complex, level of CRP may be a marker of inflammation to be considered in everyday practice in BD. Since it is a relatively low-cost biomarker and widely available in clinical settings, measurement of CRP levels might be an easy, cost-effective way to obtain information about the inflammatory pattern in BD patients, and, indirectly, on alterations in proinflammatory cytokines, which are known to modulate CRP levels. Further research pooling CRP with other markers of inflammation is needed to better elucidate the relationship between these markers across the different phases of the disease.

In BD, immune dysregulation has been associated with severity of symptoms and mood episodes. Acutely ill bipolar patients have an activation of immune response accompanied by increased levels of inflammatory markers, including proinflammatory cytokines[54] and hsCRP,[22] particularly during manic episodes. Our meta-analysis adds to the literature that shows that manic BD patients have significantly higher levels of CRP than control subjects (SMD = 0.73; 95% CI, 0.44 to 1.02; $P < .001$). Of note, a recent study demonstrated an association between elevated CRP and manic symptoms in patients having a depressive disorder.[55] Additionally, these authors, in prospective analyses, found that CRP was an important risk factor for the onset of manic symptoms in depressed men during 2 years of follow-up.[55] A proinflammatory state, thus, seems to be strongly related to manic symptoms, contributing to the idea that CRP could be a marker of state in BD. Although explanatory mechanisms of this relationship are still unclear, one possible mechanism might be linked to sleep dysfunction, which is often present in manic[56] BD patients, and is known to be associated with elevated cytokines and CRP levels.[57]

A very interesting finding in our study was also that CRP levels were significantly elevated in euthymic BD patients compared to controls, indicating there is an inflammatory component in nonacutely ill BD patients. Our meta-analysis, therefore, reinforces evidence showing that activation of the inflammatory response persists after remission,[58] suggesting that CRP could also be a trait marker in BD. However, it is important to bear in mind that many studies included in our subgroup analysis used different criteria to characterize the different mood phases of BD, raising the idea that some BD patients categorized as euthymic had subsyndromal symptoms, which could also influence CRP levels. However, the small number of studies providing data on subsyndromal conditions did not allow more in-depth subgroup analysis. Further studies stratifying patients by clinical status (including subsyndromal conditions) are needed to better evaluate the potential impact of mood symptoms on CRP levels.

Inflammation is thought to underlie the pathogenesis of several chronic diseases, such as coronary artery disease, diabetes mellitus, and obesity,[59] that are highly prevalent in patients with BD.[16] Strong evidence has shown that CRP is an independent predictor of cardiovascular disease,[18] the leading cause of excess mortality in BD patients.[19] In addition, CRP levels are associated with increased risk of cardiovascular disease and diabetes among subjects with metabolic syndrome.[60] A recent meta-analysis found that BD patients had almost twice the risk of developing metabolic syndrome compared to age- and gender-matched healthy controls (OR = 1.98; 95% CI, 1.74 to 2.25; $P < .0001$), and approximately one-half of these patients had at least 1 component of metabolic syndrome, including abdominal obesity, hypertension, fasting hyperglycemia, or an abnormal lipid profile.[61] Four studies included in our meta-analysis reported significant associations between hsCRP levels and metabolic syndrome components. In a study by Vuksan-Cusa et al,[30] the prevalence of metabolic syndrome was 31% in the BD group of patients (versus 15% in the control group), and hsCRP levels were significantly positively correlated with waist circumference and diastolic blood pressure in the euthymic BD patients. In the 3 other studies, elevated hsCRP levels were significantly associated with higher body mass index in manic[27,29] and euthymic[24] BD patients compared to control subjects. Because we

had limited metabolic syndrome data on CRP levels, we were not able to draw any conclusions on the association between levels of CRP and cardiometabolic risk in this population. Although metabolic syndrome components and cardiovascular diseases have been strongly associated with persistent low-grade inflammation, reflected by increased CRP levels,[62] the mechanisms are still unknown. Visceral adiposity triggers inflammatory cascades that in turn yield increased secretion of proinflammatory factors, including IL-1β, IL-6, and TNF-α, and appear to be a potential mechanism linking abdominal obesity and cardiovascular disease.[62] In addition, unhealthy diet and physical inactivity also contribute to the accumulation of abdominal obesity predisposing subjects to chronic conditions, such as mood disorders and cardiometabolic diseases. In contrast, growing literature has shown that physical exercise[63] and dietary habits,[64] both related to significant decreases in CRP levels, are associated with improvement in depression-like behavior and depressive symptoms.[63,65] Therefore, a substantial overlap seems to exist between psycho-immuno-endocrinologic mechanisms in BD and cardiometabolic illnesses, as well as between mediators of the systemic toxicity and biological changes (eg, dysregulation of the immune-inflammatory response) observed in BD,[66] suggesting that shared psycho-immuno-endocrinologic mechanisms may exist between these diseases. In summary, cardiometabolic risk is a key factor in the long-term health of BD patients, and CRP levels may provide more objective information on the metabolic-inflammatory status of a bipolar patient. Moreover, abdominal obesity is a reversible condition, and simple measurements (eg, waist circumference) associated with CRP levels may help psychiatrists to motivate their BD patients to improve their lifestyles (ie, lose weight and exercise), thus reducing cardiovascular disease risk. Measurement of CRP levels associated with parameters commonly used in clinical care (eg, blood pressure and lipid and glucose levels) may be a useful biomarker in BD patients at risk for cardiovascular disease, as well as in individuals who are otherwise healthy but suffer from BD.

Despite studies that have suggested that antipsychotics and lithium may exert different effects on CRP levels,[6,33,54] we could not draw any conclusions in this meta-analysis as to the association between medication use and CRP, as the available information was limited. Given that increased CRP levels reflect the presence of inflammation, therapeutic regimens to modulate inflammatory response, reducing CRP levels,[67] may be useful in the treatment of BD patients. In keeping with this view, randomized, double-blind, placebo-controlled studies have reported substantial antidepressant effects following adjunctive treatment with celecoxib (an anti-inflammatory drug) in individuals with BD[68] and depression.[69] Remarkably, recent findings suggest that patients with high inflammatory activity may respond less to antidepressants and better to anti-inflammatory medication.[70] Moreover, there is some evidence suggesting beneficial effects for aspirin in mood disorders, as well as in schizophrenia.[71] Disturbances in inflammation, however, are prominent only in a subset of subjects with BD. Recently, a study evaluated the effect of infliximab, a TNF-α antagonist currently used in the treatment of rheumatic and inflammatory bowel diseases,[72] in patients with treatment-resistant depression. Infliximab was superior to placebo in mitigating depressive symptoms only in individuals who exhibited elevated inflammation (hsCRP > 5 mg/L) at baseline.[70] In this vein, measurement of CRP levels in BD patients might be useful to stratify those patients who may respond to a specific immune or anti-inflammatory treatment, reinforcing the idea of CRP as a potential biomarker in BD. This hypothesis is still in its infancy, and studies are lacking.

To the best of our knowledge, this is the first, formal meta-analysis on CRP levels in BD. Our search, focusing on quality and stricter inclusion criteria, potentially contributed to limiting the heterogeneity of results. Given the large sample size of BD patients with measured blood CRP levels (n = 730), our analyses had enough power to find case-control dissimilarities, as well as to estimate a precise effect size. Another potential strength of our study was its 2 series of subgroup analyses (phases of disease and use of antipsychotic or lithium), which reduced heterogeneity in most cases. In addition, most of the studies included used hsCRP assay to measure CRP concentrations. Currently, hsCRP assay is the standard in clinical practice, and it has the ability to measure CRP levels accurately (ie, lower detection limits of 0.1 mg/L), which may be useful to better discriminate states of low-grade inflammation.[60]

Nevertheless, our findings must be interpreted in light of certain limitations. First, CRP alterations in BD do not necessarily reflect an underlying pathophysiologic process and may be secondary to alterations in biological pathways or presence of comorbidities. Second, we could not account for several confounding factors (body mass index, medical comorbidities, alcohol/drug abuse, or smoking) in the meta-analyses. Although all of these factors are known to influence CRP levels,[73] only a few (age, body mass index, smoking, and absence of inflammatory diseases) were controlled in most of the studies. Also, we cannot rule out that other confounding/moderator variables not examined in the included studies, such as health-related behaviors (ie, diet and physical activity),[73] chronic diseases,[17] psychological stress,[74] and sleep disturbances,[56] may also explain the association between elevated levels of CRP and BD. Third, in addition to variations due to age, gender, and lifestyle factors, CRP may also vary across different geographies and ethnic groups (eg, populations of African descent have higher average CRP levels than European-descended populations).[75] However, the available data were too limited to draw meta-analytic conclusions on ethnicity and/or geographical differences associated with CRP levels in BD patients. Taking into account the wide range of potential confounding factors related to CRP levels in BD, these issues need to be addressed in more detail in future studies given their clinical importance. Fourth, because our findings were based on cross-sectional rather than on randomized

or longitudinal data, the directionality of the association between CRP and BD cannot be clearly inferred. It is possible that inflammation, which is known to be associated with increased levels of CRP, might lead to BD. In contrast, BD symptoms, acting as a stimulus for inflammatory response, might predict CRP levels. Fifth, in some cases, heterogeneity was not reduced after subgroup analyses, suggesting that other factors such as clinical features (eg, subsyndromal conditions) or the differences in assays might have yielded heterogeneity. Sixth, there were often missing data on duration of illness and age-at-onset. Importantly, illness duration may reflect the duration of medication exposure and is related to both age-at-onset of BD and patient's age. Finally, the studies available for this meta-analysis included individuals with BD under various therapeutic regimens and did not provide stratified data on concomitant medication (except for antipsychotics, antidepressants, or lithium), also known to influence CRP levels. It is worth mentioning that conventional mood stabilizers (eg, lithium, antipsychotics, and anticonvulsants) act in varying capacities to down-regulate the production of proinflammatory mRNA and protein gene expression that might alter levels of cytokines and CRP.[76]

CONCLUSIONS

Our meta-analysis supports the association between BD and increased levels of CRP, which is a marker of systemic (low-grade) inflammation, as well as an established risk factor for cardiovascular disease. These findings could be clinically relevant, if tested and confirmed by future studies, also combining measurements of CRP levels with other inflammatory biomarkers (eg, cytokines) to obtain a more specific parameter of systemic inflammation in BD patients. Considering that inflammation appears to be implicated in the pathophysiology of BD,[7,20] healthy lifestyle interventions (smoking cessation, dietary measures, and physical activity), which appear to reduce levels of proinflammatory markers (eg, CRP),[73] might help to assuage severity of BD. Therefore, CRP measurement in individuals with BD should be considered as a possible strategy to motivate those patients toward healthy body-brain interventions.

Drug names: celecoxib (Celebrex), lithium (Lithobid and others).

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