

Peripheral Levels of C-reactive protein, tumor necrosis factor- α , interleukin-6, and interleukin-1 β across the mood spectrum in bipolar disorder: a meta-analysis of mean differences and variability

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Abstract

Importance. It is unclear whether differences exist in the magnitude and variability of pro-inflammatory mediators in the different phases of bipolar disorder (BD) and among subjects with BD, as compared to healthy controls.

Objective. To run a comparative meta-analysis of C-Reactive Protein (CRP), IL-1, IL-6, TNF- α in BD vs healthy controls, measuring mean and variability effects on all subjects. Sensitivity analyses include disease activity.

Data Sources. Systematic review of observational studies in PubMed and PsycInfo up to February 2nd, 2020.

Study Selection. Case-control studies reporting inflammatory mediators' levels in BD and controls.

Data Extraction and Synthesis. Summary distribution measures of circulating CRP, IL-1 β , IL-6, TNF- α in participants with BD and control groups were extracted. Random-effects multivariate meta-analyses were conducted based on individual study/mediator effect sizes (Hedge's g).

Main Outcomes and Measures. Co-primary outcomes were inflammatory mediators' levels (Hedge's g) and variability (coefficient of variance ratio (CVR)) differences between participants with BD across the mood spectrum and controls.

Results. Out of the initial 729 papers, 72 were assessed and then excluded after full-text review, and ultimately 53 studies were included in the systematic review, while 49 were included in the meta-analysis. The mean age was 36.96 (SD: 9.29) years, and the mean female percentage was 56.31 (SD: 16.61). CRP ($g=0.70$, 95% CI 0.31-1.09, $k=37$, BD=2,215 vs HC=3,750), IL-6 ($g=0.81$, 95% CI 0.46-1.16, $k=45$, BD=1,956 vs HC=4,106), TNF- α ($g=0.49$, 95% CI 0.19-0.78, $k=49$, BD=2,231 vs HC=3,017) were elevated in subjects with BD vs HC, but not IL-1 β ($g=-0.28$, 95% CI -0.68-0.12, $k=4$, BD=87 vs HC=66). When considering euthymic, depressive, and manic episodes separately, CRP and TNF- α were elevated in both depressive and manic episodes, but not in euthymia, while IL-6 remained elevated regardless of the disease state. No difference in CVR emerged for CRP, IL-1 β , and TNF- α , while a lower CVR was observed for IL-6. When considering disease phases, CVR was higher in BD than in HCs for CRP during depressive episodes, lower for IL-6 during euthymia, and higher during manic episodes for CRP, IL-6, and TNF- α . Sensitivity analyses after excluding outliers identified with funnel plot visual inspection, low-quality studies, and considering only studies matched per body mass index confirmed the main results. Meta-regression showed that age (IL-6, TNF- α), gender (CRP), duration of illness (CRP) moderated elevated individual inflammatory levels.

Conclusions and Relevance Peripheral pro-inflammatory marker elevations were confirmed in BD. CRP and TNF- α could represent state markers, as they were only elevated during mood episodes, while IL-6 appeared to be a trait marker for BD. Increased variability of specific inflammatory mediators in specific disease active states suggests that a subset of subjects with BD may exhibit elevated inflammation as part of a manic or depressive episode.

Keywords

Bipolar disorder, inflammation, mania, depression, cytokine, interleukin, IL-1 β , IL-6, C-reactive protein, TNF- α , meta-analysis, psychiatry, neuroscience, mental disorders.

1. Introduction

Bipolar disorder (BD) is an illness characterized by recurring mood states, ranging from depressive episodes to hypomanic, or manic episodes. (American Psychiatric Association, 2013; Carvalho et al., 2020) It has onset before age 25 in around half of the subjects and has a mean age of onset of 20, (Merikangas et al., 2011). BD can be preceded by at-risk conditions (Fusar-Poli et al., 2018). It is associated with functional impairment, high disability, and healthcare costs (American Psychiatric Association, 2013; Carvalho et al., 2020; He et al., 2020). BD is also associated with premature mortality compared to the general population, (Kessing et al., 2015; Pan et al., 2020) which is largely due to medical comorbidities, diabetes, (Vancampfort et al., 2016) metabolic syndrome, (Vancampfort et al., 2015) and cardiovascular disease in particular (Correll et al., 2017; Crump et al., 2013; Nielsen et al., 2020). Importantly, a pro-inflammatory status might also underlie the high comorbidity between BD and cardiometabolic diseases.(Correll et al., 2017; Suleiman et al., 2006)

Consistent and converging evidence has pointed toward a role of peripheral immune activation in the pathophysiology of BD and associated medical comorbidities (Maes and Carvalho, 2018; Modabbernia et al., 2013; Morris et al., 2019; Sayana et al., 2017). Differences in levels of inflammatory mediators have been reported both between subjects with BD and healthy controls(Darg  l et al., 2015; Goldsmith et al., 2016; Munkholm et al., 2013), and also within subjects with BD, across mood states in cohort studies (Jacoby et al., 2016; Munkholm et al., 2015). Despite such evidence of increased peripheral immune activation in BD, so far evidence supporting the efficacy of either anti-inflammatory or immune modulator agents for BD has been weak and inconsistent across well-designed randomized controlled trials (RCTs) (Husain et al., 2020; McIntyre et al., 2019). A previous meta-analysis of mostly small studies has suggested efficacy for these pharmacological agents (i.e anti-inflammatory agents), (Rosenblat et al., 2016) however the largest RCT conducted to date in participants with bipolar depression found no evidence of efficacy for either minocycline or celecoxib compared to placebo (Husain et al., 2020). These inconsistent findings may be at least in part due to the inclusion of participants with varying levels of peripheral immune activation (Berk et al., 2020). For example, it has been proposed that in major depressive disorder only a subset of subjects with BD may exhibit peripheral inflammation(Milaneschi et al., 2020; Miller and Raison, 2016). However, whether such a

subgroup with peripheral inflammation exists within the context of BD remains unknown. Yet, two large RCTs have stratified participants with bipolar depression according to peripheral levels of C-reactive protein with negative outcomes (Husain et al., 2020; McIntyre et al., 2019). Furthermore, a recent large meta-analysis of immune markers in depression showed no greater variability in most pro-inflammatory immune markers in depression (Osimo et al., 2020).

The most studied pro-inflammatory markers in BD are C-reactive protein (CRP), tumor necrosis factor-alpha (TNF- α), interleukin- (IL) -1 and IL-6. Thus, the current systematic review and meta-analysis aimed to confirm whether differences in such pro-inflammatory biomarkers would exist among participants with BD across different mood states compared to controls. Furthermore, a meta-analysis of variability was conducted to explore whether those with BD show a homogeneous pro-inflammatory phenotype.

2. Methods

2.1 Search, inclusion criteria

We followed an a priori protocol (available upon request to the corresponding author). This was compliant with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols [PRISMA(-P)] (Moher et al., 2015, 2009) (eTable 1, supplementary online material) and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, 2000) guidelines (eTable 2, supplementary online material).

We searched the Pubmed/MEDLINE and PsycInfo databases, last update February 2nd, 2020. The following search strategy was used in Pubmed: (((("bipolar disorder"[mesh])) or (bipolar or bipolar depression[title/abstract] or bipolar disorder[title/abstract] or mania[title/abstract] or hypomania[title/abstract]))) and (((("c-reactive protein"[mesh]) or crp or tnf or "tumor necrosis factor-alpha"[mesh]) or IL1 or IL-1 or "interleukin-1"[mesh]) or "interleukin-6"[mesh] OR IL-6 OR IL6)). A similar strategy was used for PsycInfo (see supplementary online material).

Inclusion criteria were case-control observational studies, that assayed IL-1 β , IL-6, TNF- α , or CRP in people with BD in any mood state, both in medicated and unmedicated subjects, as well as in healthy controls. Only studies including subjects with BD according to standard operational criteria were considered (e.g., ICD-10, DSM-5) (American Psychiatric Association, 2013; WHO, n.d.). Studies published in any language were considered for inclusion. Studies that assayed other immune mediators, preclinical studies as well as studies that did not enroll participants with BD according to established diagnostic criteria were excluded.

MF, GC, BB, and MS (all MDs with expertise in meta-research) independently searched the literature and selected the eligible studies. Any disagreement was resolved by consensus, or by a third author (MS).

2.2 Data extraction

The following information was extracted into a pre-defined spreadsheet: author, year, country, study design, diagnostic criteria for BD, age, female %, sample size, marker centrality and dispersion measures, assay method and medium, mood phase, treatment status, body mass index, duration of illness and smoking %. Only studies reporting both mean and SD or SEM; or median and interquartile ranges were included. Where data were only available in diagrammatic format, data were extracted using the Plot Digitizer tool.(Rohatgi, 2020) When data needed to include the study in the meta-analysis were not available, we contacted authors up to two times (two weeks apart) to include the study in our meta-analysis. The same authors who conducted the screening also extracted the data, with an additional check from two authors (MS, EO).

2.3 Quality assessment

The methodological quality of each eligible study was assessed using the NIH tool for case-control studies (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>). As no consensus is

available on a high-quality threshold for this tool, we categorized quality in tertiles – this resulted in a threshold score of 7 in this study.

2.4 Statistical analysis

Analyses were performed on log-transformed data since the Cochrane Collaboration recommends log transformation for the normalization of positive skew, (Higgins et al., 2020, 2008) as meta-analyses based on means are appropriate only for data that are at least approximately normally distributed. Data not presented directly as log-transformed in the original manuscripts were transformed, as described by Higgins and colleagues (Higgins et al., 2020, 2008). As most studies published data on several parameters from the same subjects, multivariate meta-analyses were used. This allows simultaneous estimation of summary effect sizes across multiple correlated parameters, also reducing the risk of false positives due to multiple comparisons (Bender et al., 2008).

The meta-analyses of mean group differences in immune parameters were performed using Hedges g as a measure of effect size. A random-effects model (restricted maximum likelihood) was used to consider methodological differences across studies.

Variability was measured through the natural log of the ratio of estimates of the population standard deviations for each group, to give the log variability ratio (VR), as previously described (Osimo et al., 2020). In biological systems, variance often scales with the mean (Eisler and Kertész, 2007). Thus, to account for between-group differences in mean, we performed a meta-analysis of relative variability of subjects with BD compared to control immune parameters scaled to group means. The log coefficient of variation ratio (CVR) (the natural logarithm of the ratio of estimates of population coefficients of variation) controls for between-group differences in mean. To aid interpretation, summary effect sizes for $\ln VR$ and $\ln CVR$ were transformed back to a linear scale, as previously described (Brugger and Howes, 2017; Osimo et al., 2020). Thus, for example, a CVR (or VR) of 1 indicates equal variability in patient and control groups, while a CVR (or VR) greater than 1 indicates greater relative variability in patient groups. Yet, CVR accounts for between-differences in mean.

2.5. Publication bias, sensitivity, and meta-regression analyses

Publication bias was assessed via visual inspection of the funnel plot, and studies falling outside of the funnel plot were excluded in sensitivity analyses. Further sensitivity analyses explored whether disease/mood state, medication status (including only studies with untreated subjects), BMI matching (excluding BMI not mentioned or matched), smoking matching, and quality of included studies affected results (excluding lowest-scoring studies). Also, we explored via meta-regression whether age, sex, duration of illness, sample size, and ethnicity moderated results, whenever information was available.

3. Results

3.1 Study selection

Out of the initial 729 references assessed at the title/abstract level, 125 were assessed at the full-text level. Of these, 72 were excluded, with specific reasons reported in eTable 3, Supplementary online material. Ultimately, 53 studies were eligible for the systematic review. Four of these did not provide data suitable for the analyses (Boufidou et al., 2004; Karabulut et al., 2019; Kauer-Sant'Anna et al., 2008; Sanjay et al., 2017); 49 were included in the meta-analysis (Aas et al., 2017; Bai et al., 2015; Barbosa et al., 2017, 2013, 2012b, 2012a, 2011; Brietzke et al., 2009; Chakrabarty et al., 2019; Chang et al., 2017; Civil Arslan et al., n.d.; Cunha et al., 2008; da Silva et al., 2017; De Berardis et al., 2008; Dickerson et al., 2007; Doganavsargil-Baysal et al., 2013; Glaus et al., 2018; Guloksuz et al., 2010; Hope et al., 2015, 2011, 2009; Hornig et al., 1998; Huang and Lin, 2007; Hung et al., 2007; Jacoby et al., 2016; Kapczinski et al., 2011; Kim et al., 2007; King et al., 2019; Koga et al., 2019; Lesh et al., 2018; Mao et al., 2018; Mizuno et al., 2016; Mondin et al., 2016; Mora et al., 2019; Ortiz-Domínguez et al., 2007; Pantović-Stefanović et al., 2018; Quidé et al., 2019; Remlinger-Molenda et al., 2012; Scola et al., 2016; Tsai et al., 2012; Tunç et al., 2019; van den Ameele et al., 2018; Vasconcelos-Moreno et al., 2017; Wadee et al., 2002; Wang et al., 2016; Wieck et al., 2014; Wiener et al., 2019, 2017; Wu et al., 2017) (see eFigure 1, supplementary online material).

Data on more than one inflammatory mediator were reported in most of the 49 studies, yielding 135 data points, specifically 37 for CRP, 4 for IL-1 β , 45 for IL-6, and 49 for TNF- α . Details on the distribution of outcomes across included studies as well as further characteristics on outcomes are reported in Table 1. Subjects' mean age was 36.96 years (standard deviation 9.29), and the mean female percentage was 56.31 (SD 16.61). Data were synthesized from 8,837 participants (3,528 participants with BD and 5,309 controls).

3.2 Mean difference in levels of inflammatory mediators

The results of the comparative meta-analysis on levels of a-priori selected inflammatory mediators is reported in Figure 1. All mediators except IL-1 were elevated in BD compared to controls. Specifically, CRP ($g=0.70$, 95% CI 0.31-1.09, $I^2=97.05\%$, $k=37$, BD=2,215 vs HC=3,750), IL-6 ($g=0.81$, 95% CI 0.46-1.16, $I^2=96.12\%$, $k=45$, BD=1,956 vs HC=4,106), TNF- α ($g=0.49$, 95% CI 0.19-0.78, $I^2=93.96\%$,

k=49, BD=2,231 vs HC=3,017) were elevated in subjects with BD vs healthy controls, whilst no difference emerged for IL-1 β ($g=-0.28$, 95% CI -0.68 to 0.12, $I^2=18.65\%$, k=4, BD=87 vs HC=66).

3.3 Variability of levels of inflammatory mediators

Results of meta-analyses of variability ratios are reported in Figures 3-4, and eFigures 8-9.

When considering the whole sample, no difference in CVR emerged for CRP (CVR=1.06, 95% CI 0.94-1.19, k=37, BD=2,215 vs HC=3,750), IL-1 β (CVR=1.05, 95% CI 0.58-1.93, k=4, BD=87 vs HC=66), and TNF- α (CVR=0.95, 95% CI 0.84-1.07, k=49, BD=2,231 vs HC=3,017), while lower CVR was observed for IL-6 (CVR=0.84, 95% CI 0.75-0.95, k=45, BD=1956 vs HC=4106).

When considering disease phases, no significant difference in mean-scaled variability between cases and controls were observed in euthymia and in mixed states for CRP (CVR=1.05, 95% CI 0.91-1.22, k=8, BD=340 vs HC=1882 ; CVR=1.05, 95% CI 0.90-1.23, k=13, BD=1285 vs HC=1424), TNF- α (CVR=0.98, 95% CI 0.87-1.10, k=16, BD=535 vs HC=1997 ; CVR=0.92, 95% CI 0.72-1.18, k=16, BD=1138 vs HC=656) and IL-6 (CVR=0.82, 95% CI 0.70-0.97, k=13, BD=442 vs HC=1973 ; CVR=0.84, 95% CI 0.72-0.99, k=14, BD=920 vs HC=1660). During depressive episodes, CVR was larger among participants with BD for CRP (CVR=1.38, 95% CI 1.14-1.69, k=7, BD=300 vs HC=228) but not for IL-6 (CVR=0.91, 95% CI 0.70-1.18, k=10, BD=341 vs HC=236) and TNF- α (CVR=0.70, 95% CI 0.49-1.02, k=7, BD=236 vs HC=112). During mania, CVR was larger in participants with BD for all immune mediators with available data: CRP (CVR=5.45, 95% CI 2.08-14.29, k=9, BD=290 vs HC=216), IL-6 (CVR=3.50, 95% CI 1.72-7.11, k=8, BD=253 vs HC=237) and TNF- α (CVR=2.94, 95% CI 1.00-8.60, k=10, BD=322 vs HC=253).

When including only untreated samples in sensitivity analyses, CVR differences were attenuated for IL-6 (CVR=0.82, 95% CI 0.64-1.06, k=8, BD=420 vs HC=998), and for TNF- α (CVR=0.85, 95% CI 0.65-1.12, k=7, BD=239 vs HC=240).

Finally, the analysis of variability ratios revealed a lower ratio for CRP (VR=0.59, 95% CI 0.44-0.80, k=37, BD=2215 vs HC=3750) and TNF- α (VR=0.75, 95% CI 0.58-0.98, k=49, BD=2231 vs HC=3017), a higher ratio for IL-1 β (VR=2.56, 95% CI 1.13-5.77, k=4, BD=87 vs HC=66), and no difference for IL-6 (VR=0.62, 95% CI 0.35-1.08, k=45, BD=1956 vs HC=4106).

3.3.1 Sensitivity analyses

Results of sensitivity analyses are reported in Figure 2, and eFigures 3-7. When considering different disease states, levels of all the considered immune mediators were elevated in all acute illness phases. Specifically, CRP, IL-6 and TNF- α were elevated among participants with BD in a major depressive episode compared to healthy controls (CRP $g=1.72$, 95% CI 0.52-2.92, k=7, BD=300 vs HC=228 ; IL-6 $g=1.00$, 95% CI 0.22-1.77, k=10, BD=341 vs HC=236 ; TNF- α $g=2.32$, 95% CI 0.76-3.89, k=7, BD=236 vs HC=112), as well as in participants with mania (CRP $g=1.70$, 95% CI 0.73-2.66, k=9,

BD=290 vs HC=216 ; IL-6 $g=1.25$, 95% CI 0.54-1.96, $k=8$, BD=253 vs HC=237 ; TNF- α $g=1.08$, 95% CI 0.00-2.15, $k=10$, BD=322 vs HC=253) and in mixed states (CRP $g=0.48$, 95% CI 0.06-0.90, $k=13$, BD=1,285 vs HC=1424 ; IL-6 $g=0.69$, 95% CI 0.25-1.14, $k=14$, BD=920 vs HC=1,660 ; TNF- α $g=0.33$, 95% CI 0.12-0.54, $k=16$, BD=1,138 vs HC=656, respectively). In euthymia, only IL-6 levels were elevated in participants with BD compared to healthy controls ($g=0.40$, 95% CI 0.11-0.69, $k=13$, BD=442 vs HC=1,973), but not CRP ($g=0.50$, 95% CI -0.24-1.23, $k=8$, BD=340 vs HC=1882) or TNF- α ($g=0.15$, 95% CI -0.27-0.57, $k=16$, BD=535 vs HC=1,997).

Those results remained unaltered after the exclusion of outliers, identified with funnel plot visual inspection, and the exclusion of studies with low methodological quality. Specifically, elevation persisted for CRP ($g=0.55$, 95% CI 0.27-0.82, $k=33$, BD=2099 vs HC=3,715 ; $g=0.83$, 95% CI 0.16-1.50, $k=26$, BD=1,658 vs HC=2923), IL-6 ($g=0.61$, 95% CI 0.31-0.91, $k=44$, BD=1946 vs HC=4,073 ; $g=0.90$, 95% CI 0.44-1.35, $k=36$, BD=1722 vs HC=3922) and TNF- α ($g=0.36$, 95% CI 0.18-0.55, $k=45$, BD=2,162 vs HC=2,969 ; $g=0.61$, 95% CI 0.12-1.10, $k=37$, BD=1,857 vs HC=2,680).

Similar results were obtained including only BMI-matched samples for CRP ($g=0.94$, 95% CI 0.37-1.51, $k=21$, BD=1,113 vs HC=2780), IL-6 ($g=0.73$, 95% CI 0.35-1.11, $k=23$, BD=1091 vs HC=2,618), and TNF- α ($g=0.49$, 95% CI 0.17-0.81, $k=22$, BD=929 vs HC=2,187).

When including only untreated samples,(Chang et al., 2017; Guloksuz et al., 2010; Huang and Lin, 2007; Kim et al., 2007; Lesh et al., 2018; Mao et al., 2018; Ortiz-Domínguez et al., 2007; Pantović-Stefanović et al., 2018; Scola et al., 2016; Wiener et al., 2017, 2019; Wu et al., 2017) data were available only for IL-6 and TNF- α . Only IL-6 showed higher elevated levels in participants with BD relative to HCs ($g=1.22$, 95% CI 0.26-2.18, $k=8$, BD=420 vs HC=998), while no significant differences were observed for TNF- α ($g=1.11$, 95% CI -0.77-2.98, $k=7$, BD=239 vs HC=240).

With the inclusion of only smoking-matched samples, both CRP ($g=0.28$, 95% CI -0.17-0.74, $k=4$, BD=333 vs HC=2099) and IL-6 ($g=0.16$, 95% CI -0.75-1.06, $k=4$, BD=267 vs HC=2065) did not differ between participants with BD and controls.

3.3.2 Meta-regression

Meta-regression analyses showed that age was a moderator for IL-6 ($r=-0.04$, $p<0.001$) and TNF- α ($r=-0.05$, $p<0.001$), while CRP was moderated by gender ($r=-0.02$, $p=0.021$) and duration of illness ($r=-$

0.116, $p=0.046$). Duration of illness, publication year, Caucasian ethnicity, and sample size did not moderate levels of any of the considered immune mediators.

3.4 Publication bias, study quality

Publication bias emerged from funnel plot visual inspection, and a sensitivity analysis was run without outliers (see above). Details on study quality are reported in eTable 5, Supplementary online material. The median study quality was 7 (IQR 6-9). Low quality emerged most frequently on item 5 (“Was a sample size justification, power description, or variance and effect estimates provided?”), with only two studies meeting this criterion (Jacoby et al., 2016; Mizuno et al., 2016).

4. Discussion

To our knowledge, this is the largest systematic review and meta-analysis conducted to date assessing inflammatory mediators in participants with BD relative to controls. For instance, the current meta-analytic review included 1.83 more studies than the previous largest meta-analysis (Modabbernia et al., 2013). Our findings point to an elevation of pro-inflammatory immune biomarkers, namely CRP, IL-6, TNF- α among participants with BD relative to controls, providing evidence that peripheral inflammation is part of the pathophysiology in BD.

When acute phases of the illness were considered, elevations in CRP, IL-6, and TNF- α were observed in major depressive episodes, manic episodes, and in mixed states among participants with BD compared to controls. However, only IL-6 remained elevated in euthymia. These novel findings indicate that while CRP and TNF- α might be regarded as “mood episode” markers of BD, IL-6 might be a trait marker of this illness. It is noteworthy that subjects with BD have a higher rate of medical comorbidities (e.g., obesity) and addictive disorders (e.g., tobacco smoking) compared to the general population (Firth et al., 2019; Momen et al., 2020). Sensitivity analyses including only studies that matched for body mass index and smoking status confirmed our main findings thereby adding robustness to our results. Furthermore, a subset of subjects with BD exhibit neuroprogression reflected as an increase in functional impairment, treatment refractoriness, and cognitive dysfunction with recurring affective episodes of BD (Berk et al., 2011; Carvalho et al., 2020). Peripheral immune activation is thought to contribute to neuroprogression in BD (Quevedo et al., 2021). Inflammation

likely also drives the parallel process of somatoprogession and physical comorbidity (Morris et al., 2019). In our meta-regression analysis, however, we only observed a marginally significant inverse and negligible association between that CRP levels and duration of BD.

Interestingly we did not observe an increase in IL-1 β levels in participants with BD compared to controls (Goldsmith et al., 2016). This was an unexpected finding since both TNF- α and IL-1 β are predominantly secreted by macrophages (Maes and Carvalho, 2018). However, few studies ($k=4$) assayed IL-1 β in the periphery and there was a large heterogeneity across studies (Carvalho et al., 2020).

Notwithstanding our findings support the view that IL-6 might be considered a trait marker for BD, this per se does not provide conclusive evidence that the illness is characterized by peripheral inflammation. Leucocytes, hepatocytes, and megakaryocytes express IL-6 receptors with two functional membrane receptors namely the IL-6-binding IL-6R (CD126) and glycoprotein 130 (gp130, CD130), which is highly expressed in most cells. While the classic IL-6 signaling pathway is confined to cells that express the IL-6R, the IL-6-IL-6R complex induces IL-6 trans-signaling in most cell types (Maes et al., 2014). The classical IL-6 signaling pathway is predominantly inflammatory, whilst the trans-signaling pathway is predominantly anti-inflammatory and regenerative (Fonseka et al., 2015). The relative balance of activation of the trans-signaling pathway versus the classical pathway within the context of BD remains relatively unexplored and could thus be a promising area of investigation. Moreover, the action of IL-6 and other inflammatory mediators acts via their interaction with receptors, whose expression is altered in BD (Pandey et al., 2015), and whose role could not be assessed within this evidence synthesis effort.

4.1. Meta-analysis of variability

Across all eligible studies, there were no statistically significant differences in the log of the coefficient of variation ratios (CVRs) for any of the immune biomarkers assessed. This indicates either a homogeneous increase in those biomarkers (except IL-1) in BD, or a type 2 error. However, statistically significant differences in CVRs were observed during acute phases of the illness as well as in euthymia. More specifically, in participants with an acute depressive episode, the variability of data distribution for CRP was higher for participants with BD than for controls. This is of relevance since CRP has been

used to stratify subjects with bipolar depression who could benefit from treatment with anti-inflammatory agents (Husain et al., 2020; McIntyre et al., 2019). However, at least two large trials have provided disappointingly negative results after stratification (Husain et al., 2020; McIntyre et al., 2019). Thus, an individual participant-level data meta-analysis (IPD-MA) could shed more light on this question (i.e., whether a subgroup of subjects with elevated CRP levels in bipolar depression could exist). In manic episodes, CVRs for CRP and IL-6 were statistically significant and > 1 , indicating that the variability of distribution was higher for participants with BD than for controls. If a subgroup of subjects with “inflamed mania” is confirmed by an IPD-MA, this could provide a rationale to use those biomarkers to stratify subjects with mania who could be more likely to benefit from immune modulators and anti-inflammatory agents. In euthymia, the CVR for IL-6 was statistically significant and < 1 , indicating that the distribution of IL-6 was more homogeneous for euthymic participants with BD than for controls.

4.2. Strengths and limitations

The main strength of this work is the use of the largest sample of studies assessing inflammatory mediators in BD conducted to date. In addition, potential confounders were systematically addressed in sensitivity analyses. Furthermore, even if we could not make any assumption on the shape of the distribution of the data, such as modality, as this would require an IPD-MA, we were able to obtain interesting albeit preliminary findings in our meta-analysis of variability.

Our findings, however, should be interpreted considering some limitations. First, we included studies in which a diagnosis of BD was established through different methods (e.g., DSM, ICD). Second, other potential confounders (e.g., assay sensitivity and more subtle medical and psychiatric comorbidities) could not be controlled for. Third, we selected an a-priori a panel of immune biomarkers which was not exhaustive. Fourth, high heterogeneity affected results. Fifth, sensitivity analyses had much smaller sample size than main analyses, and if negative might represent type 2 errors. Sixth, cross-sectional studies were included, including one-time sampling, limiting causal inferences. Seventh, it was not possible to exclude all co-morbidities due to original data quality. Finally, the finding on persistent elevation of inflammatory mediators in “remission” phase should be interpreted with caution, as the duration of remission ranged from two weeks to six months, suggesting that the elevated levels

of IL-6 may be due to a possibly slower decrease after an acute episode in some studies (with shorter duration of remission).

4.3. Conclusion and future research directions

In this largest meta-analytic review conducted to date, we found evidence that key inflammatory biomarkers were elevated in BD vs healthy controls, and they displayed higher variability in acute episodes of BD compared to controls. The robustness of our findings was confirmed by a series of sensitivity analyses. This provides preliminary evidence that deserves confirmation in an IPD-MA of the existence of possible “inflamed depression” or “inflamed manic” subgroups within the context of BD. This is an area of acute interest since this could provide the basis to stratify subjects based on those specific biomarkers who could benefit from adjunctive anti-inflammatory therapies within the emerging framework of precision psychiatry (Vieta, 2015) and subsequent developments that are being put in place through global collaborative research (Fernandes et al., 2020, 2017; Manchia et al., 2020). Finally, our data confirm that across the mood spectrum BD is an illness characterized by peripheral immune activation.

Conflict of interest disclosure

PFP received research support from Lundbeck and honoraria from Lundbeck, Angelini, Menarini, Boehringer-Ingelheim, outside the current work. MS received honoraria/has been a consultant for Angelini, Lundbeck. MF received honoraria/has been a consultant for Angelini, Shire.

EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, Abbott, AbbVie, Angelini, Boehringer-Ingelheim, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, GH Research, Janssen, Lundbeck, Novartis, Otsuka, Sage, Sanofi-Aventis, Sunovion, and Takeda, outside the submitted work.

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Development, Janssen and Janssen, Lundbeck Merck, Pfizer and Servier – all unrelated to this work.

Other authors report no conflict of interest.

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FIGURE LEGENDS

Fig 1. Meta-analysis of levels of inflammatory markers in bipolar affective disorder (BAD) vs healthy controls (Ctr).

Fig. 2. Sensitivity analysis of levels of inflammatory markers across disease state.

Fig. 3. Meta-analysis of log coefficient of variation ratios of inflammatory markers in bipolar affective disorder (BAD) vs healthy controls (Ctr).

Fig. 4. Meta-analysis of log coefficient of variation ratio of inflammatory markers in bipolar affective disorder (BAD) vs healthy controls across disease state.

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<https://doi.org/10.1038/srep40530>

Table 1. Characteristics of included studies

Author and year	N cases	N controls	Cytokine	BD states	Age case (mean)	Age ctrl (mean)	% female cases	% female ctrls	Treatment status	Country	Diagnosis criteria	Assay
Aas M. et al., 2017(Aas et al., 2017)	123	212	CRP	ns	32.3	30.9	59	86	ns	Norway	DSM-IV	ELISA
Bai Y-M et al., 2015(Bai et al., 2015)	130	130	CRP	mixed	44.5	41.8	67.9	64.6	treated	Taiwan	DSM-IV	ELISA
Barbosa et al., 2011(Barbosa et al., 2011)	19	38	TNF- α	euthymia	44.5	42.9	57.9	52.6	treated	Brazil	DSM-IV	ELISA
	34			mania	49.6		61.8					
Barbosa et al., 2012 A(Barbosa et al., 2012b)	30	30	TNF- α	euthymia	49.03	47.13	76.7	60	treated	Brazil	DSM-IV	ELISA
Barbosa et al., 2012 B(Barbosa et al., 2012a)	25	25	TNF- α	Euthymia	50.88	48.04	68	56	treated	Brazil	DSM-IV	ELISA
Barbosa et al, 2013(Barbosa et al., 2013)	15	12	IL-6, TNF- α	euthymia	52	53	73.3	75	treated	Brazil	DSM-IV	other
Barbosa et al, 2017(Barbosa et al., 2017)	42	50	TNF- α	mania	46.9	46.8	60.6	70	treated	Brazil	DSM-IV	ELISA
	38											
Boufidou et al., 2004(Boufidou et al., 2004)	40	20	IL-6	ns	42.8	49	50	50	treated, untreated	Greece	DSM-IV	ELISA
Brietzke E et al., 2009(Brietzke et al., 2009)	14	25	IL-6	euthymia	44.2	43.4	71.4	80	ns	Brazil	DSM-IV	other
	24			dep	45		62.5					
	23		IL-6, TNF- α	mania	40.8		52.2					
Chakrabarty et al., 2019(Chakrabarty et al., 2019)	51	20	IL-1, IL-6, TNF- α	mixed	23.16	24.86	53	55	treated	Canada	DSM-IV	ELISA
Chang et al., 2017(Chang et al., 2017)	88	96	CRP	dep	31.74	33.3	50	57.3	untreated	China	DSM-IV	ELISA
Civil-Arslan et al., 2017(Civil Arslan et al., n.d.)	36	38	IL-6	euthymia	38	37.94	61.1	52.6	treated	Turkey	DSM-IV	ELISA
Cunha et al., 2008(Cunha et al., 2008)	30	32	CRP	mania	40.13	40.69	43.8	65.6	ns	Brazil	DSM-IV	other
	20			dep	40.71		71.4					
	30			euthymia	40.28		62.5					
Da Silva et al, 2017(da Silva et al., 2017)	31	33	TNF- α	mixed	41.71	41	80.6	81.8	treated	Brazil	DSM-IV	other
De Berardis et al., 2008(De Berardis et al., 2008)	30	30	CRP	Mania	34.5	34.4	46.67	46.67	treated	Italy	DSM-IV	other
				dep	33.6		40					
				Euthymia	38.9		53.33					
Dickerson et al., 2007(Dickerson et al., 2007)	81	165	CRP	mixed	41	34.3	67.9	73.9	treated	USA	DSM-IV	ELISA
	41				40.2		78					
Doganavsargil-Baysal et al., 2013(Doganavsargil-Baysal et al., 2013)	54	18	TNF- α	euthymia	39.46	38.33	36	13	mixed	Turkey	DSM-IV	ELISA
Hope et al, 2009(Hope et al., 2009)	125	244	IL-6, CRP	mixed	35	36	62	56	mixed	Norway	DSM-IV	ELISA
Hope et al, 2011(Hope et al., 2011)	58	239	IL-6, CRP	dep	35	36	60	56	treated	Norway	DSM-IV	ELISA
	26			euthymia	36		54					
	17			mania	36		65					
Hope et al, 2015(Hope et al., 2015)	111	241	IL-6, CRP	mixed	33	36	46	61	mixed	Norway	DSM-IV	ELISA
Hornig et al, 1998(Hornig et al., 1998)	79	22	TNF- α	mixed	51.5	41.1	54.4	36.4	mixed	USA	DSM-III-TR	other
	24			mixed								

Author and year	N cases	N controls	Cytokine	BD states	Age case (mean)	Age ctrl (mean)	% female cases	% female ctrls	Treatment status	Country	Diagnosis criteria	Assay
Huang et al., 2007(Huang and Lin, 2007)	13	31	CRP	mania	36.9	30.5	38.5	42	untreated	Taiwan	DSM-IV	other
Hung et al, 2007(Hung et al., 2007)	15	14	IL-6, TNF- α , CRP	dep	23.8	23.8	ns	ns	ns	Taiwan	DSM-IV	ELISA
Glaus et al, 2017(Glaus et al., 2018)	55	1696	IL-6, TNF- α , CRP	euthymia	51.15	51.53	47.27	44.1	treated	USA	DSM-IV	other
Guloksuz et al., 2010(Guloksuz et al., 2010)	16	16	TNF- α	Euthymia	32.3	31.8	33.33	33.33	untreated	Turkey	DSM-IV	other
	15				31.8		33.36		treated			
Jacoby et al., 2016(Jacoby et al., 2016)	60	35	IL-6, TNF- α , CRP	Euthymia	42.7	36.7	38.3	42.9	treated	Denmark	ICD-10	ELISA
				Mania								
				dep								
				Mixed								
Kapczinski et al, 2011(Kapczinski et al., 2011)	20	20	IL-6, TNF- α	mania	37.9	40.7	60	60	treated	Brazil	DSM-IV	ELISA
				dep	46.1		80					
				euthymia	46.6		60					
Karabulut et al., 2019(Karabulut et al., 2019)	77	30	IL-6, TNF- α	mixed	37.8	31.7	42.8	43.3	treated	Turkey	DSM-IV	ELISA
	30				25.3		76.6					
Kauer Sant'Anna et al., 2008(Kauer-Sant'Anna et al., 2008)	30	30	IL-6, TNF- α	mixed	22.4	22.1	56.7	66.7	treated	Canada	DSM-IV	ELISA
					41.4	43.2	60	63.3				
Kim Y-K. et al, 2007(Kim et al., 2007)	37	74	IL-6, TNF- α	mania	37.8	37.5	62.2	62.2	untreated	Korea	DSM-IV	ELISA
King et al., 2019(King et al., 2019)	13	10	IL-6, TNF- α , CRP	mixed	ns	ns	ns	ns	mixed	United Kingdom	DSM-IV	other
Koga et al, 2019(Koga et al., 2019)	65	90	IL-6, TNF- α	ns	40	40	55.4	53.3	mixed	Japan	DSM-IV	other
Lesh et al., 2018(Lesh et al., 2018)	16	53	TNF- α	mixed	21.4	19.5	25	36	untreated	USA	DSM-IV-TR	other
Mao et al., 2018(Mao et al., 2018)	61	62	IL-6, TNF- α	dep	29.52	30.81	50.81	53.23	untreated	China	DSM-IV-TR	ELISA
	29			euthymia								
Mizuno et al., 2016(Mizuno et al., 2016)	57	57	CRP	euthymia	50.2	41	53.3	50	ns	Japan	DSM-IV	ELISA
Mondin et al., 2016(Mondin et al., 2016)	48	94	IL-6, TNF- α	mixed	21.92	22.4	75	57.4	ns	Brazil	DSM-IV	ELISA
Mora et al, 2019(Mora et al., 2019)	52	49	IL-6, TNF- α	euthymia	47.52	48.3	50	57.1	treated	Spain	DSM-IV-TR	ELISA
	32			mania	41.25		43.7					
Ortiz-Dominguez et al., 2007(Ortiz-Domínguez et al., 2007)	10	33	IL-1, IL-6, TNF- α	dep	39.7	32.3	80	84.84	untreated	Mexico	DSM-IV	ELISA
			IL-1, TNF- α	Mania	28.9		70		ns			
Pantovic-Stefanovic et al, 2018(Pantović-Stefanović et al., 2018)	83	73	IL-6, TNF- α	mixed	45.61	45.82	63.6	56.8	untreated	Serbia	DSM-IV	ELISA
									treated			
Quide et al, 2019(Quidé et al., 2019)	66	67	IL-6	mixed	38.11	36.17	66.7	47.2	treated	Australia	ICD-10	ELISA
	66	68	TNF- α									
	61	68	CRP									
Remlinger-Molenda et al, 2012(Remlinger-Molenda et al., 2012)	35	78	IL-6, TNF- α	mania	39	35	62.9	55.1	treated	Poland	DSM-IV	other
	41			dep	45		75.6					

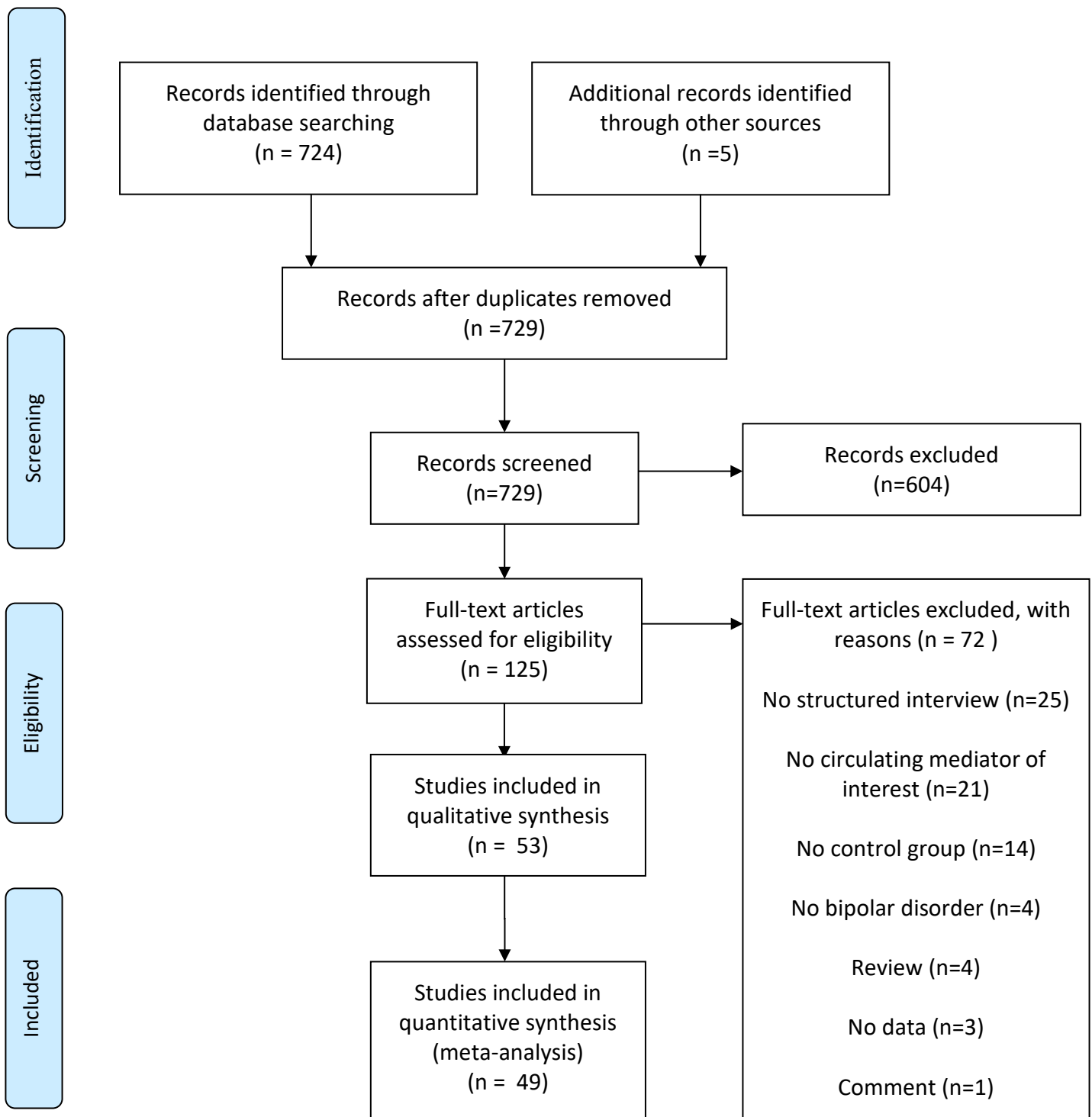
Author and year	N cases	N controls	Cytokine	BD states	Age case (mean)	Age ctrl (mean)	% female cases	% female ctrls	Treatment status	Country	Diagnosis criteria	Assay
	45			euthymia	58		66.7					
Sanjay et al., 2017(Sanjay et al., 2017)	28	18	IL-6	euthymia	26.2	28.9	46.4	22.2	ns	India	DSM-5	ELISA
Scola et al, 2016(Scola et al., 2016)	16	13	IL-1, IL-6, TNF- α	mixed	15.5	17.8	62.5	46.1	untreated	USA	DSM-IV-TR	ELISA
Tsai et al, 2012(Tsai et al., 2012)	33	33	CRP	mania	31.6	28.9	36.4	36.4	treated	Taiwan	DSM-IV	ELISA
	33			hypomania	31.6		36.4					
	33			euthymia	31.6		36.4					
Tunc et al, 2019(Tunç et al., 2019)	37	32	CRP	mixed	33.86	31	ns	ns	treated	Turkey	DSM-IV	ns
van den Ameele et al, 2018(van den Ameele et al., 2018)	29	35	IL-6, TNF- α , CRP	dep	43.3	42.7	58.2	54.3	treated	Belgium	DSM-IV	other
				mania								
	9			mixed								
	49			euthymia								
Vasconcelos-Moreno et al, 2017(Vasconcelos-Moreno et al., 2017)	36	44	IL-6	euthymia	47.2	45.8	75	54.5	treated	Brazil	DSM-IV	other
Wadee et al, 2002(Wadee et al., 2002)	45	45	CRP	mania	32.7	31.2	46.7	ns	ns	South Africa	DSM-IV	other
Wang et al., 2016(Wang et al., 2016)	234	140	CRP	mixed	33.6	31.9	50.85	58.84	ns	Taiwan	DSM-IV	other
			TNF- α	ns								
	260		TNF- α , CRP	ns	31.6		48.07					
Wiener et al, 2017(Wiener et al., 2017)	48	48	IL-6	mixed	21.92	21.88	75	75	untreated	Brazil	DSM-IV	ELISA
Wiener et al, 2019(Wiener et al., 2019)	142	743	IL-6	mixed	ns	ns	59.2	47.6	untreated	Brazil	DSM-IV	ELISA
Wieck et al, 2014(Wieck et al., 2014)	13	15	IL-6, TNF- α	euthymia	46.36	48.07	100	100	treated	Brazil	DSM-IV	other
Wu et al, 2017(Wu et al., 2017)	23	20	IL-6	dep	31.61	35.75	47.83	45	untreated	China	DSM-IV	other

Legend. BD, bipolar disorder; CRP, C-reactive protein; DSM, diagnostic and statistical manual; IL, interleukin; TNF, tumor necrosis factor.

Supplementary Online Material

eFigure 1- PRISMA flowchart.

eFigure 1- PRISMA flowchart.



eTable 1. PRISMA checklist(Moher et al., 2009)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow	5

		diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5, eTable 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5-7, eTable 6, eFigure 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5, figure 2 to 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5, figure 2, 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7, eTable 6, eFigure 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6,7, eFigure 2-8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7,8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

eTable 2. MOOSE Checklist for Meta-analyses of Observational studies(Stroup et al., 2000)

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	3
2	Hypothesis statement	3
3	Description of study outcome(s)	3
4	Type of exposure or intervention used	3
5	Type of study designs used	3
6	Study population	3
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	4
8	Search strategy, including time period included in the synthesis and key words	4
9	Effort to include all available studies, including contact with authors	5
10	Databases and registries searched	4
11	Search software used, name and version, including special features used (eg, explosion)	4
12	Use of hand searching (eg, reference lists of obtained articles)	3,4
13	List of citations located and those excluded, including justification	5, eTable 1, 4
14	Method of addressing articles published in languages other than English	3
15	Method of handling abstracts and unpublished studies	3
16	Description of any contact with authors	4
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	3
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	4
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	5
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	4, 5
22	Assessment of heterogeneity	5
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	
24	Provision of appropriate tables and graphics	eTable 3-6, eFigure 1-8
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figures 2-4
26	Table giving descriptive information for each study included	eTable 1
27	Results of sensitivity testing (eg, subgroup analysis)	5-7, Figure 3,5 eFigures 2-8
28	Indication of statistical uncertainty of findings	5-7, Table 2,3,4

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	7-9
30	Justification for exclusion (eg, exclusion of non-English language citations)	7-9
31	Assessment of quality of included studies	7-9, eTable 6
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	7-8
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	7-8
34	Guidelines for future research	8
35	Disclosure of funding source	9

Search strategy

PubMed/MEDLINE

((("bipolar disorder"[mesh])) or (bipolar or bipolar depression[title/abstract] or bipolar disorder[title/abstract] or mania[title/abstract] or hypomania[title/abstract]))) and (((("c-reactive protein"[mesh]) or crp or tnf or "tumor necrosis factor-alpha"[mesh]) or IL1 or IL-1 or "interleukin-1"[mesh]) or "interleukin-6"[mesh] OR IL-6 OR IL6))

PsycINFO

Search 1: C-reactive protein.mp.

Search 2: CRP.mp.

Search 3: Interleukin-6.mp.

Search 4: IL-6.mp.

Search 5: exp Tumor Necrosis Factor/

Search 6: IL-1.mp.

Search 7: Interleukin-1.mp.

Search 8: #1 or #2 or #3 or #4 or #5 or #6 or #7

Search 9: exp Bipolar Disorder/

Search 10: bipolar depression.mp.

Search 11: exp Mania/

Search 12: exp Hypomania/

Search 13: #9 or #10 or #11 or #12

Search 14: #8 and #13

eTable 4. List of excluded studies after full-text assessment, with reason for exclusion.

Author, year	Reason(s)
Lotrich, 2014 (Lotrich et al., 2014)	Assay IL1RA only
Siwek, 2017 (Siwek et al., 2017)	Assayed IL and TNF receptors
Tsai, 2014 (Tsai et al., 2014)	Assayed IL and TNF receptors
Tsai, 1999 (Tsai et al., 1999)	Assayed sIL2-R and sIL-6R
(Teixeira et al., 2015)	Assayed Soluble receptors of TNF
Sowa-Kucma, 2018 (Sowa-Kucma et al., 2018)	Assayed soluble receptors
Tsai, 2001 (Tsai et al., 2001)	Assayed sIL2-R
Dickerson, 2017 (Dickerson et al., 2017)	Association between suicide attempt and levels of markers of gastrointestinal inflammation
Tsai, 2017 (Tsai et al., 2017)	Case report
Brietzke, 2010 (Brietzke and Teixeira, 2010)	Comment to HOPE study
Aguglia, 2019 (Aguglia et al., 2019)	compares high vs low lethality of suicidal attempts
Brunoni, 2020 (Brunoni et al., 2020)	control group MDD - no healthy ctrl
Kunz, 2011 (Kunz et al., 2011)	Excluded, Diagnosis made by clinical interview. Only healthy controls received non-patient version of SCID
Cingi Yirun, 2017 (Cingi Yirun et al., 2017)	Excluded, Measured TWEAK and TRAIL and not TNF directly.
Wollenhaupt-Aguiar, 2020 (Wollenhaupt-Aguiar et al., 2020)	Excluded. ML approach to differentiate Unipolar from bipolar Depression.
Maes, 1995 (Maes et al., 1995)	Excluded. No formal diagnosis of Bipolar Disorder. Patients in acute phase of Mania and symptoms as measured by Schedule for Affective Disorders and Schizophrenia.
Liu, 2004 (Liu et al., 2004)	Failed to meet our inclusion criteria: not even one of our protocol determined cytokines
Ghafari-Fard, 2019 (Ghafari-Fard et al., 2019)	genetic expression evaluation
Monfrim, 2014 (Monfrim et al., 2014)	IL-B assayed
Mota, 2013 (Mota et al., 2013)	IL-B assayed
Soderlund, 2011 (Söderlund et al., 2011)	IL-B assayed
Ascoli, 2019 (Ascoli et al., 2019)	In vitro study
Do Prado, 2013 (do Prado et al., 2013)	In vitro study
Drexhage, 2011 (Drexhage et al., 2011)	in vitro study
Knijff, 2007 (Knijff et al., 2007)	In vitro study
Munkhol, 2013 (Munkholm et al., 2013)	Meta-analysis
Bond, 2016 (Bond et al., 2016)	no available data comparing cytokines levels between pts and controls at baseline
Aas, 2020 (Aas et al., 2020)	no BD only
Benedetti, 2002 (Benedetti et al., 2002)	no control group
Goldstein, 2015 (Goldstein et al., 2015)	no control group
Pedrotti Moreira, 2019 (Pedrotti Moreira et al., 2019)	No control group
Bai, 2020 (Bai et al., 2020)	no controls included
Chung, 2013 (Chung et al., 2013)	no controls included
Dickerson, 2013 (Dickerson et al., 2013)	no controls included
Guloksuz, 2012 (Guloksuz et al., 2012)	no controls included
Kargar, 2014 (Kargar et al., 2014)	no controls included
Dolsen, 2018 (Dolsen et al., 2018)	no reliable control group
Hope, 2013 (Hope et al., 2013)	no reliable control group
Morch, 2016 (Mørch et al., 2016)	No separate data for bipolar disorder. Patients with MDD, Bipolar Disorder were grouped together in "affective disorder" group for analysis.

Morch, 2017 (Mørch et al., 2017)	No seprate data for bipolar disorder. Patients with MDD, Bipolar Disorder were grouped together in "affective disorder" group for analysis.
Fiedorowicz, 2015 (Fiedorowicz et al., 2015)	No structured interview
Li, 2015 (Li et al., 2015)	No structured interview
Luo, 2016 (Luo et al., 2016)	no structured/semi-structured diagnostic instruments used
Mikowitz, 2016 (Miklowitz et al., 2016)	no structured/semi-structured diagnostic instruments used
Millet, 2019 (Millett et al., 2019)	no structured/semi-structured diagnostic instruments used
Munkholm, 2015 (Munkholm et al., 2015)	no structured/semi-structured diagnostic instruments used
Munkholm, 2018 (Munkholm et al., 2018)	no structured/semi-structured diagnostic instruments used
Munkholm, 2019 (Munkholm et al., 2019)	no structured/semi-structured diagnostic instruments used
Murata, 2020 (Murata et al., 2020)	no structured/semi-structured diagnostic instruments used
O'Brien, 2006 (O'Brien et al., 2006)	no structured/semi-structured diagnostic instruments used
Palacio, 2016 (Palacio et al., 2016)	no structured/semi-structured diagnostic instruments used
Papiol, 2004 (Papiol, 2004)	no structured/semi-structured diagnostic instruments used
Remlinger-Molenda, 2012 (Remlinger-Molenda et al., 2012)	no structured/semi-structured diagnostic instruments used
Sahin, 2019 (Sahin et al., 2019)	no structured/semi-structured diagnostic instruments used
Su, 2011 (Su et al., 2011)	no structured/semi-structured diagnostic instruments used
Tanaka, 2017 (Tanaka et al., 2017)	no structured/semi-structured diagnostic instruments used
Tatay-Manteiga, 2017 (Tatay-Manteiga et al., 2017)	no structured/semi-structured diagnostic instruments used
Uyanik, 2015 (Uyanik et al., 2015)	no structured/semi-structured diagnostic instruments used
Lu, 2019 (Lu et al., 2019)	No structured/semi-structured diagnostic instruments used, Both BPD and MDD patients included.
Osimo, 2018 (Osimo et al., 2018)	no structured/semi-structured diagnostic instruments used, No control group
Marie-Claire, 2019 (Marie-Claire et al., 2019)	no structured/semi-structured diagnostic instruments used, Only Assayed HMGB1.
Benedetti, 2017 (Benedetti et al., 2017)	No structured/semistructured interview
Chen, 2019 (Chen et al., 2019)	No structured/semistructured interview
Horsdal, 2017 (Horsdal et al., 2017)	No structured/semistructured interview
Palomino, 2006 (Palomino et al., 2006)	Only assayed BDNF
Maes, 1996 (Maes et al., 1996)	Patients with Schizophrenia and MDD, no Bipolar Disorder
Lin, 2020 (Lin et al., 2020)	Population: Bipolar Offspring (not BDs)
Wieck, 2016 (Wieck et al., 2016)	Proinflammatory cytokines were measured in the supernatant of monocyte cultured with specific TLR ligand
Chandra, 2014 (Chandra, 2014)	Review
Drexhage, 2010 (Drexhage et al., 2010)	Review
Kramer, 2019 (Kramer et al., 2019)	Review
Ghafelehbash, 2017 (Ghafelehbash et al., 2017)	RNA transcript evaluation

eTable 5. Meta-regression analyses

Moderator	Inflammatory mediator	Estimate	Standard error	Z value	P value
Age	CRP	-0.041	0.023	-1.775	0.076
	IL-1 β	0.308	0.061	5.008	<0.001
	IL-6	-0.043	0.012	-3.455	<0.001
	TNF- α	-0.051	0.011	-4.488	<0.001
Female sex	CRP	-0.024	0.011	-2.304	0.021
	IL-1 β	0.334	0.044	7.609	<0.001
	IL-6	-0.007	0.009	-0.876	0.381
	TNF- α	-0.011	0.007	-1.491	0.136
Duration of illness	CRP	-0.106	0.053	-1.989	0.046
	IL-1 β	NA	NA	NA	NA
	IL-6	-0.005	0.027	-0.202	0.840
	TNF- α	-0.006	0.021	-0.287	0.774
Publication year	CRP	0.011	0.044	0.254	0.799
	IL-1 β	0.003	0.042	0.069	0.945
	IL-6	-0.039	0.044	-0.895	0.371
	TNF- α	-0.031	0.034	-0.905	0.366
Caucasian ethnicity	CRP	-0.058	0.050	-1.170	0.242
	IL-1 β	NA	NA	NA	NA

Sample size	IL-6	-0.021	0.014	-1.536	0.125
	TNF- α	-0.024	0.031	-0.793	0.428
	CRP	-0.001	0.001	-1.092	0.275
	IL-1 β	-0.008	0.009	-0.909	0.363
	IL-6	-0.001	0.001	-1.177	0.239
	TNF- α	-0.001	0.001	-1.403	0.160

Legend. CRP, C-reactive protein; IL, interleukin; TNF, tumor necrosis factor.

eTable 6. Quality appraisal of included studies

Author, year	1. Was the research question or objective in this paper clearly stated?	2. Was the study population clearly specified and defined?	3. Was the participation rate of eligible persons at least 50%?	4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	5. Was a sample size justification, power description, or variance and effect estimates provided?	6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	10. Was the exposure(s) assessed more than once over time?	11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	12. Were the outcome assessors blinded to the exposure status of participants?	13. Was loss to follow-up after baseline 20% or less?	14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	NIH tool Total score
Aas et al., 2017(Aas et al., 2017)	1	1	1	1	0	0	0	0	0	0	0	0	0	0	4
Bai et al., 2015(Bai et al., 2015)	1	1	1	1	0	0	0	0	0	0	1	0	0	0	5
Barbosa et al., 2011(Barbosa et al., 2011)	1	1	1	1	0	0	0	0	0	0	1	0	0	0	5
Barbosa et al., 2012 A(Barbosa et al., 2012b)	1	1	1	1	0	0	0	0	0	0	1	0	0	0	5
Barbosa et al., 2012 B(Barbosa et al., 2012a)	1	0	1	0	0	1	1	0	1	0	1	0	0	0	6
Barbosa et al., 2013(Barbosa et al., 2013)	1	1	1	1	0	0	0	0	1	0	1	0	0	0	6

Barbosa et al., 2017(Barbosa et al., 2017)	1	1	1	0	0	0	0	0	1	0	1	0	0	1	6
Boufidou et al., 2004(Boufidou et al., 2004)	1	1	1	0	0	1	1	0	1	1	1	0	1	0	9
Brietzke et al., 2009(Brietzke et al., 2009)	1	1	1	1	0	0	0	0	0	0	1	0	0	0	5
Chakrabarty et al., 2019(Chakrabarty et al., 2019)	1	1	1	1	0	0	0	0	1	0	1	0	0	1	7
Chang et al., 2017(Chang et al., 2017)	1	1	1	1	0	0	1	0	0	1	1	0	1	1	9
Civil-Arslan et al., 2017(Civil Arslan et al., 2017)	1	1	1	1	0	0	0	0	0	0	0	0	0	1	5
Cunha et al., 2008(Cunha et al., 2008)	1	1	1	1	0	0	0	0	1	0	1	0	0	0	6
Da Silva et al., 2017(da Silva et al., 2017)	1	1	1	1	0	0	0	0	0	0	1	0	0	1	6
De Berdardis et al., 2008(De Berardis et al., 2008)	1	0	1	0	0	1	1	1	1	0	1	0	0	0	7
Dickerson et al., 2007(Dickerson et al., 2007)	1	1	0	0	0	1	1	1	1	0	1	0	0	1	8
Doganavsargil- Baysal et al., 2013(Doganavsargil- Baysal et al., 2013)	1	1	1	1	0	0	0	0	1	0	1	0	0	1	7
Glaus et al., 2017(Glaus et al., 2018)	1	1	1	1	0	1	1	0	1	1	1	0	0	1	10

Guloksuz et al., 2010(Guloksuz et al., 2010)	1	0	1	1	0	1	1	1	1	0	1	0	0	0	8
Hope et al., 2009(Hope et al., 2009)	1	1	1	1	0	0	0	0	1	0	1	0	0	1	7
Hope et al., 2011(Hope et al., 2011)	1	1	1	1	0	0	0	0	1	0	1	0	0	1	7
Hope et al., 2015(Hope et al., 2015)	1	1	1	1	0	0	0	0	1	0	1	0	0	1	7
Hornig et al., 1998(Hornig et al., 1998)	1	1	1	1	0	0	0	0	0	0	1	0	0	1	6
Huang et al., 2007(Huang and Lin, 2007)	1	1	1	1	0	0	0	0	0	0	1	0	0	1	6
Hung et al., 2007(Hung et al., 2007)	1	1	1	1	0	0	0	0	0	0	1	0	0	1	6
Jacoby et al., 2016(Jacoby et al., 2016)	1	1	0	0	1	1	1	1	1	0	1	1	0	1	10
Kapczinski et al., 2011(Kapczinski et al., 2011)	1	1	1	1	0	0	0	0	1	0	1	0	0	1	7
Karabulut et al., 2018(Karabulut et al., 2019)	1	1	1	1	0	0	0	0	0	0	1	0	0	0	5
Kauer-Sant'Anna et al., 2008(Kauer-Sant'Anna et al., 2008)	1	1	1	0	0	0	0	0	1	0	1	0	0	0	5
Kim et al., 2007(Kim et al., 2007)	1	1	1	1	0	0	1	0	0	1	1	0	0	0	7

King et al., 2019(King et al., 2019)	1	1	1	0	0	0	0	0	0	0	1	0	0	0	4
Koga et al., 2019(Koga et al., 2019)	1	1	1	1	0	0	0	0	1	0	1	0	0	1	7
Lesh et al., 2018(Lesh et al., 2018)	1	0	0	0	0	1	1	1	1	0	1	0	0	1	7
Mao et al., 2018(Mao et al., 2018)	1	1	0	1	0	1	1	1	1	0	1	0	0	1	9
Mizuno et al., 2016(Mizuno et al., 2016)	1	1	1	1	1	1	1	0	1	0	1	1	0	1	11
Mondin et al., 2016(Mondin et al., 2016)	1	1	1	1	0	1	1	1	1	0	1	0	0	0	9
Mora et al., 2019(Mora et al., 2019)	1	1	0	0	0	1	1	1	1	0	1	0	0	1	8
Ortiz-Dominguez et al., 2007(Ortiz- Domínguez et al., 2007)	1	1	1	1	0	1	1	1	1	0	1	0	0	0	9
Pantovic-Stefanovic et al., 2018(Pantović- Stefanović et al., 2018)	1	1	1	1	0	1	1	1	1	1	1	0	0	1	11
Quide et al., 2019(Quidé et al., 2019)	1	1	0	1	0	1	0	0	1	0	1	0	0	0	6
Remlinger-Molenda et al., 2012(Remlinger- Molenda et al., 2012)	1	1	0	0	0	1	1	1	1	0	1	0	0	0	7

Sanjay et al., 2017(Sanjay et al., 2017)	1	1	0	0	0	1	1	0	0	0	1	0	0	0	5
Scola et al., 2016(Scola et al., 2016)	1	1	0	1	0	1	1	0	1	0	1	1	0	1	9
Tsai et al., 2012(Tsai et al., 2012)	1	1	0	1	0	1	1	1	1	1	1	0	0	1	10
Tunc et al., 2019(Tunç et al., 2019)	1	1	1	1	0	1	1	1	1	0	1	0	1	1	11
Van den Ameele et al., 2018(van den Ameele et al., 2018)	1	1	0	1	0	1	1	1	1	1	1	0	0	1	10
Vasconcelos- Moreno et al., 2017(Vasconcelos- Moreno et al., 2017)	1	1	0	1	0	1	1	0	1	0	1	0	0	1	8
Wadee et al., 2002(Wadee et al., 2002)	1	1	0	0	0	1	1	0	1	0	1	0	1	0	7
Wang et al., 2016(Wang et al., 2016)	1	0	1	0	0	1	1	1	1	0	1	1	0	1	9
Wiener et al., 2017(Wiener et al., 2017)	1	1	0	1	0	1	1	0	1	0	1	0	1	0	8
Wiener et al., 2019(Wiener et al., 2019)	1	1	0	1	0	1	1	0	1	0	1	0	1	1	9
Wieck et al., 2014(Wieck et al., 2014)	1	1	1	0	0	1	1	0	1	1	1	0	1	0	9
Wu et al., 2017(Wu et al., 2017)	1	1	0	1	0	1	1	0	1	0	1	0	1	0	8

n (%) studies in lower tertile (0 – 4)

n (%) studies in middle tertile (5 – 9)

n (%) studies in upper tertile (10 – 14)

Median (IQR) NIH total score

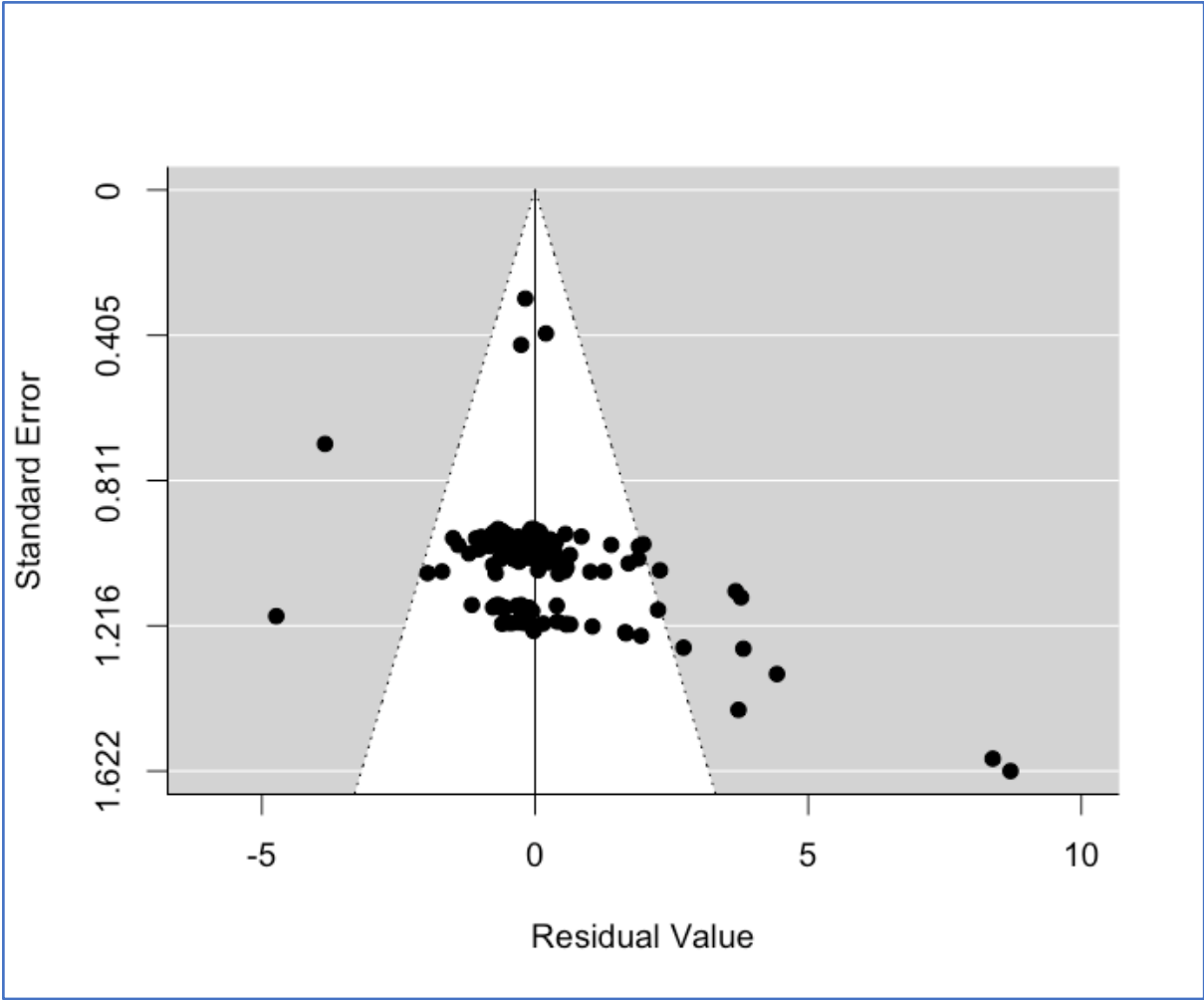
2 (3.77%)

44 (83.0%)

7 (13.2%)

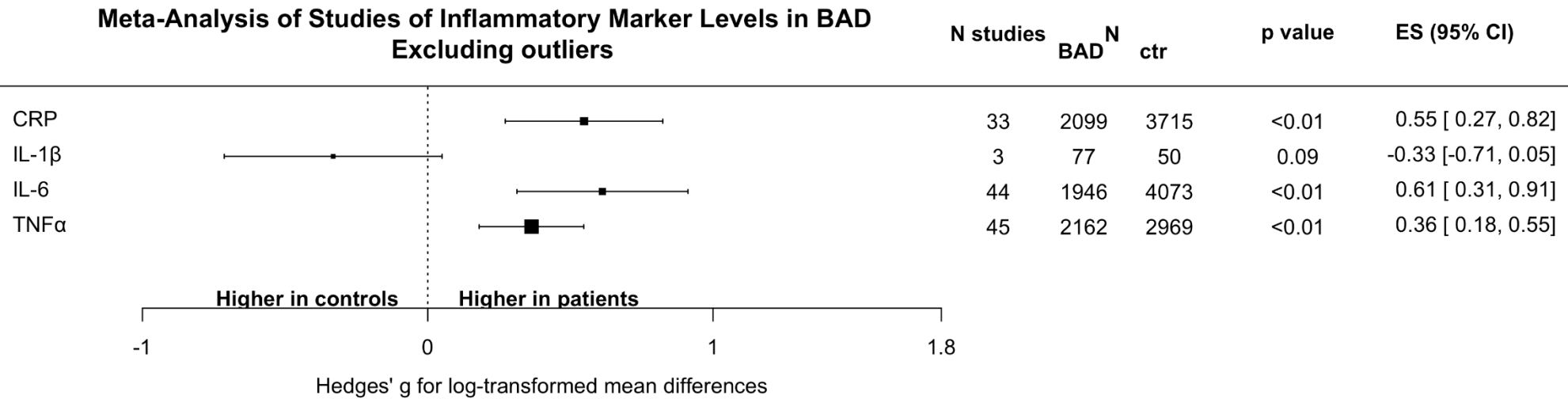
7 (6 - 9)

eFigure 2. Funnel plot for assessment of publication bias

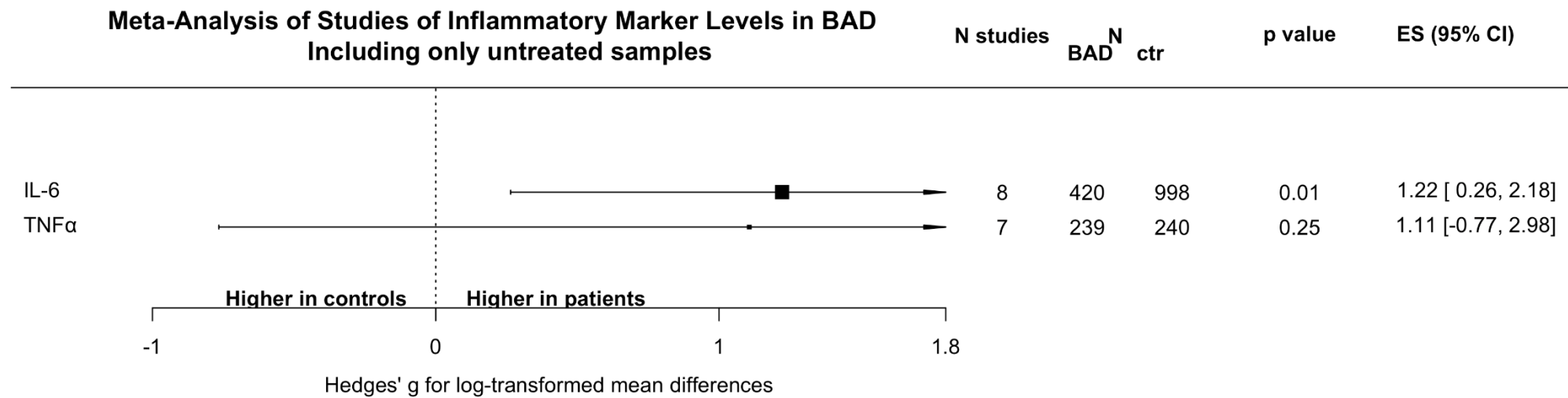


eFigure3. Sensitivity analysis excluding outliers.

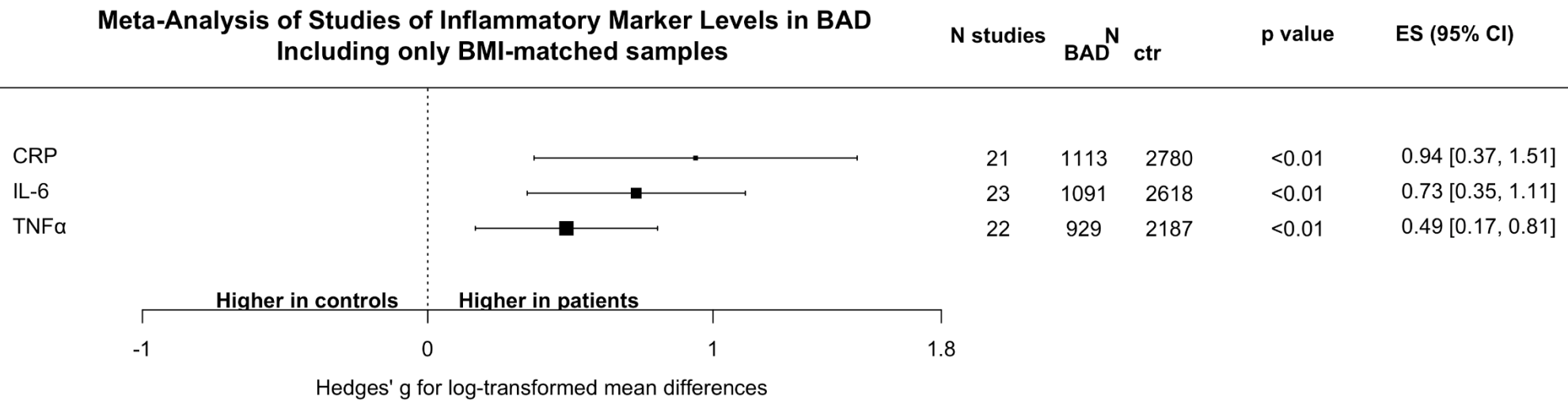
eFigur



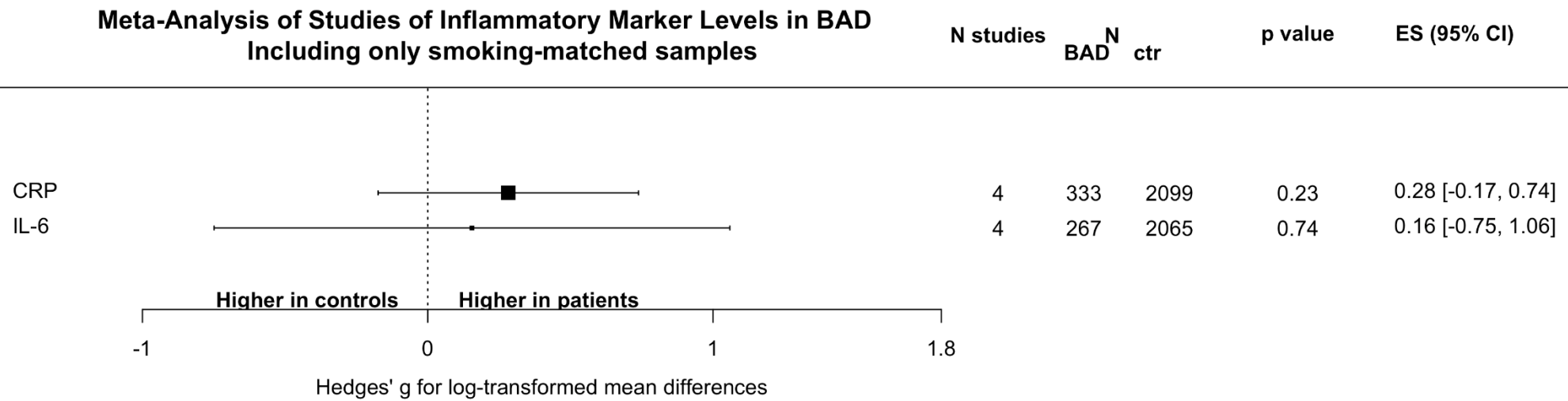
eFigure 4. Sensitivity analyses only including untreated samples



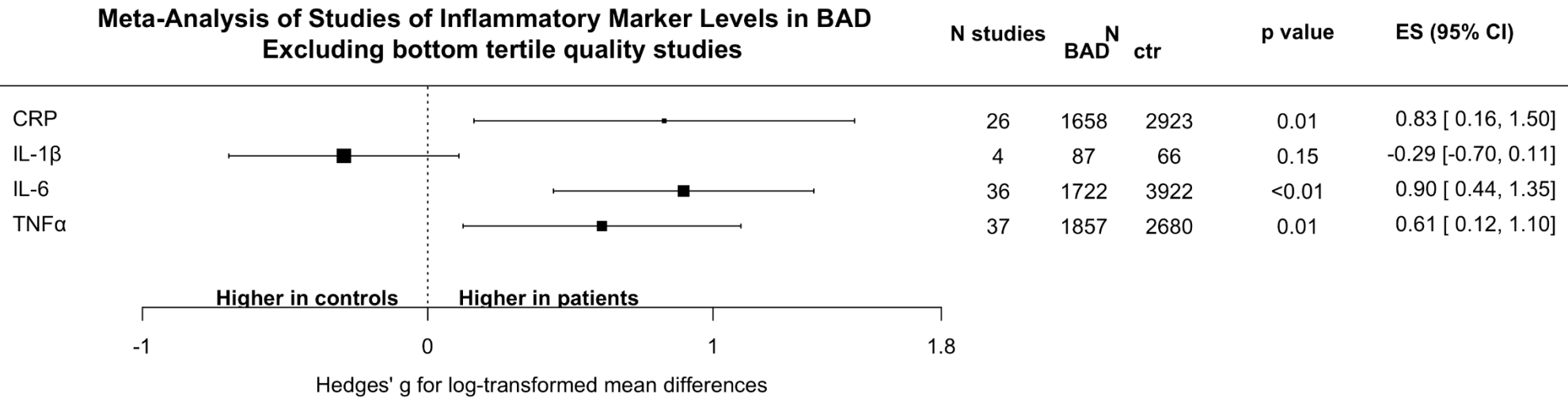
eFigure 5. Sensitivity analyses only including body mass index-matched samples



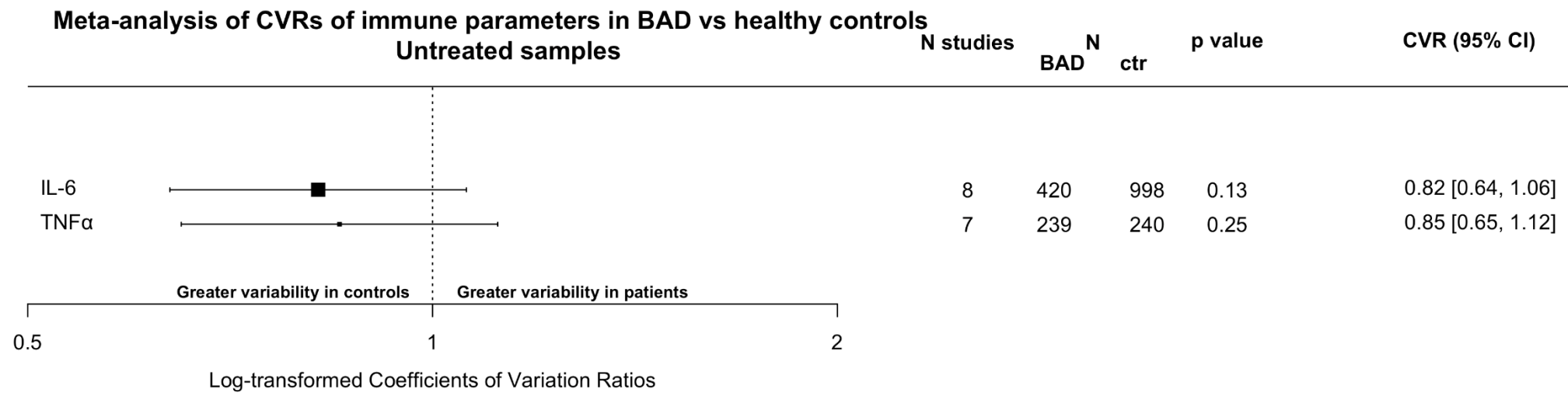
eFigure 6. Sensitivity analyses only including smoking-matched samples



eFigure 7. Sensitivity analyses only including higher quality studies.



eFigure 8. Sensitivity analyses of CVR only including untreated samples



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