**Peripheral Levels of C-reactive protein, tumor necrosis factor-α, interleukin-6, and interleukin-1β 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-1β, 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-1β (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-1β, 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-1β, IL-6, C-reactive protein, TNF-α, meta-analysis, psychiatry, neuroscience, mental disorders.

# 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(Dargél 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.

# 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-1β, 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).](about:blank) 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 lnVR and lnCVR 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.

# 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-1β, 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, I2=97.05%, k=37, BD=2,215 vs HC=3,750), IL-6 (g=0.81, 95% CI 0.46-1.16, I2=96.12%,k=45, BD=1,956 vs HC=4,106), TNF-α (g=0.49, 95% CI 0.19-0.78, I2=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-1β (g=-0.28, 95% CI -0.68 to 0.12, I2=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-1β (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-1β (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).

# 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 somatoprogression 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-1β levels in participants with BD compared to controls(Goldsmith et al., 2016). This was an unexpected finding since both TNF-α and IL-1β are predominantly secreted by macrophages (Maes and Carvalho, 2018). However, few studies (k=4) assayed IL-1β 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,

Boheringer-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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# 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.

# References

Aas, M., Dieset, I., Hope, S., Hoseth, E., Mørch, R., Reponen, E., Steen, N.E., Laskemoen, J.F., Ueland, T., Aukrust, P., Agartz, I., Andreassen, O.A., Melle, I., 2017. Childhood maltreatment severity is associated with elevated C-reactive protein and body mass index in adults with schizophrenia and bipolar diagnoses. Brain. Behav. Immun. 65, 342–349. https://doi.org/https://doi.org/10.1016/j.bbi.2017.06.005

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V). American Psychiatric Association, Washington.

Bai, Y.-M., Su, T.-P., Li, C.-T., Tsai, S.-J., Chen, M.-H., Tu, P.-C., Chiou, W.-F., 2015. Comparison of pro-inflammatory cytokines among patients with bipolar disorder and unipolar depression and normal controls. Bipolar Disord. 17, 269–277. https://doi.org/https://doi.org/10.1111/bdi.12259

Barbosa, I.G., Huguet, R.B., Mendonça, V.A., Sousa, L.P., Neves, F.S., Bauer, M.E., Teixeira, A.L., 2011. Increased plasma levels of soluble TNF receptor i in patients with bipolar disorder. Eur. Arch. Psychiatry Clin. Neurosci. 261, 139–143. https://doi.org/10.1007/s00406-010-0116-z

Barbosa, I.G., Nogueira, C.R.C., Rocha, N.P., Queiroz, A.L.L., Vago, J.P., Tavares, L.P., Assis, F., Fagundes, C.T., Huguet, R.B., Bauer, M.E., Teixeira, A.L., de Sousa, L.P., 2013. Altered intracellular signaling cascades in peripheral blood mononuclear cells from BD patients. J. Psychiatr. Res. 47, 1949–1954. https://doi.org/https://doi.org/10.1016/j.jpsychires.2013.08.019

Barbosa, I.G., Rocha, N.P., Huguet, R.B., Ferreira, R.A., Salgado, J.V., Carvalho, L.A., Pariante, C.M., Teixeira, A.L., 2012a. Executive dysfunction in euthymic bipolar disorder patients and its association with plasma biomarkers. J. Affect. Disord. 137, 151–155. https://doi.org/10.1016/j.jad.2011.12.034

Barbosa, I.G., Rocha, N.P., Miranda, A.S. de, Magalhães, P.V. da S., Huguet, R.B., Souza, L.P. de, Kapczinski, F., Teixeira, A.L., 2012b. Increased levels of adipokines in bipolar disorder. J. Psychiatr. Res. 46, 389–393. https://doi.org/https://doi.org/10.1016/j.jpsychires.2011.11.010

Barbosa, I.G., Vaz, G.N., Rocha, N.P., Machado-Vieira, R., Ventura, M.R.D., Huguet, R.B., Bauer, M.E., Berk, M., Teixeira, A.L., 2017. Plasma Levels of Tumor Necrosis Factor Superfamily Molecules Are Increased in Bipolar Disorder. Clin. Psychopharmacol. Neurosci. 15, 269–275. https://doi.org/10.9758/cpn.2017.15.3.269

Bender, R., Bunce, C., Clarke, M., Gates, S., Lange, S., Pace, N.L., Thorlund, K., 2008. Attention should be given to multiplicity issues in systematic reviews. J. Clin. Epidemiol. 61, 857–865. https://doi.org/https://doi.org/10.1016/j.jclinepi.2008.03.004

Berk, M., Kapczinski, F., Andreazza, A.C., Dean, O.M., Giorlando, F., Maes, M., Yücel, M., Gama, C.S., Dodd, S., Dean, B., Magalhães, P.V.S., Amminger, P., McGorry, P., Malhi, G.S., 2011. Pathways underlying neuroprogression in bipolar disorder: Focus on inflammation, oxidative stress and neurotrophic factors. Neurosci. Biobehav. Rev. 35, 804–817. https://doi.org/https://doi.org/10.1016/j.neubiorev.2010.10.001

Berk, M., Vieta, E., Dean, O.M., 2020. Anti-inflammatory treatment of bipolar depression: promise and disappointment. The Lancet Psychiatry 7, 467–468. https://doi.org/10.1016/S2215-0366(20)30155-3

Boufidou, F., Nikolaou, C., Alevizos, B., Liappas, I.A., Christodoulou, G.N., 2004. Cytokine production in bipolar affective disorder patients under lithium treatment. J. Affect. Disord. 82, 309–313. https://doi.org/https://doi.org/10.1016/j.jad.2004.01.007

Brietzke, E., Stertz, L., Fernandes, B.S., Kauer-Sant’Anna, M., Mascarenhas, M., Escosteguy Vargas, A., Chies, J.A., Kapczinski, F., 2009. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J. Affect. Disord. 116, 214–217. https://doi.org/https://doi.org/10.1016/j.jad.2008.12.001

Brugger, S.P., Howes, O.D., 2017. Heterogeneity and Homogeneity of Regional Brain Structure in Schizophrenia: A Meta-analysis. JAMA Psychiatry 74, 1104–1111. https://doi.org/10.1001/jamapsychiatry.2017.2663

Carvalho, Andre F, Firth, J., Vieta, E., 2020. Bipolar Disorder. N. Engl. J. Med. 383, 58–66. https://doi.org/10.1056/NEJMra1906193

Carvalho, André F, Solmi, M., Sanches, M., Machado, M.O., Stubbs, B., Ajnakina, O., Sherman, C., Sun, Y.R., Liu, C.S., Brunoni, A.R., Pigato, G., Fernandes, B.S., Bortolato, B., Husain, M.I., Dragioti, E., Firth, J., Cosco, T.D., Maes, M., Berk, M., Lanctôt, K.L., Vieta, E., Pizzagalli, D.A., Smith, L., Fusar-Poli, P., Kurdyak, P.A., Fornaro, M., Rehm, J., Herrmann, N., 2020. Evidence-based umbrella review of 162 peripheral biomarkers for major mental disorders. Transl. Psychiatry 10, 152. https://doi.org/10.1038/s41398-020-0835-5

Chakrabarty, T., Torres, I.J., Bond, D.J., Yatham, L.N., 2019. Inflammatory cytokines and cognitive functioning in early-stage bipolar I disorder. J. Affect. Disord. 245, 679–685. https://doi.org/https://doi.org/10.1016/j.jad.2018.11.018

Chang, H.H., Wang, T.-Y., Lee, I.H., Lee, S.-Y., Chen, K.C., Huang, S.-Y., Yang, Y.K., Lu, R.-B., Chen, P.S., 2017. C-reactive protein: A differential biomarker for major depressive disorder and bipolar II disorder. World J. Biol. Psychiatry 18, 63–70. https://doi.org/10.3109/15622975.2016.1155746

Civil Arslan, F., Tiryaki, A., Özkorumak Karagüzel, E., Aral, G., Sarıoğlu, O.., İnce, İ., Çankaya, S., Alver, A., n.d. The Relationship of Interleukin-18 and Interleukin-6 Levels with Cognitive Functions in Bipolar Disorder. Turk Psikiyatr. Derg 28(2), 81–88.

Correll, C.U., Solmi, M., Veronese, N., Bortolato, B., Rosson, S., Santonastaso, P., Thapa-Chhetri, N., Fornaro, M., Gallicchio, D., Collantoni, E., Pigato, G., Favaro, A., Monaco, F., Kohler, C., Vancampfort, D., Ward, P.B., Gaughran, F., Carvalho, A.F., Stubbs, B., 2017. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry 16. https://doi.org/10.1002/wps.20420

Crump, C., Sundquist, K., Winkleby, M.A., Sundquist, J., 2013. Comorbidities and mortality in bipolar disorder: A Swedish national cohort study. JAMA Psychiatry 70, 931–939. https://doi.org/10.1001/jamapsychiatry.2013.1394

Cunha, Â.B., Andreazza, A.C., Gomes, F.A., Frey, B.N., da Silveira, L.E., Gonçalves, C.A., Kapczinski, F., 2008. Investigation of serum high-sensitive C-reactive protein levels across all mood states in bipolar disorder. Eur. Arch. Psychiatry Clin. Neurosci. 258, 300–304. https://doi.org/10.1007/s00406-007-0797-0

da Silva, E.G., Pfaffenseller, B., Walz, J., Stertz, L., Fries, G., Rosa, A.R., Magalhães, P. V, 2017. Peripheral insulin-like growth factor 1 in bipolar disorder. Psychiatry Res. 250, 30–34. https://doi.org/https://doi.org/10.1016/j.psychres.2017.01.061

Dargél, A.A., Godin, O., Kapczinski, F., Kupfer, D.J., Leboyer, M., 2015. C-reactive protein alterations in bipolar disorder: A meta-analysis. J. Clin. Psychiatry 76, 142–150. https://doi.org/10.4088/JCP.14r09007

De Berardis, D., Conti, C.M., Campanella, D., Carano, A., Scali, M., Valchera, A., Serroni, N., Pizzorno, A.M., D’Albenzio, A., Fulcheri, M., Gambi, F., La Rovere, R., Cotellessa, C., Salerno, R.M., Ferro, F.M., 2008. Evaluation of C-reactive protein and total serum cholesterol in adult patients with bipolar disorder. Int. J. Immunopathol. Pharmacol. 21, 319–324. https://doi.org/10.1177/039463200802100208

Dickerson, F., Stallings, C., Origoni, A., Boronow, J., Yolken, R., 2007. Elevated serum levels of C-reactive protein are associated with mania symptoms in outpatients with bipolar disorder. Prog. Neuro-Psychopharmacology Biol. Psychiatry 31, 952–955. https://doi.org/10.1016/j.pnpbp.2007.02.018

Doganavsargil-Baysal, O., Cinemre, B., Aksoy, U.M., Akbas, H., Metin, O., Fettahoglu, C., Gokmen, Z., Davran, F., 2013. Levels of TNF-α, soluble TNF receptors (sTNFR1, sTNFR2), and cognition in bipolar disorder. Hum. Psychopharmacol. Clin. Exp. 28, 160–167. https://doi.org/https://doi.org/10.1002/hup.2301

Eisler, Z., Kertész, J., 2007. Fluctuation scaling in complex systems.

Fernandes, B.S., Borgwardt, S., Carvalho, A.F., Steiner, J., 2020. Editorial: Back to the Future: On the Road Towards Precision Psychiatry. Front. Psychiatry 11, 112. https://doi.org/10.3389/fpsyt.2020.00112

Fernandes, B.S., Williams, L.M., Steiner, J., Leboyer, M., Carvalho, A.F., Berk, M., 2017. The new field of ‘precision psychiatry.’ BMC Med. 15, 80. https://doi.org/10.1186/s12916-017-0849-x

Firth, J., Siddiqi, N., Koyanagi, A., Siskind, D., Rosenbaum, S., Galletly, C., Allan, S., Caneo, C., Carney, R., Carvalho, A.F., Chatterton, M. Lou, Correll, C.U., Curtis, J., Gaughran, F., Heald, A., Hoare, E., Jackson, S.E., Kisely, S., Lovell, K., Maj, M., McGorry, P.D., Mihalopoulos, C., Myles, H., O’Donoghue, B., Pillinger, T., Sarris, J., Schuch, F.B., Shiers, D., Smith, L., Solmi, M., Suetani, S., Taylor, J., Teasdale, S.B., Thornicroft, G., Torous, J., Usherwood, T., Vancampfort, D., Veronese, N., Ward, P.B., Yung, A.R., Killackey, E., Stubbs, B., 2019. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. The Lancet Psychiatry. https://doi.org/10.1016/S2215-0366(19)30132-4

Fonseka, T.M., McIntyre, R.S., Soczynska, J.K., Kennedy, S.H., 2015. Novel investigational drugs targeting IL-6 signaling for the treatment of depression. Expert Opin. Investig. Drugs. https://doi.org/10.1517/13543784.2014.998334

Fusar-Poli, P., De Micheli, A., Rocchetti, M., Cappucciati, M., Ramella-Cravaro, V., Rutigliano, G., Bonoldi, I., McGuire, P., Falkenberg, I., 2018. Semistructured Interview for Bipolar At Risk States (SIBARS). Psychiatry Res. 264, 302–309. https://doi.org/https://doi.org/10.1016/j.psychres.2018.03.074

Glaus, J., von Känel, R., Lasserre, A.M., Strippoli, M.-P.F., Vandeleur, C.L., Castelao, E., Gholam-Rezaee, M., Marangoni, C., Wagner, E.-Y.N., Marques-Vidal, P., Waeber, G., Vollenweider, P., Preisig, M., Merikangas, K.R., 2018. Mood disorders and circulating levels of inflammatory markers in a longitudinal population-based study. Psychol. Med. 48, 961–973. https://doi.org/DOI: 10.1017/S0033291717002744

Goldsmith, D.R., Rapaport, M.H., Miller, B.J., 2016. A meta-analysis of blood cytokine network alterations in psychiatric patients: Comparisons between schizophrenia, bipolar disorder and depression, in: Molecular Psychiatry. Nature Publishing Group, pp. 1696–1709. https://doi.org/10.1038/mp.2016.3

Guloksuz, S., Aktas Cetin, E., Cetin, T., Deniz, G., Oral, E.T., Nutt, D.J., 2010. Cytokine levels in euthymic bipolar patients. J. Affect. Disord. 126, 458–462. https://doi.org/10.1016/j.jad.2010.04.027

He, H., Hu, C., Ren, Z., Bai, L., Gao, F., Lyu, J., 2020. Trends in the incidence and DALYs of bipolar disorder at global, regional, and national levels: Results from the global burden of Disease Study 2017. J. Psychiatr. Res. 125, 96–105. https://doi.org/https://doi.org/10.1016/j.jpsychires.2020.03.015

Higgins, J., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M., Welch, V., 2020. Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training [WWW Document]. URL https://training.cochrane.org/cochrane-handbook-systematic-reviews-interventions#how-to-cite (accessed 10.29.20).

Higgins, J.P.T., White, I.R., Anzures-Cabrera, J., 2008. Meta-analysis of skewed data: combining results reported on log-transformed or raw scales. Stat. Med. 27, 6072–6092. https://doi.org/10.1002/sim.3427

Hope, S., Dieset, I., Agartz, I., Steen, N.E., Ueland, T., Melle, I., Aukrust, P., Andreassen, O.A., 2011. Affective symptoms are associated with markers of inflammation and immune activation in bipolar disorders but not in schizophrenia. J. Psychiatr. Res. 45, 1608–1616. https://doi.org/https://doi.org/10.1016/j.jpsychires.2011.08.003

Hope, S., Hoseth, E., Dieset, I., Mørch, R.H., Aas, M., Aukrust, P., Djurovic, S., Melle, I., Ueland, Torill, Agartz, I., Ueland, Thor, Westlye, L.T., Andreassen, O.A., 2015. Inflammatory markers are associated with general cognitive abilities in schizophrenia and bipolar disorder patients and healthy controls. Schizophr. Res. 165, 188–194. https://doi.org/https://doi.org/10.1016/j.schres.2015.04.004

Hope, S., Melle, I., Aukrust, P., Steen, N.E., Birkenaes, A.B., Lorentzen, S., Agartz, I., Ueland, T., Andreassen, O.A., 2009. Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor. Bipolar Disord. 11, 726–734. https://doi.org/https://doi.org/10.1111/j.1399-5618.2009.00757.x

Hornig, M., Goodman, D.B.P., Kamoun, M., Amsterdam, J.D., 1998. Positive and negative acute phase proteins in affective subtypes. J. Affect. Disord. 49, 9–18. https://doi.org/https://doi.org/10.1016/S0165-0327(97)00180-8

Huang, T.-L., Lin, F.-C., 2007. High-sensitivity C-reactive protein levels in patients with major depressive disorder and bipolar mania. Prog. Neuro-Psychopharmacology Biol. Psychiatry 31, 370–372. https://doi.org/https://doi.org/10.1016/j.pnpbp.2006.09.010

Hung, Y.-J., Hsieh, C.-H., Chen, Y.-J., Pei, D., Kuo, S.-W., Shen, D.-C., Sheu, W.H.-H., Chen, Y.-C., 2007. Insulin sensitivity, proinflammatory markers and adiponectin in young males with different subtypes of depressive disorder. Clin. Endocrinol. (Oxf). 67, 784–789. https://doi.org/https://doi.org/10.1111/j.1365-2265.2007.02963.x

Husain, M.I., Chaudhry, I.B., Khoso, A.B., Husain, M.O., Hodsoll, J., Ansari, M.A., Naqvi, H.A., Minhas, F.A., Carvalho, A.F., Meyer, J.H., Deakin, B., Mulsant, B.H., Husain, N., Young, A.H., 2020. Minocycline and celecoxib as adjunctive treatments for bipolar depression: a multicentre, factorial design randomised controlled trial. The Lancet Psychiatry 7, 515–527. https://doi.org/10.1016/S2215-0366(20)30138-3

Jacoby, A.S., Munkholm, K., Vinberg, M., Pedersen, B.K., Kessing, L.V., 2016. Cytokines, brain-derived neurotrophic factor and C-reactive protein in bipolar i disorder - Results from a prospective study. J. Affect. Disord. 197, 167–174. https://doi.org/10.1016/j.jad.2016.03.040

Kapczinski, F., Dal-Pizzol, F., Teixeira, A.L., Magalhaes, P.V.S., Kauer-Sant’Anna, M., Klamt, F., Moreira, J.C.F., Augusto de Bittencourt Pasquali, M., Fries, G.R., Quevedo, J., Gama, C.S., Post, R., 2011. Peripheral biomarkers and illness activity in bipolar disorder. J. Psychiatr. Res. 45, 156–161. https://doi.org/https://doi.org/10.1016/j.jpsychires.2010.05.015

Karabulut, S., Tasdemir, I., Akcan, U., Kucukali, C., Tüzün, E., Cakir, S., 2019. Inflammation and Neurodegeneration in Patients with Early-Stage and Chronic Bipolar Disorder. Turkish J. Psychiatry 30. https://doi.org/10.5080/u18376

Kauer-Sant’Anna, M., Kapczinski, F., Andreazza, A., Bond, D., Lam, R., Young, L., Yatham, L., 2008. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. Int. J. Neuropsychopharmacol. 12, 447–458. https://doi.org/10.1017/S1461145708009310

Kessing, L.V., Vradi, E., McIntyre, R.S., Andersen, P.K., 2015. Causes of decreased life expectancy over the life span in bipolar disorder. J. Affect. Disord. https://doi.org/10.1016/j.jad.2015.03.027

Kim, Y.-K., Jung, H.-G., Myint, A.-M., Kim, H., Park, S.-H., 2007. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. J. Affect. Disord. 104, 91–95. https://doi.org/https://doi.org/10.1016/j.jad.2007.02.018

King, S., Jelen, L.A., Horne, C.M., Cleare, A., Pariante, C.M., Young, A.H., Stone, J.M., 2019. Inflammation, glutamate, and cognition in bipolar disorder type II: A proof of concept study. Front. Psychiatry 10. https://doi.org/10.3389/fpsyt.2019.00066

Koga, N., Ogura, J., Yoshida, F., Hattori, K., Hori, H., Aizawa, E., Ishida, I., Kunugi, H., 2019. Altered polyunsaturated fatty acid levels in relation to proinflammatory cytokines, fatty acid desaturase genotype, and diet in bipolar disorder. Transl. Psychiatry 9, 208. https://doi.org/10.1038/s41398-019-0536-0

Lesh, T.A., Careaga, M., Rose, D.R., McAllister, A.K., Van de Water, J., Carter, C.S., Ashwood, P., 2018. Cytokine alterations in first-episode schizophrenia and bipolar disorder: Relationships to brain structure and symptoms. J. Neuroinflammation 15. https://doi.org/10.1186/s12974-018-1197-2

Maes, M., Anderson, G., Kubera, M., Berk, M., 2014. Targeting classical IL-6 signalling or IL-6 trans-signalling in depression? Expert Opin. Ther. Targets 18, 495–512. https://doi.org/10.1517/14728222.2014.888417

Maes, M., Carvalho, A.F., 2018. The Compensatory Immune-Regulatory Reflex System (CIRS) in Depression and Bipolar Disorder. Mol. Neurobiol. 55, 8885–8903. https://doi.org/10.1007/s12035-018-1016-x

Manchia, M., Vieta, E., Smeland, O.B., Altimus, C., Bechdolf, A., Bellivier, F., Bergink, V., Fagiolini, A., Geddes, J.R., Hajek, T., Henry, C., Kupka, R., Lagerberg, T. V, Licht, R.W., Martinez-Cengotitabengoa, M., Morken, G., Nielsen, R.E., Pinto, A.G., Reif, A., Rietschel, M., Ritter, P., Schulze, T.G., Scott, J., Severus, E., Yildiz, A., Kessing, L.V., Bauer, M., Goodwin, G.M., Andreassen, O.A., 2020. Translating big data to better treatment in bipolar disorder - a manifesto for coordinated action. Eur. Neuropsychopharmacol. 36, 121–136. https://doi.org/https://doi.org/10.1016/j.euroneuro.2020.05.006

Mao, R., Zhang, C., Chen, J., Zhao, G., Zhou, R., Wang, F., Xu, J., Yang, T., Su, Y., Huang, J., Wu, Z., Cao, L., Wang, Y., Hu, Y., Yuan, C., Yi, Z., Hong, W., Wang, Z., Peng, D., Fang, Y., 2018. Different levels of pro- and anti-inflammatory cytokines in patients with unipolar and bipolar depression. J. Affect. Disord. 237, 65–72. https://doi.org/10.1016/j.jad.2018.04.115

McIntyre, R.S., Subramaniapillai, M., Lee, Y., Pan, Z., Carmona, N.E., Shekotikhina, M., Rosenblat, J.D., Brietzke, E., Soczynska, J.K., Cosgrove, V.E., Miller, S., Fischer, E.G., Kramer, N.E., Dunlap, K., Suppes, T., Mansur, R.B., 2019. Efficacy of Adjunctive Infliximab vs Placebo in the Treatment of Adults With Bipolar I/II Depression: A Randomized Clinical Trial. JAMA psychiatry 76, 783–790. https://doi.org/10.1001/jamapsychiatry.2019.0779

Merikangas, K.R., Jin, R., He, J.P., Kessler, R.C., Lee, S., Sampson, N.A., Viana, M.C., Andrade, L.H., Hu, C., Karam, E.G., Ladea, M., Medina-Mora, M.E., Ono, Y., Posada-Villa, J., Sagar, R., Wells, J.E., Zarkov, Z., 2011. Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative. Arch. Gen. Psychiatry 68, 241–251. https://doi.org/10.1001/archgenpsychiatry.2011.12

Milaneschi, Y., Lamers, F., Berk, M., Penninx, B.W.J.H., 2020. Depression Heterogeneity and Its Biological Underpinnings: Toward Immunometabolic Depression. Biol. Psychiatry 88, 369–380. https://doi.org/10.1016/j.biopsych.2020.01.014

Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16, 22–34. https://doi.org/10.1038/nri.2015.5

Mizuno, Y., Hofer, A., Suzuki, T., Frajo-Apor, B., Wartelsteiner, F., Kemmler, G., Saruta, J., Tsukinoki, K., Mimura, M., Fleischhacker, W.W., Uchida, H., 2016. Clinical and biological correlates of resilience in patients with schizophrenia and bipolar disorder: A cross-sectional study. Schizophr. Res. 175, 148–153. https://doi.org/10.1016/j.schres.2016.04.047

Modabbernia, A., Taslimi, S., Brietzke, E., Ashrafi, M., 2013. Cytokine Alterations in Bipolar Disorder: A Meta-Analysis of 30 Studies. Biol. Psychiatry 74, 15–25. https://doi.org/10.1016/j.biopsych.2013.01.007

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J. Clin. Epidemiol. 62, 1006–1012. https://doi.org/10.1016/j.jclinepi.2009.06.005

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberatî, A., Petticrew, M., Shekelle, P., Stewart, L.A., Group, P.-P., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. https://doi.org/10.1186/2046-4053-4-1

Momen, N.C., Plana-Ripoll, O., Agerbo, E., Benros, M.E., Børglum, A.D., Christensen, M.K., Dalsgaard, S., Degenhardt, L., de Jonge, P., Debost, J.-C.P.G., Fenger-Grøn, M., Gunn, J.M., Iburg, K.M., Kessing, L. V, Kessler, R.C., Laursen, T.M., Lim, C.C.W., Mors, O., Mortensen, P.B., Musliner, K.L., Nordentoft, M., Pedersen, C.B., Petersen, L. V, Ribe, A.R., Roest, A.M., Saha, S., Schork, A.J., Scott, K.M., Sievert, C., Sørensen, H.J., Stedman, T.J., Vestergaard, M., Vilhjalmsson, B., Werge, T., Weye, N., Whiteford, H.A., Prior, A., McGrath, J.J., 2020. Association between Mental Disorders and Subsequent Medical Conditions. N. Engl. J. Med. 382, 1721–1731. https://doi.org/10.1056/NEJMoa1915784

Mondin, T.C., de Azevedo Cardoso, T., Moreira, F.P., Wiener, C., Oses, J.P., de Mattos Souza, L.D., Jansen, K., da Silva Magalhães, P.V., Kapczinski, F., da Silva, R.A., 2016. Circadian preferences, oxidative stress and inflammatory cytokines in bipolar disorder: A community study. J. Neuroimmunol. 301, 23–29. https://doi.org/10.1016/j.jneuroim.2016.10.012

Mora, E., Portella, M.J., Piñol-Ripoll, G., López, R., Cuadras, D., Forcada, I., Teres, M., Vieta, E., Mur, M., 2019. High BDNF serum levels are associated to good cognitive functioning in bipolar disorder. Eur. Psychiatry 60, 97–107. https://doi.org/10.1016/j.eurpsy.2019.02.006

Morris, G., Puri, B.K., Walker, A.J., Maes, M., Carvalho, A.F., Bortolasci, C.C., Walder, K., Berk, M., 2019. Shared pathways for neuroprogression and somatoprogression in neuropsychiatric disorders. Neurosci. Biobehav. Rev. 107, 862–882. https://doi.org/https://doi.org/10.1016/j.neubiorev.2019.09.025

Munkholm, K., Braüner, J.V., Kessing, L.V., Vinberg, M., 2013. Cytokines in bipolar disorder vs. healthy control subjects: A systematic review and meta-analysis. J. Psychiatr. Res. 47, 1119–1133. https://doi.org/10.1016/j.jpsychires.2013.05.018

Munkholm, K., Weikop, P., Kessing, L.V., Vinberg, M., 2015. Elevated levels of IL-6 and IL-18 in manic and hypomanic states in rapid cycling bipolar disorder patients. Brain. Behav. Immun. 43, 205–213. https://doi.org/10.1016/j.bbi.2014.09.021

Nielsen, R.E., Banner, J., Jensen, S.E., 2020. Cardiovascular disease in patients with severe mental illness. Nat. Rev. Cardiol. https://doi.org/10.1038/s41569-020-00463-7

Ortiz-Domínguez, A., Hernández, M.E., Berlanga, C., Gutiérrez-Mora, D., Moreno, J., Heinze, G., Pavón, L., 2007. Immune variations in bipolar disorder: phasic differences. Bipolar Disord. 9, 596–602. https://doi.org/https://doi.org/10.1111/j.1399-5618.2007.00493.x

Osimo, E.F., Pillinger, T., Rodriguez, I.M., Khandaker, G.M., Pariante, C.M., Howes, O.D., 2020. Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. Brain. Behav. Immun. 87, 901–909. https://doi.org/10.1016/j.bbi.2020.02.010

Pan, Y.J., Yeh, L.L., Chan, H.Y., Chang, C.K., 2020. Excess mortality and shortened life expectancy in people with major mental illnesses in Taiwan. Epidemiol. Psychiatr. Sci. 29, e156. https://doi.org/10.1017/S2045796020000694

Pandey, G.N., Ren, X., Rizavi, H.S., Zhang, H., 2015. Abnormal gene expression of proinflammatory cytokines and their receptors in the lymphocytes of patients with bipolar disorder. Bipolar Disord. 17, 636–644. https://doi.org/10.1111/bdi.12320

Pantović-Stefanović, M., Petronijević, N., Dunjić-Kostić, B., Velimirović, M., Nikolić, T., Jurišić, V., Lačković, M., Damjanović, A., Totić-Poznanović, S., Jovanović, A.A., Ivković, M., 2018. sVCAM-1, sICAM-1, TNF-α and IL-6 levels in bipolar disorder type I: Acute, longitudinal and therapeutic implications. World J. Biol. Psychiatry 19, S41–S51. https://doi.org/10.1080/15622975.2016.1259498

Quevedo, J., Carvalho, A., Vieta, E., 2021. Neurobiology of bipolar disorder. Road to novel therapeutics., Academic P. ed. London.

Quidé, Y., Bortolasci, C.C., Spolding, B., Kidnapillai, S., Watkeys, O.J., Cohen-Woods, S., Berk, M., Carr, V.J., Walder, K., Green, M.J., 2019. Association between childhood trauma exposure and pro-inflammatory cytokines in schizophrenia and bipolar-I disorder. Psychol. Med. 49, 2736–2744. https://doi.org/10.1017/S0033291718003690

Remlinger-Molenda, A., Wójciak, P., Michalak, M., Rybakowski, J., 2012. [Activity of selected cytokines in bipolar patients during manic and depressive episodes]. Psychiatr. Pol. 46, 599–611.

Rohatgi, A., 2020. WebPlotDigitizer.

Rosenblat, J.D., Kakar, R., Berk, M., Kessing, L. V, Vinberg, M., Baune, B.T., Mansur, R.B., Brietzke, E., Goldstein, B.I., McIntyre, R.S., 2016. Anti-inflammatory agents in the treatment of bipolar depression: a systematic review and meta-analysis. Bipolar Disord. 18, 89–101. https://doi.org/https://doi.org/10.1111/bdi.12373

Sanjay, T.N., Shivakumar, V., Subbanna, M., Biradar, S.U., Muralidharan, K., Venkatasubramanian, G., 2017. Plasma interleukin-6 in remitted early bipolar I disorder and subjects at high-risk for bipolar disorder. Asian J. Psychiatr. https://doi.org/10.1016/j.ajp.2017.03.014

Sayana, P., Colpo, G.D., Simões, L.R., Giridharan, V.V., Teixeira, A.L., Quevedo, J., Barichello, T., 2017. A systematic review of evidence for the role of inflammatory biomarkers in bipolar patients. J. Psychiatr. Res. 92, 160–182. https://doi.org/https://doi.org/10.1016/j.jpsychires.2017.03.018

Scola, G., McNamara, R.K., Croarkin, P.E., Leffler, J.M., Cullen, K.R., Geske, J.R., Biernacka, J.M., Frye, M.A., Delbello, M.P., Andreazza, A.C., 2016. Lipid peroxidation biomarkers in adolescents with or at high-risk for bipolar disorder. J. Affect. Disord. 192, 176–183. https://doi.org/10.1016/j.jad.2015.12.020

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, R.D., 2000. MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies. Jama.

Suleiman, M., Khatib, R., Agmon, Y., Mahamid, R., Boulos, M., Kapeliovich, M., Levy, Y., Beyar, R., Markiewicz, W., Hammerman, H., Aronson, D., 2006. Early inflammation and risk of long-term development of heart failure and mortality in survivors of acute myocardial infarction: Predictive role of C-reactive protein. J. Am. Coll. Cardiol. 47, 962–968. https://doi.org/10.1016/j.jacc.2005.10.055

Tsai, S.Y., Chung, K.H., Wu, J.Y., Kuo, C.J., Lee, H.C., Huang, S.H., 2012. Inflammatory markers and their relationships with leptin and insulin from acute mania to full remission in bipolar disorder. J. Affect. Disord. 136, 110–116. https://doi.org/10.1016/j.jad.2011.08.022

Tunç, S., Atagün, M.İ., Başbuğ, H.S., Erel, Ö., 2019. Serum ceruloplasmin-ferroxidase activity in bipolar disorder is elevated compared to major depressive disorder and schizophrenia: a controlled study. Psychiatry Clin. Psychopharmacol. 29, 307–314. https://doi.org/10.1080/24750573.2019.1584489

van den Ameele, S., Fuchs, D., Coppens, V., de Boer, P., Timmers, M., Sabbe, B., Morrens, M., 2018. Markers of inflammation and monoamine metabolism indicate accelerated aging in bipolar disorder. Front. Psychiatry 9. https://doi.org/10.3389/fpsyt.2018.00250

Vancampfort, D., Correll, C.U., Galling, B., Probst, M., De Hert, M., Ward, P.B., Rosenbaum, S., Gaughran, F., Lally, J., Stubbs, B., 2016. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: A systematic review and large scale meta-analysis. World Psychiatry 15, 166–174. https://doi.org/10.1002/wps.20309

Vancampfort, D., Stubbs, B., Mitchell, A.J., De Hert, M., Wampers, M., Ward, P.B., Rosenbaum, S., Correll, C.U., 2015. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry 14, 339–347. https://doi.org/10.1002/wps.20252

Vasconcelos-Moreno, M.P., Fries, G.R., Gubert, C., Dos Santos, B.T.M.Q., Fijtman, A., Sartori, J., Ferrari, P., Grun, L.K., Parisi, M.M., Guma, F.T.C.R., Barbé-Tuana, F.M., Kapczinski, F., Rosa, A.R., Yatham, L.N., Kauer-Sant’Anna, M., 2017. Telomere Length, Oxidative Stress, Inflammation and BDNF Levels in Siblings of Patients with Bipolar Disorder: Implications for Accelerated Cellular Aging. Int. J. Neuropsychopharmacol. 20, 445–454. https://doi.org/10.1093/ijnp/pyx001

Vieta, E., 2015. Personalized medicine applied to mental health: Precision psychiatry. Rev. Psiquiatr. y Salud Ment. (English Ed. 8, 117–118. https://doi.org/10.1016/j.rpsmen.2015.03.007

Wadee, A.A., Kuschke, R.H., Wood, L.A., Berk, M., Ichim, L., Maes, M., 2002. Serological observations in patients suffering from acute manic episodes. Hum. Psychopharmacol. 17, 175–179. https://doi.org/10.1002/hup.390

Wang, T.Y., Lee, S.Y., Chen, S.L., Chung, Y.L., Li, C.L., Chang, Y.H., Wang, L.J., Chen, P.S., Chen, S.H., Chu, C.H., Huang, S.Y., Tzeng, N.S., Hsieh, T.H., Chiu, Y.C., Lee, I.H., Chen, K.C., Yang, Y.K., Hong, J.S., Lu, R.B., 2016. The differential levels of inflammatory cytokines and bdnf among bipolar spectrum disorders. Int. J. Neuropsychopharmacol. 19, 1–8. https://doi.org/10.1093/ijnp/pyw012

WHO, n.d. International Classification of Diseases - 10 (ICD-10). Version: 2019., World Health Organization.

Wieck, A., Grassi-Oliveira, R., do Prado, C.H., Rizzo, L.B., de Oliveira, A.S., Kommers-Molina, J., Viola, T.W., Marciano Vieira, É.L., Teixeira, A.Ô.L., Bauer, M.E., 2014. Pro-inflammatory cytokines and soluble receptors in response to acute psychosocial stress: Differential reactivity in bipolar disorder. Neurosci. Lett. https://doi.org/10.1016/j.neulet.2014.07.040

Wiener, C.D., Moreira, F.P., Cardoso, T.A., Mondin, T.C., da Silva Magalhães, P.V., Kapczinski, F., de Mattos Souza, L.D., da Silva, R.A., Oses, J.P., Jansen, K., 2017. Inflammatory cytokines and functional impairment in drug-free subjects with mood disorder. J. Neuroimmunol. 307, 33–36. https://doi.org/10.1016/j.jneuroim.2017.03.003

Wiener, C.D., Moreira, F.P., Portela, L.V., Strogulski, N.R., Lara, D.R., da Silva, R.A., Souza, L.D. de M., Jansen, K., Oses, J.P., 2019. Interleukin-6 and Interleukin-10 in mood disorders: A population-based study. Psychiatry Res. 273, 685–689. https://doi.org/10.1016/j.psychres.2019.01.100

Wu, W., Zheng, Y.L., Tian, L.P., Lai, J.B., Hu, C.C., Zhang, P., Chen, J.K., Hu, J.B., Huang, M.L., Wei, N., Xu, W.J., Zhou, W.H., Lu, S.J., Lu, J., Qi, H.L., Wang, D.D., Zhou, X.Y., Duan, J.F., Xu, Y., Hu, S.H., 2017. Circulating T lymphocyte subsets, cytokines, and immune checkpoint inhibitors in patients with bipolar II or major depression: A preliminary study. Sci. Rep. 7. 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 |  |  |  |  |  |  |  |  |
| 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 |  |  |  |  |  |
| 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

**SUPPLEMENTARY ONLINE MATERIALeFigure 1- PRISMA flowchart.**

# eFigure 1- PRISMA flowchart.

Records identified through database searching  
(n = 724)

Additional records identified through other sources  
(n =5)

Identification

Records after duplicates removed  
(n =729)

Screening

Records excluded  
(n=604)

Records screened  
(n=729)

Full-text articles excluded, with reasons (n = 72 )

No structured interview (n=25)

No circulating mediator of interest (n=21)

No control group (n=14)

No bipolar disorder (n=4)

Review (n=4)

No data (n=3)

Comment (n=1)

Full-text articles assessed for eligibility  
(n = 125)

Eligibility

Studies included in qualitative synthesis  
(n = 53)

Included

Studies included in quantitative synthesis (meta-analysis)  
(n = 49)

# 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., I2) 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 diagram. | 5 | |
| 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, eFigure1 | |
| 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 Slouble receptors of TNF |
| Sowa-Kucma, 2018 (Sowa-Kućma et al., 2018) | Assayed soluble receptors |
| Tsai, 2001 (Tsai et al., 2001) | Assayes 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 od SCID |
| Cingi Yirun, 2017 (Cingi Yirün 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 |
| Ghafouri-Fard, 2019 (Ghafouri-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 |
| Goldestein, 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 seprate 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) | Proinfllmatory 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 |
| Ghafelehbashi, 2017 (Ghafelehbashi et al., 2017) | RNA transcript evaluation |

# eTable 5. Meta-regression analyses

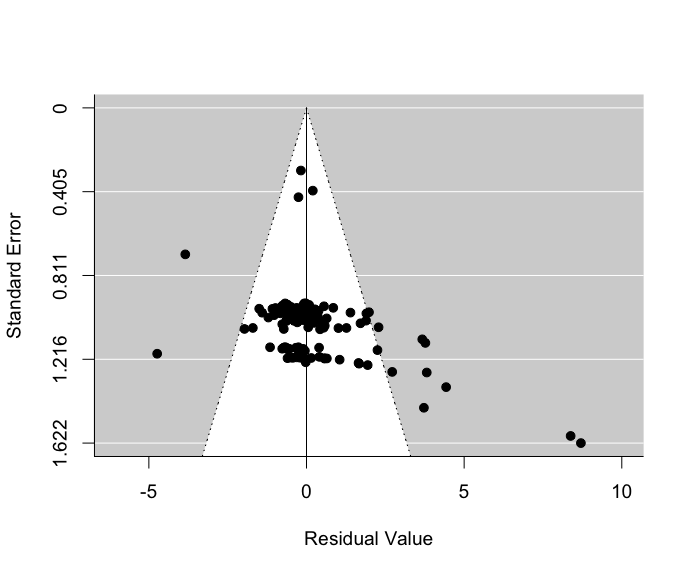
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Moderator** | **Inflammatory mediator** | **Estimate** | **Standard error** | **Z value** | **P value** |
| Age | CRP | -0.041 | 0.023 | -1.775 | 0.076 |
|  | IL-1β | 0.308 | 0.061 | 5.008 | <0.001 |
|  | IL-6 | -0.043 | 0.012 | -3.455 | <0.001 |
|  | TNF-α | -0.051 | 0.011 | -4.488 | <0.001 |
| Female sex | CRP | -0.024 | 0.011 | -2.304 | 0.021 |
|  | IL-1β | 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-1β | 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-1β | 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-1β | NA | NA | NA | NA |
|  | IL-6 | -0.021 | 0.014 | -1.536 | 0.125 |
|  | TNF-α | -0.024 | 0.031 | -0.793 | 0.428 |
| Sample size | CRP | -0.001 | 0.001 | -1.092 | 0.275 |
|  | IL-1β | -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.

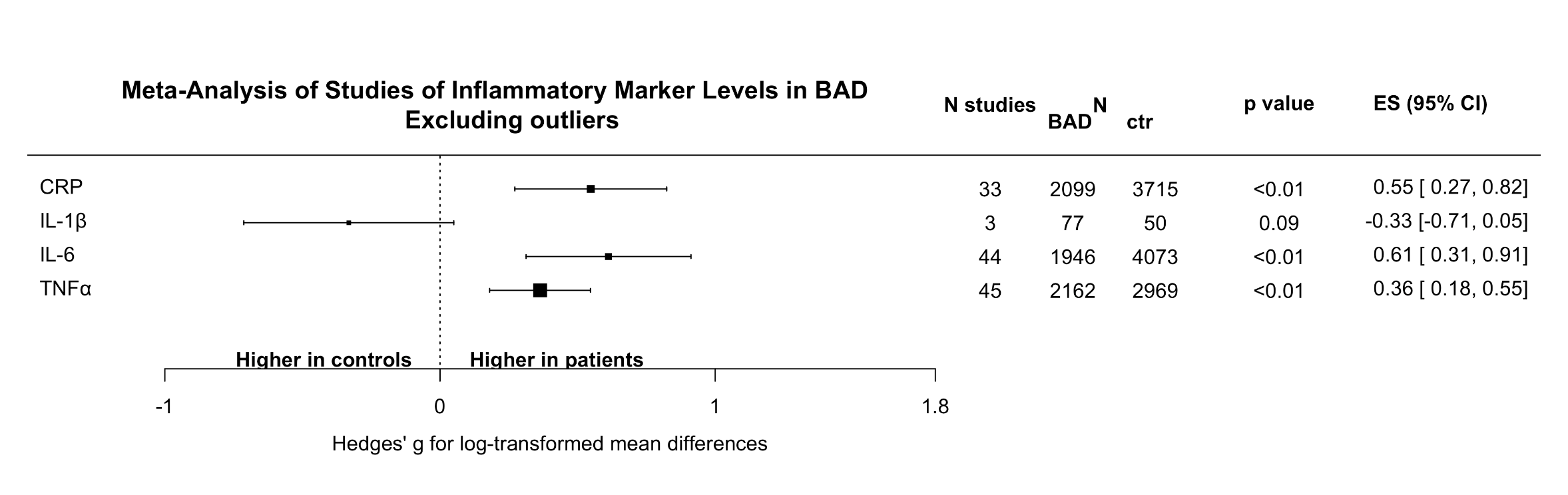
# eTable 6. Quality appraisal of included studies

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **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) | | | |

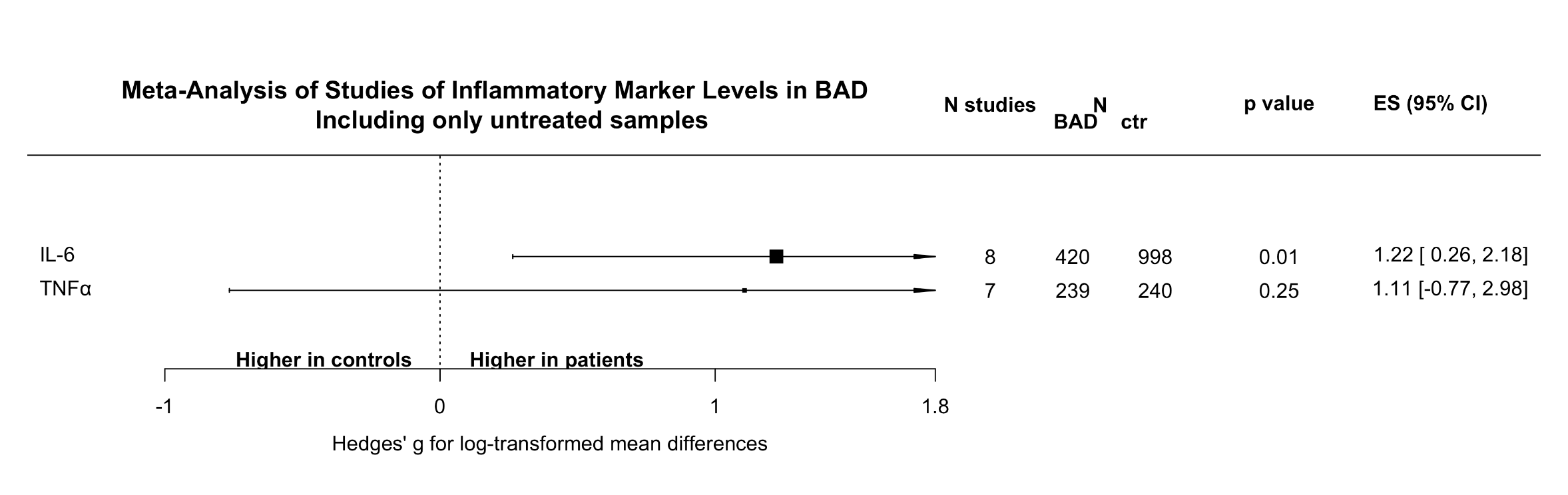
# eFigure 2. Funnel plot for assessment of publication bias



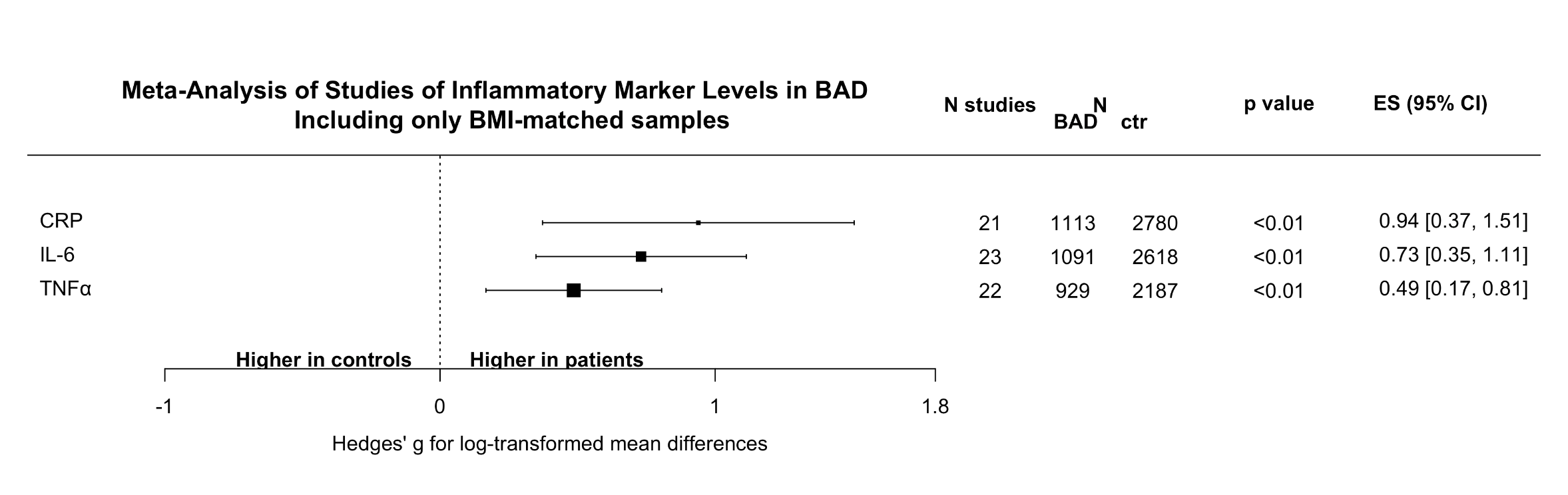
# eFigure3. Sensitivity analysis excluding outliers.

eFigur

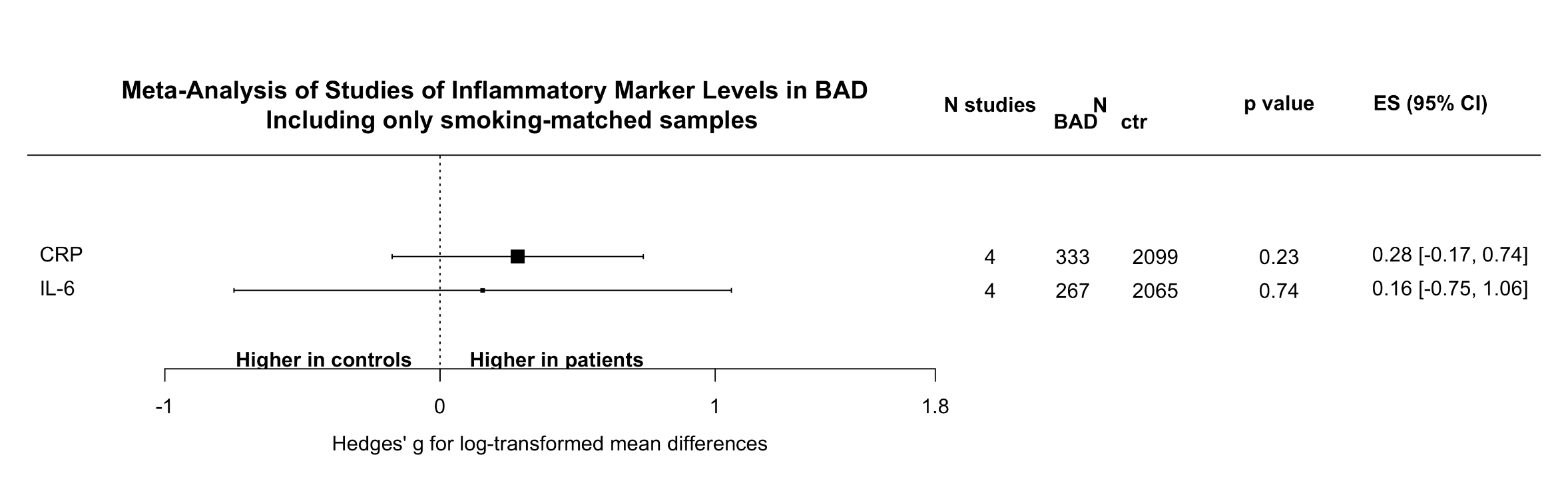
# eFigure 4. Sensitivity analyses only including untreated samples



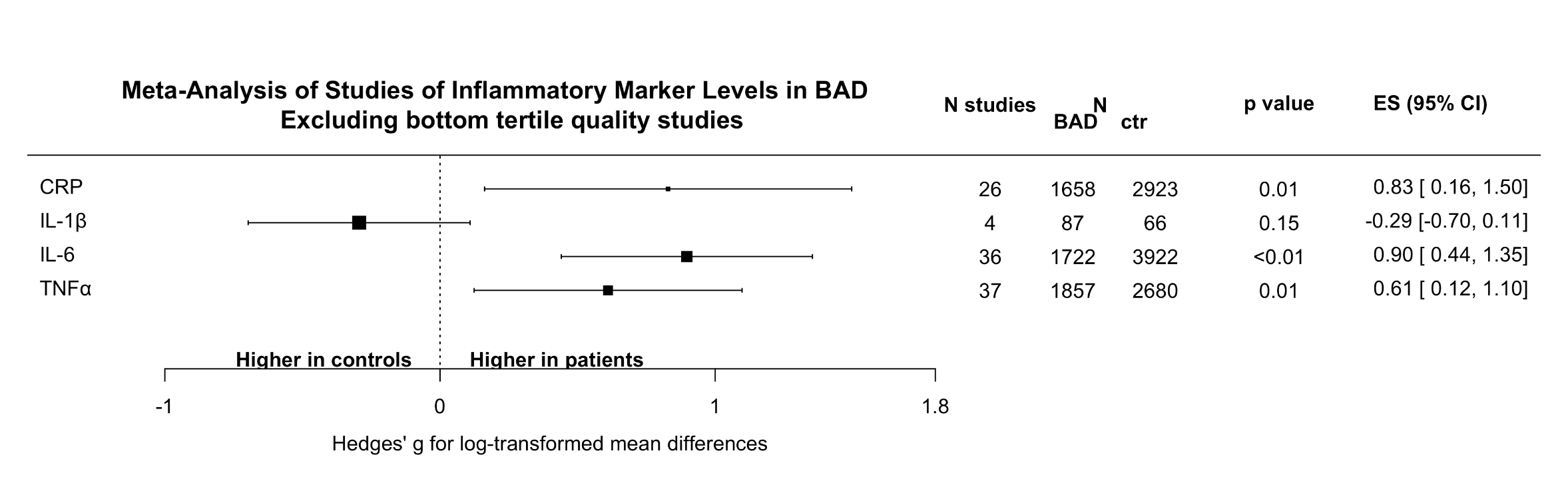
# eFigure 5. Sensitivity analyses only including body mass index-matched samples



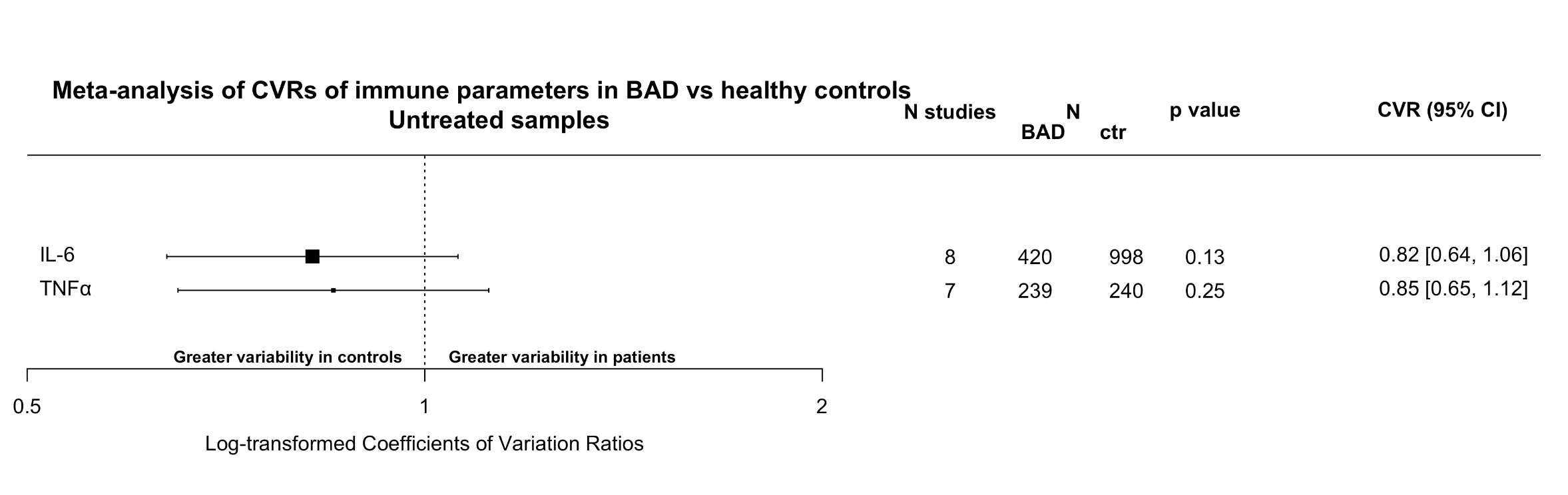
# eFigure 6. Sensitivity analyses only including smoking-matched samples



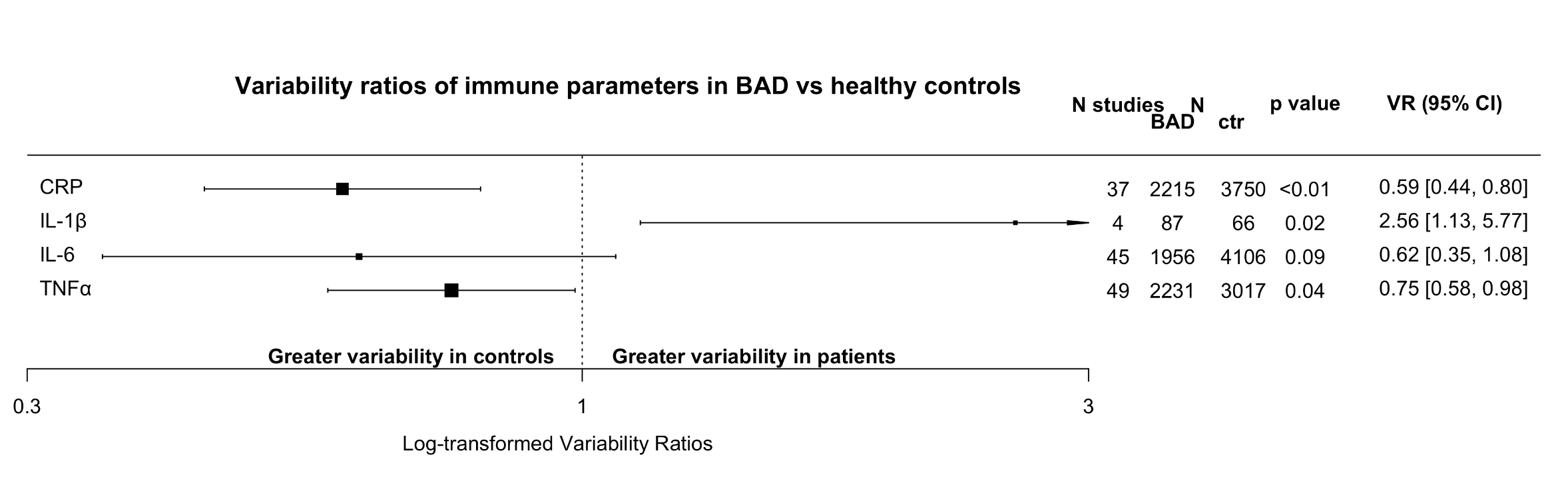
# eFigure 7. Sensitivity analyses only including higher quality studies.



# eFigure 8. Sensitivity analyses of CVR only including untreated samples



# eFigure 9. Variability ratios of inflammatory markers in bipolar disorders in healthy controls



# References

Aas, M., Dieset, I., Hope, S., Hoseth, E., Mørch, R., Reponen, E., Steen, N.E., Laskemoen, J.F., Ueland, T., Aukrust, P., Agartz, I., Andreassen, O.A., Melle, I., 2017. Childhood maltreatment severity is associated with elevated C-reactive protein and body mass index in adults with schizophrenia and bipolar diagnoses. Brain. Behav. Immun. 65, 342–349. https://doi.org/https://doi.org/10.1016/j.bbi.2017.06.005

Aas, M., Vecchio, C., Pauls, A., Mehta, M., Williams, S., Hazelgrove, K., Biaggi, A., Pawlby, S., Conroy, S., Seneviratne, G., Mondelli, V., Pariante, C.M., Dazzan, P., 2020. Biological stress response in women at risk of postpartum psychosis: The role of life events and inflammation. Psychoneuroendocrinology 113, 104558. https://doi.org/10.1016/j.psyneuen.2019.104558

Aguglia, A., Solano, P., Giacomini, G., Caprino, M., Conigliaro, C., Romano, M., Aguglia, E., Serafini, G., Amore, M., 2019. The Association Between Dyslipidemia and Lethality of Suicide Attempts: A Case-Control Study. Front. Psychiatry 10. https://doi.org/10.3389/fpsyt.2019.00070

Ascoli, B.M., Parisi, M.M., Bristot, G., Antqueviezc, B., Géa, L.P., Colombo, R., Kapczinski, F., Guma, F.T.C.R., Brietzke, E., Barbé-Tuana, F.M., Rosa, A.R., 2019. Attenuated inflammatory response of monocyte-derived macrophage from patients with BD: a preliminary report. Int. J. Bipolar Disord. 7, 13. https://doi.org/10.1186/s40345-019-0148-x

Bai, Y.-M., Chen, M.-H., Hsu, J.-W., Huang, K.-L., Tu, P.-C., Chang, W.-C., Su, T.-P., Li, C.T., Lin, W.-C., Tsai, S.-J., 2020. A comparison study of metabolic profiles, immunity, and brain gray matter volumes between patients with bipolar disorder and depressive disorder. J. Neuroinflammation 17, 42. https://doi.org/10.1186/s12974-020-1724-9

Bai, Y.-M., Su, T.-P., Li, C.-T., Tsai, S.-J., Chen, M.-H., Tu, P.-C., Chiou, W.-F., 2015. Comparison of pro-inflammatory cytokines among patients with bipolar disorder and unipolar depression and normal controls. Bipolar Disord. 17, 269–277. https://doi.org/https://doi.org/10.1111/bdi.12259

Barbosa, I.G., Huguet, R.B., Mendonça, V.A., Sousa, L.P., Neves, F.S., Bauer, M.E., Teixeira, A.L., 2011. Increased plasma levels of soluble TNF receptor i in patients with bipolar disorder. Eur. Arch. Psychiatry Clin. Neurosci. https://doi.org/10.1007/s00406-010-0116-z

Barbosa, I.G., Nogueira, C.R.C., Rocha, N.P., Queiroz, A.L.L., Vago, J.P., Tavares, L.P., Assis, F., Fagundes, C.T., Huguet, R.B., Bauer, M.E., Teixeira, A.L., de Sousa, L.P., 2013. Altered intracellular signaling cascades in peripheral blood mononuclear cells from BD patients. J. Psychiatr. Res. 47, 1949–1954. https://doi.org/https://doi.org/10.1016/j.jpsychires.2013.08.019

Barbosa, I.G., Rocha, N.P., Huguet, R.B., Ferreira, R.A., Salgado, J.V., Carvalho, L.A., Pariante, C.M., Teixeira, A.L., 2012a. Executive dysfunction in euthymic bipolar disorder patients and its association with plasma biomarkers. J. Affect. Disord. 137, 151–155. https://doi.org/10.1016/j.jad.2011.12.034

Barbosa, I.G., Rocha, N.P., Miranda, A.S. de, Magalhães, P.V. da S., Huguet, R.B., Souza, L.P. de, Kapczinski, F., Teixeira, A.L., 2012b. Increased levels of adipokines in bipolar disorder. J. Psychiatr. Res. 46, 389–393. https://doi.org/https://doi.org/10.1016/j.jpsychires.2011.11.010

Barbosa, I.G., Vaz, G.N., Rocha, N.P., Machado-Vieira, R., Ventura, M.R.D., Huguet, R.B., Bauer, M.E., Berk, M., Teixeira, A.L., 2017. Plasma Levels of Tumor Necrosis Factor Superfamily Molecules Are Increased in Bipolar Disorder. Clin. Psychopharmacol. Neurosci. 15, 269–275. https://doi.org/10.9758/cpn.2017.15.3.269

Benedetti, F., Lucca, A., Brambilla, F., Colombo, C., Smeraldi, E., 2002. Interleukine-6 serum levels correlate with response to antidepressant sleep deprivation and sleep phase advance. Prog. Neuro-Psychopharmacology Biol. Psychiatry 26, 1167–1170. https://doi.org/10.1016/S0278-5846(02)00255-5

Benedetti, F., Poletti, S., Hoogenboezem, T.A., Locatelli, C., de Wit, H., Wijkhuijs, A.J.M., Colombo, C., Drexhage, H.A., 2017. Higher Baseline Proinflammatory Cytokines Mark Poor Antidepressant Response in Bipolar Disorder. J. Clin. Psychiatry 78, e986–e993. https://doi.org/10.4088/JCP.16m11310

Bond, D.J., Andreazza, A.C., Hughes, J., Dhanoa, T., Torres, I.J., Kozicky, J.M., Young, L.T., Lam, R.W., Yatham, L.N., 2016. Association of peripheral inflammation with body mass index and depressive relapse in bipolar disorder. Psychoneuroendocrinology 65, 76–83. https://doi.org/10.1016/j.psyneuen.2015.12.012

Boufidou, F., Nikolaou, C., Alevizos, B., Liappas, I.A., Christodoulou, G.N., 2004. Cytokine production in bipolar affective disorder patients under lithium treatment. J. Affect. Disord. 82, 309–313. https://doi.org/https://doi.org/10.1016/j.jad.2004.01.007

Brietzke, E., Stertz, L., Fernandes, B.S., Kauer-Sant’Anna, M., Mascarenhas, M., Escosteguy Vargas, A., Chies, J.A., Kapczinski, F., 2009. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. J. Affect. Disord. 116, 214–217. https://doi.org/https://doi.org/10.1016/j.jad.2008.12.001

Brietzke, E., Teixeira, A.L., 2010. Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor. Bipolar Disord. 12, 453–454. https://doi.org/10.1111/j.1399-5618.2010.00822.x

Brunoni, A.R., Supasitthumrong, T., Teixeira, A.L., Vieira, E.L., Gattaz, W.F., Benseñor, I.M., Lotufo, P.A., Lafer, B., Berk, M., Carvalho, A.F., Maes, M., 2020. Differences in the immune-inflammatory profiles of unipolar and bipolar depression. J. Affect. Disord. 262, 8–15. https://doi.org/10.1016/j.jad.2019.10.037

Chakrabarty, T., Torres, I.J., Bond, D.J., Yatham, L.N., 2019. Inflammatory cytokines and cognitive functioning in early-stage bipolar I disorder. J. Affect. Disord. 245, 679–685. https://doi.org/https://doi.org/10.1016/j.jad.2018.11.018

Chandra, P., 2014. Prospects and advancements in C-reactive protein detection. World J. Methodol. 4, 1. https://doi.org/10.5662/wjm.v4.i1.1

Chang, H.H., Wang, T.-Y., Lee, I.H., Lee, S.-Y., Chen, K.C., Huang, S.-Y., Yang, Y.K., Lu, R.-B., Chen, P.S., 2017. C-reactive protein: A differential biomarker for major depressive disorder and bipolar II disorder. World J. Biol. Psychiatry 18, 63–70. https://doi.org/10.3109/15622975.2016.1155746

Chen, M.-H., Chang, W.-C., Hsu, J.-W., Huang, K.-L., Tu, P.-C., Su, T.-P., Li, C.-T., Lin, W.-C., Bai, Y.-M., 2019. Correlation of proinflammatory cytokines levels and reduced gray matter volumes between patients with bipolar disorder and unipolar depression. J. Affect. Disord. 245, 8–15. https://doi.org/10.1016/j.jad.2018.10.106

Chung, K.-H., Huang, S.-H., Wu, J.-Y., Chen, P.-H., Hsu, J.-L., Tsai, S.-Y., 2013. The Link between High-Sensitivity C-Reactive Protein and Orbitofrontal Cortex in Euthymic Bipolar Disorder. Neuropsychobiology 68, 168–173. https://doi.org/10.1159/000353613

Cingi Yirün, M., Yirün, O., Ünal, K., Yüksel, R.N., Altunsoy, N., Tatlidil Yaylaci, E., Aydemir, M.Ç., Göka, E., 2017. Serum TNF-related weak inducer of apoptosis (TWEAK) and TNF-related apoptosis-inducing ligand (TRAIL) levels of patients with bipolar disorder in manic episode, in remission and healthy controls. Psychiatry Res. 257, 338–345. https://doi.org/10.1016/j.psychres.2017.07.067

Civil Arslan, F., Tiryaki, A., Özkorumak Karagüzel, E., Aral, G., Sarıoğlu, O.., İnce, İ., Çankaya, S., Alver, A., 2017. The Relationship of Interleukin-18 and Interleukin-6 Levels with Cognitive Functions in Bipolar Disorder. Turk Psikiyatr. Derg 28(2), 81–88.

Cunha, Â.B., Andreazza, A.C., Gomes, F.A., Frey, B.N., da Silveira, L.E., Gonçalves, C.A., Kapczinski, F., 2008. Investigation of serum high-sensitive C-reactive protein levels across all mood states in bipolar disorder. Eur. Arch. Psychiatry Clin. Neurosci. 258, 300–304. https://doi.org/10.1007/s00406-007-0797-0

da Silva, E.G., Pfaffenseller, B., Walz, J., Stertz, L., Fries, G., Rosa, A.R., Magalhães, P. V, 2017. Peripheral insulin-like growth factor 1 in bipolar disorder. Psychiatry Res. 250, 30–34. https://doi.org/https://doi.org/10.1016/j.psychres.2017.01.061

De Berardis, D., Conti, C.M., Campanella, D., Carano, A., Scali, M., Valchera, A., Serroni, N., Pizzorno, A.M., D’Albenzio, A., Fulcheri, M., Gambi, F., La Rovere, R., Cotellessa, C., Salerno, R.M., Ferro, F.M., 2008. Evaluation of C-reactive protein and total serum cholesterol in adult patients with bipolar disorder. Int. J. Immunopathol. Pharmacol. 21, 319–324. https://doi.org/10.1177/039463200802100208

Dickerson, F., Adamos, M., Katsafanas, E., Khushalani, S., Origoni, A., Savage, C., Schweinfurth, L., Stallings, C., Sweeney, K., Alaedini, A., Uhde, M., Severance, E., Wilcox, H.C., Yolken, R., 2017. The association between immune markers and recent suicide attempts in patients with serious mental illness: A pilot study. Psychiatry Res. 255, 8–12. https://doi.org/10.1016/j.psychres.2017.05.005

Dickerson, F., Stallings, C., Origoni, A., Boronow, J., Yolken, R., 2007. Elevated serum levels of C-reactive protein are associated with mania symptoms in outpatients with bipolar disorder. Prog. Neuro-Psychopharmacology Biol. Psychiatry 31, 952–955. https://doi.org/10.1016/j.pnpbp.2007.02.018

Dickerson, F., Stallings, C., Origoni, A., Vaughan, C., Khushalani, S., Yolken, R., 2013. Elevated C-reactive protein and cognitive deficits in individuals with bipolar disorder. J. Affect. Disord. 150, 456–459. https://doi.org/10.1016/j.jad.2013.04.039

do Prado, C.H., Rizzo, L.B., Wieck, A., Lopes, R.P., Teixeira, A.L., Grassi-Oliveira, R., Bauer, M.E., 2013. Reduced regulatory T cells are associated with higher levels of Th1/TH17 cytokines and activated MAPK in type 1 bipolar disorder. Psychoneuroendocrinology 38, 667–676. https://doi.org/10.1016/j.psyneuen.2012.08.005

Doganavsargil-Baysal, O., Cinemre, B., Aksoy, U.M., Akbas, H., Metin, O., Fettahoglu, C., Gokmen, Z., Davran, F., 2013. Levels of TNF-α, soluble TNF receptors (sTNFR1, sTNFR2), and cognition in bipolar disorder. Hum. Psychopharmacol. Clin. Exp. 28, 160–167. https://doi.org/https://doi.org/10.1002/hup.2301

Dolsen, M.R., Soehner, A.M., Harvey, A.G., 2018. Proinflammatory Cytokines, Mood, and Sleep in Interepisode Bipolar Disorder and Insomnia. Psychosom. Med. 80, 87–94. https://doi.org/10.1097/PSY.0000000000000529

Drexhage, R.C., Hoogenboezem, T.H., Versnel, M.A., Berghout, A., Nolen, W.A., Drexhage, H.A., 2011. The activation of monocyte and T cell networks in patients with bipolar disorder. Brain. Behav. Immun. 25, 1206–1213. https://doi.org/10.1016/j.bbi.2011.03.013

Drexhage, R.C., Knijff, E.M., Padmos, R.C., Heul-Nieuwenhuijzen, L. van der, Beumer, W., Versnel, M.A., Drexhage, H.A., 2010. The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. Expert Rev. Neurother. 10, 59–76. https://doi.org/10.1586/ern.09.144

Fiedorowicz, J.G., Prossin, A.R., Johnson, C.P., Christensen, G.E., Magnotta, V.A., Wemmie, J.A., 2015. Peripheral inflammation during abnormal mood states in bipolar I disorder. J. Affect. Disord. 187, 172–178. https://doi.org/10.1016/j.jad.2015.08.036

Ghafelehbashi, H., Pahlevan Kakhki, M., Kular, L., Moghbelinejad, S., Ghafelehbashi, S.H., 2017. Decreased Expression of IFNG-AS1 , IFNG and IL-1B Inflammatory Genes in Medicated Schizophrenia and Bipolar Patients. Scand. J. Immunol. 86, 479–485. https://doi.org/10.1111/sji.12620

Ghafouri-Fard, S., Oskooei, V.K., Omrani, M.D., Taheri, M., 2019. Dysregulation of cytokine coding genes in peripheral blood of bipolar patients. J. Affect. Disord. 256, 578–583. https://doi.org/10.1016/j.jad.2019.06.028

Glaus, J., von Känel, R., Lasserre, A.M., Strippoli, M.-P.F., Vandeleur, C.L., Castelao, E., Gholam-Rezaee, M., Marangoni, C., Wagner, E.-Y.N., Marques-Vidal, P., Waeber, G., Vollenweider, P., Preisig, M., Merikangas, K.R., 2018. Mood disorders and circulating levels of inflammatory markers in a longitudinal population-based study. Psychol. Med. 48, 961–973. https://doi.org/DOI: 10.1017/S0033291717002744

Goldstein, B.I., Lotrich, F., Axelson, D.A., Gill, M.K., Hower, H., Goldstein, T.R., Fan, J., Yen, S., Diler, R., Dickstein, D., Strober, M.A., Iyengar, S., Ryan, N.D., Keller, M.B., Birmaher, B., 2015. Inflammatory Markers Among Adolescents and Young Adults With Bipolar Spectrum Disorders. J. Clin. Psychiatry 76, 1556–1563. https://doi.org/10.4088/JCP.14m09395

Guloksuz, S., Aktas Cetin, E., Cetin, T., Deniz, G., Oral, E.T., Nutt, D.J., 2010. Cytokine levels in euthymic bipolar patients. J. Affect. Disord. 126, 458–462. https://doi.org/10.1016/j.jad.2010.04.027

Guloksuz, S., Altinbas, K., Aktas Cetin, E., Kenis, G., Bilgic Gazioglu, S., Deniz, G., Oral, E.T., van Os, J., 2012. Evidence for an association between tumor necrosis factor-alpha levels and lithium response. J. Affect. Disord. 143, 148–152. https://doi.org/10.1016/j.jad.2012.04.044

Hope, S., Dieset, I., Agartz, I., Steen, N.E., Ueland, T., Melle, I., Aukrust, P., Andreassen, O.A., 2011. Affective symptoms are associated with markers of inflammation and immune activation in bipolar disorders but not in schizophrenia. J. Psychiatr. Res. 45, 1608–1616. https://doi.org/https://doi.org/10.1016/j.jpsychires.2011.08.003

Hope, S., Hoseth, E., Dieset, I., Mørch, R.H., Aas, M., Aukrust, P., Djurovic, S., Melle, I., Ueland, Torill, Agartz, I., Ueland, Thor, Westlye, L.T., Andreassen, O.A., 2015. Inflammatory markers are associated with general cognitive abilities in schizophrenia and bipolar disorder patients and healthy controls. Schizophr. Res. 165, 188–194. https://doi.org/https://doi.org/10.1016/j.schres.2015.04.004

Hope, S., Melle, I., Aukrust, P., Steen, N.E., Birkenaes, A.B., Lorentzen, S., Agartz, I., Ueland, T., Andreassen, O.A., 2009. Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor. Bipolar Disord. 11, 726–734. https://doi.org/https://doi.org/10.1111/j.1399-5618.2009.00757.x

Hope, S., Ueland, T., Steen, N.E., Dieset, I., Lorentzen, S., Berg, A.O., Agartz, I., Aukrust, P., Andreassen, O.A., 2013. Interleukin 1 receptor antagonist and soluble tumor necrosis factor receptor 1 are associated with general severity and psychotic symptoms in schizophrenia and bipolar disorder. Schizophr. Res. 145, 36–42. https://doi.org/10.1016/j.schres.2012.12.023

Hornig, M., Goodman, D.B.P., Kamoun, M., Amsterdam, J.D., 1998. Positive and negative acute phase proteins in affective subtypes. J. Affect. Disord. 49, 9–18. https://doi.org/https://doi.org/10.1016/S0165-0327(97)00180-8

Horsdal, H.T., Köhler-Forsberg, O., Benros, M.E., Gasse, C., 2017. C-reactive protein and white blood cell levels in schizophrenia, bipolar disorders and depression - associations with mortality and psychiatric outcomes: a population-based study. Eur. Psychiatry 44, 164–172. https://doi.org/10.1016/j.eurpsy.2017.04.012

Huang, T.-L., Lin, F.-C., 2007. High-sensitivity C-reactive protein levels in patients with major depressive disorder and bipolar mania. Prog. Neuro-Psychopharmacology Biol. Psychiatry 31, 370–372. https://doi.org/https://doi.org/10.1016/j.pnpbp.2006.09.010

Hung, Y.-J., Hsieh, C.-H., Chen, Y.-J., Pei, D., Kuo, S.-W., Shen, D.-C., Sheu, W.H.-H., Chen, Y.-C., 2007. Insulin sensitivity, proinflammatory markers and adiponectin in young males with different subtypes of depressive disorder. Clin. Endocrinol. (Oxf). 67, 784–789. https://doi.org/https://doi.org/10.1111/j.1365-2265.2007.02963.x

Jacoby, A.S., Munkholm, K., Vinberg, M., Pedersen, B.K., Kessing, L.V., 2016. Cytokines, brain-derived neurotrophic factor and C-reactive protein in bipolar i disorder - Results from a prospective study. J. Affect. Disord. 197, 167–174. https://doi.org/10.1016/j.jad.2016.03.040

Kapczinski, F., Dal-Pizzol, F., Teixeira, A.L., Magalhaes, P.V.S., Kauer-Sant’Anna, M., Klamt, F., Moreira, J.C.F., Augusto de Bittencourt Pasquali, M., Fries, G.R., Quevedo, J., Gama, C.S., Post, R., 2011. Peripheral biomarkers and illness activity in bipolar disorder. J. Psychiatr. Res. 45, 156–161. https://doi.org/https://doi.org/10.1016/j.jpsychires.2010.05.015

Karabulut, S., Tasdemir, I., Akcan, U., Kucukali, C., Tüzün, E., Cakir, S., 2019. Inflammation and Neurodegeneration in Patients with Early-Stage and Chronic Bipolar Disorder. Turkish J. Psychiatry 30. https://doi.org/10.5080/u18376

Kargar, M., Yousefi, A., Mojtahedzadeh, M., Akhondzadeh, S., Artounian, V., Abdollahi, A., Ahmadvand, A., Ghaeli, P., 2014. Effects of celecoxib on inflammatory markers in bipolar patients undergoing electroconvulsive therapy: a placebo-controlled, double-blind, randomised study. Swiss Med. Wkly. https://doi.org/10.4414/smw.2014.13880

Kauer-Sant’Anna, M., Kapczinski, F., Andreazza, A., Bond, D., Lam, R., Young, L., Yatham, L., 2008. Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. Int. J. Neuropsychopharmacol. 12, 447–458. https://doi.org/10.1017/S1461145708009310

Kim, Y.-K., Jung, H.-G., Myint, A.-M., Kim, H., Park, S.-H., 2007. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. J. Affect. Disord. 104, 91–95. https://doi.org/https://doi.org/10.1016/j.jad.2007.02.018

King, S., Jelen, L.A., Horne, C.M., Cleare, A., Pariante, C.M., Young, A.H., Stone, J.M., 2019. Inflammation, glutamate, and cognition in bipolar disorder type II: A proof of concept study. Front. Psychiatry 10. https://doi.org/10.3389/fpsyt.2019.00066

Knijff, E.M., Nadine Breunis, M., Kupka, R.W., de Wit, H.J., Ruwhof, C., Akkerhuis, G.W., Nolen, W.A., Drexhage, H.A., 2007. An imbalance in the production of IL-1β and IL-6 by monocytes of bipolar patients: restoration by lithium treatment. Bipolar Disord. 9, 743–753. https://doi.org/10.1111/j.1399-5618.2007.00444.x

Koga, N., Ogura, J., Yoshida, F., Hattori, K., Hori, H., Aizawa, E., Ishida, I., Kunugi, H., 2019. Altered polyunsaturated fatty acid levels in relation to proinflammatory cytokines, fatty acid desaturase genotype, and diet in bipolar disorder. Transl. Psychiatry 9, 208. https://doi.org/10.1038/s41398-019-0536-0

Kramer, N.E., Cosgrove, V.E., Dunlap, K., Subramaniapillai, M., McIntyre, R.S., Suppes, T., 2019. A clinical model for identifying an inflammatory phenotype in mood disorders. J. Psychiatr. Res. 113, 148–158. https://doi.org/10.1016/j.jpsychires.2019.02.005

Kunz, M., Ceresér, K.M., Goi, P.D., Fries, G.R., Teixeira, A.L., Fernandes, B.S., Belmonte-de-Abreu, P.S., Kauer-Sant’Anna, M., Kapczinski, F., Gama, C.S., 2011. Serum levels of IL-6, IL-10 and TNF-α in patients with bipolar disorder and schizophrenia: differences in pro- and anti-inflammatory balance. Rev. Bras. Psiquiatr. 33, 268–274. https://doi.org/10.1590/S1516-44462011000300010

Lesh, T.A., Careaga, M., Rose, D.R., McAllister, A.K., Van de Water, J., Carter, C.S., Ashwood, P., 2018. Cytokine alterations in first-episode schizophrenia and bipolar disorder: Relationships to brain structure and symptoms. J. Neuroinflammation 15. https://doi.org/10.1186/s12974-018-1197-2

Li, H., Hong, W., Zhang, C., Wu, Z., Wang, Z., Yuan, C., Li, Z., Huang, J., Lin, Z., Fang, Y., 2015. IL-23 and TGF-β1 levels as potential predictive biomarkers in treatment of bipolar I disorder with acute manic episode. J. Affect. Disord. 174, 361–366. https://doi.org/10.1016/j.jad.2014.12.033

Lin, K., Shao, R., Wang, R., Lu, W., Zou, W., Chen, K., Gao, Y., Brietzke, E., McIntyre, R.S., Mansur, R.B., Zhang, L., Yau, S.-Y., Su, H., Xu, G., So, K.-F., 2020. Inflammation, brain structure and cognition interrelations among individuals with differential risks for bipolar disorder. Brain. Behav. Immun. 83, 192–199. https://doi.org/10.1016/j.bbi.2019.10.010

Liu, H.-C., Yang, Y.-Y., Chou, Y.-M., Chen, K.-P., Shen, W.W., Leu, S.-J., 2004. Immunologic variables in acute mania of bipolar disorder. J. Neuroimmunol. 150, 116–122. https://doi.org/10.1016/j.jneuroim.2004.01.006

Lotrich, F.E., Butters, M.A., Aizenstein, H., Marron, M.M., Reynolds, C.F., Gildengers, A.G., 2014. The relationship between interleukin-1 receptor antagonist and cognitive function in older adults with bipolar disorder. Int. J. Geriatr. Psychiatry 29, 635–644. https://doi.org/10.1002/gps.4048

Lu, Y.-R., Rao, Y.-B., Mou, Y.-J., Chen, Y., Lou, H.-F., Zhang, Y., Zhang, D.-X., Xie, H.-Y., Hu, L.-W., Fang, P., 2019. High concentrations of serum interleukin-6 and interleukin-8 in patients with bipolar disorder. Medicine (Baltimore). 98, e14419. https://doi.org/10.1097/MD.0000000000014419

Luo, Y., He, H., Zhang, M., Huang, X., Fan, N., 2016. Altered serum levels of TNF-α, IL-6 and IL-18 in manic, depressive, mixed state of bipolar disorder patients. Psychiatry Res. 244, 19–23. https://doi.org/10.1016/j.psychres.2016.07.027

Maes, M., Bosmans, E., Calabrese, J., Smith, R., Meltzer, H.Y., 1995. Interleukin-2 and interleukin-6 in schizophrenia and mania: Effects of neuroleptics and mood stabilizers. J. Psychiatr. Res. 29, 141–152. https://doi.org/10.1016/0022-3956(94)00049-W

Maes, M., Meester, Scharpé, S., Desnyder, R., Ranjan, R., Meltzer, H.Y., 1996. Alterations in plasma dipeptidyl peptidase IV enzyme activity in depression and schizophrenia: effects of antidepressants and antipsychotic drugs. Acta Psychiatr. Scand. 93, 1–8. https://doi.org/10.1111/j.1600-0447.1996.tb10612.x

Mao, R., Zhang, C., Chen, J., Zhao, G., Zhou, R., Wang, F., Xu, J., Yang, T., Su, Y., Huang, J., Wu, Z., Cao, L., Wang, Y., Hu, Y., Yuan, C., Yi, Z., Hong, W., Wang, Z., Peng, D., Fang, Y., 2018. Different levels of pro- and anti-inflammatory cytokines in patients with unipolar and bipolar depression. J. Affect. Disord. 237, 65–72. https://doi.org/10.1016/j.jad.2018.04.115

Marie-Claire, C., Courtin, C., Curis, E., Bouaziz-Amar, E., Laplanche, J.-L., Jacob, A., Etain, B., Blanchard, A., Bellivier, F., 2019. Increased plasma levels of high mobility group box 1 protein in patients with bipolar disorder: A pilot study. J. Neuroimmunol. 334, 576993. https://doi.org/10.1016/j.jneuroim.2019.576993

Miklowitz, D.J., Portnoff, L.C., Armstrong, C.C., Keenan-Miller, D., Breen, E.C., Muscatell, K.A., Eisenberger, N.I., Irwin, M.R., 2016. Inflammatory cytokines and nuclear factor-kappa B activation in adolescents with bipolar and major depressive disorders. Psychiatry Res. 241, 315–322. https://doi.org/10.1016/j.psychres.2016.04.120

Millett, C.E., Perez-Rodriguez, M., Shanahan, M., Larsen, E., Yamamoto, H.S., Bukowski, C., Fichorova, R., Burdick, K.E., 2019. C-reactive protein is associated with cognitive performance in a large cohort of euthymic patients with bipolar disorder. Mol. Psychiatry. https://doi.org/10.1038/s41380-019-0591-1

Mizuno, Y., Hofer, A., Suzuki, T., Frajo-Apor, B., Wartelsteiner, F., Kemmler, G., Saruta, J., Tsukinoki, K., Mimura, M., Fleischhacker, W.W., Uchida, H., 2016. Clinical and biological correlates of resilience in patients with schizophrenia and bipolar disorder: A cross-sectional study. Schizophr. Res. 175, 148–153. https://doi.org/10.1016/j.schres.2016.04.047

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J. Clin. Epidemiol. 62, 1006–1012. https://doi.org/10.1016/j.jclinepi.2009.06.005

Mondin, T.C., de Azevedo Cardoso, T., Moreira, F.P., Wiener, C., Oses, J.P., de Mattos Souza, L.D., Jansen, K., da Silva Magalhães, P.V., Kapczinski, F., da Silva, R.A., 2016. Circadian preferences, oxidative stress and inflammatory cytokines in bipolar disorder: A community study. J. Neuroimmunol. 301, 23–29. https://doi.org/10.1016/j.jneuroim.2016.10.012

Monfrim, X., Gazal, M., De Leon, P.B., Quevedo, L., Souza, L.D., Jansen, K., Oses, J.P., Pinheiro, R.T., Silva, R.A., Lara, D.R., Ghisleni, G., Spessato, B., Kaster, M.P., 2014. Immune dysfunction in bipolar disorder and suicide risk: is there an association between peripheral corticotropin-releasing hormone and interleukin-1β? Bipolar Disord. 16, 741–747. https://doi.org/10.1111/bdi.12214

Mora, E., Portella, M.J., Piñol-Ripoll, G., López, R., Cuadras, D., Forcada, I., Teres, M., Vieta, E., Mur, M., 2019. High BDNF serum levels are associated to good cognitive functioning in bipolar disorder. Eur. Psychiatry 60, 97–107. https://doi.org/10.1016/j.eurpsy.2019.02.006

Mørch, R.H., Dieset, I., Faerden, A., Hope, S., Aas, M., Nerhus, M., Gardsjord, E.S., Haram, M., Falk, R.S., Joa, I., Morken, G., Agartz, I., Aukrust, P., Djurovic, S., Melle, I., Ueland, T., Andreassen, O.A., 2017. Persistent increase in TNF and IL-1 markers in severe mental disorders suggests trait-related inflammation: a one year follow-up study. Acta Psychiatr. Scand. 136, 400–408. https://doi.org/10.1111/acps.12783

Mørch, R.H., Dieset, I., Færden, A., Hope, S., Aas, M., Nerhus, M., Gardsjord, E.S., Joa, I., Morken, G., Agartz, I., Aukrust, P., Djurovic, S., Melle, I., Ueland, T., Andreassen, O.A., 2016. Inflammatory evidence for the psychosis continuum model. Psychoneuroendocrinology 67, 189–197. https://doi.org/10.1016/j.psyneuen.2016.02.011

Mota, R., Gazal, M., Acosta, B.A., de Leon, P.B., Jansen, K., Pinheiro, R.T., Souza, L.D., Silva, R.A., Oses, J.P., Quevedo, L., Lara, D.R., Ghisleni, G., Kaster, M.P., 2013. Interleukin-1β is associated with depressive episode in major depression but not in bipolar disorder. J. Psychiatr. Res. 47, 2011–2014. https://doi.org/10.1016/j.jpsychires.2013.08.020

Munkholm, K., Braüner, J.V., Kessing, L.V., Vinberg, M., 2013. Cytokines in bipolar disorder vs. healthy control subjects: A systematic review and meta-analysis. J. Psychiatr. Res. 47, 1119–1133. https://doi.org/10.1016/j.jpsychires.2013.05.018

Munkholm, K., Jacoby, A.S., Lenskjold, T., Bruunsgaard, H., Vinberg, M., Kessing, L.V., 2018. Leukocytes in peripheral blood in patients with bipolar disorder – Trait and state alterations and association with levels of cytokines and C-reactive protein. Psychiatry Res. 261, 383–390. https://doi.org/10.1016/j.psychres.2018.01.022

Munkholm, K., Vinberg, M., Pedersen, B.K., Poulsen, H.E., Ekstrøm, C.T., Kessing, L. V., 2019. A multisystem composite biomarker as a preliminary diagnostic test in bipolar disorder. Acta Psychiatr. Scand. 139, 227–236. https://doi.org/10.1111/acps.12983

Munkholm, K., Weikop, P., Kessing, L.V., Vinberg, M., 2015. Elevated levels of IL-6 and IL-18 in manic and hypomanic states in rapid cycling bipolar disorder patients. Brain. Behav. Immun. 43, 205–213. https://doi.org/10.1016/j.bbi.2014.09.021

Murata, S., Murphy, M., Hoppensteadt, D., Fareed, J., Welborn, A., Halaris, A., 2020. Effects of adjunctive inflammatory modulation on IL-1β in treatment resistant bipolar depression. Brain. Behav. Immun. 87, 369–376. https://doi.org/10.1016/j.bbi.2020.01.004

O’Brien, S.M., Scully, P., Scott, L. V., Dinan, T.G., 2006. Cytokine profiles in bipolar affective disorder: Focus on acutely ill patients. J. Affect. Disord. 90, 263–267. https://doi.org/10.1016/j.jad.2005.11.015

Ortiz-Domínguez, A., Hernández, M.E., Berlanga, C., Gutiérrez-Mora, D., Moreno, J., Heinze, G., Pavón, L., 2007. Immune variations in bipolar disorder: phasic differences. Bipolar Disord. 9, 596–602. https://doi.org/https://doi.org/10.1111/j.1399-5618.2007.00493.x

Osimo, E.F., Cardinal, R.N., Jones, P.B., Khandaker, G.M., 2018. Prevalence and correlates of low-grade systemic inflammation in adult psychiatric inpatients: An electronic health record-based study. Psychoneuroendocrinology 91, 226–234. https://doi.org/10.1016/j.psyneuen.2018.02.031

Palacio, J.D., Guzman, S., Vargas, C., Díaz-Zuluaga, A.M., López-Jaramillo, C., 2016. Comparación de biomarcadores inflamatorios en pacientes con trastorno afectivo bipolar tipo I y sujetos controles. Rev. Colomb. Psiquiatr. 45, 8–13. https://doi.org/10.1016/j.rcp.2015.06.002

Palomino, A., Vallejo-Illarramendi, A., González-Pinto, A., Aldama, A., González-Gómez, C., Mosquera, F., González-García, G., Matute, C., 2006. Decreased levels of plasma BDNF in first-episode schizophrenia and bipolar disorder patients. Schizophr. Res. 86, 321–322. https://doi.org/10.1016/j.schres.2006.05.028

Pantović-Stefanović, M., Petronijević, N., Dunjić-Kostić, B., Velimirović, M., Nikolić, T., Jurišić, V., Lačković, M., Damjanović, A., Totić-Poznanović, S., Jovanović, A.A., Ivković, M., 2018. sVCAM-1, sICAM-1, TNF-α and IL-6 levels in bipolar disorder type I: Acute, longitudinal and therapeutic implications. World J. Biol. Psychiatry 19, S41–S51. https://doi.org/10.1080/15622975.2016.1259498

Papiol, S., 2004. Interleukin-1 cluster is associated with genetic risk for schizophrenia and bipolar disorder. J. Med. Genet. 41, 219–223. https://doi.org/10.1136/jmg.2003.012914

Pedrotti Moreira, F., Cardoso, T.C., Mondin, T.C., Wiener, C.D., de Mattos Souza, L.D., Oses, J.P., Jansen, K., Silva, R.A., 2019. Serum level of nerve growth factor is a potential biomarker of conversion to bipolar disorder in women with major depressive disorder. Psychiatry Clin. Neurosci. 73, 590–593. https://doi.org/10.1111/pcn.12896

Quidé, Y., Bortolasci, C.C., Spolding, B., Kidnapillai, S., Watkeys, O.J., Cohen-Woods, S., Berk, M., Carr, V.J., Walder, K., Green, M.J., 2019. Association between childhood trauma exposure and pro-inflammatory cytokines in schizophrenia and bipolar-I disorder. Psychol. Med. 49, 2736–2744. https://doi.org/10.1017/S0033291718003690

Remlinger-Molenda, A., Wójciak, P., Michalak, M., Rybakowski, J., 2012. [Activity of selected cytokines in bipolar patients during manic and depressive episodes]. Psychiatr. Pol. 46, 599–611.

Sahin, B., Inanli, I., Caliskan, A., Uysal, S., 2019. Chitinase-3-like protein 1 levels in bipolar disorder. Saudi Med. J. 40, 26–32. https://doi.org/10.15537/smj.2019.1.23396

Sanjay, T.N., Shivakumar, V., Subbanna, M., Biradar, S.U., Muralidharan, K., Venkatasubramanian, G., 2017. Plasma interleukin-6 in remitted early bipolar I disorder and subjects at high-risk for bipolar disorder. Asian J. Psychiatr. https://doi.org/10.1016/j.ajp.2017.03.014

Scola, G., McNamara, R.K., Croarkin, P.E., Leffler, J.M., Cullen, K.R., Geske, J.R., Biernacka, J.M., Frye, M.A., Delbello, M.P., Andreazza, A.C., 2016. Lipid peroxidation biomarkers in adolescents with or at high-risk for bipolar disorder. J. Affect. Disord. 192, 176–183. https://doi.org/10.1016/j.jad.2015.12.020

Siwek, M., Sowa-Kućma, M., Styczeń, K., Misztak, P., Nowak, R.J., Szewczyk, B., Dudek, D., Rybakowski, J.K., Nowak, G., Maes, M., 2017. Associations of Serum Cytokine Receptor Levels with Melancholia, Staging of Illness, Depressive and Manic Phases, and Severity of Depression in Bipolar Disorder. Mol. Neurobiol. 54, 5883–5893. https://doi.org/10.1007/s12035-016-0124-8

Söderlund, J., Olsson, S., Samuelsson, M., Walther-Jallow, L., Johansson, C., Erhardt, S., Landén, M., Engberg, G., 2011. Elevation of cerebrospinal fluid interleukin-1β in bipolar disorder. J. Psychiatry Neurosci. 36, 114–118. https://doi.org/10.1503/jpn.100080

Sowa-Kućma, M., Styczeń, K., Siwek, M., Misztak, P., Nowak, R.J., Dudek, D., Rybakowski, J.K., Nowak, G., Maes, M., 2018. Are there differences in lipid peroxidation and immune biomarkers between major depression and bipolar disorder: Effects of melancholia, atypical depression, severity of illness, episode number, suicidal ideation and prior suicide attempts. Prog. Neuro-Psychopharmacology Biol. Psychiatry 81, 372–383. https://doi.org/10.1016/j.pnpbp.2017.08.024

Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Becker, B.J., Sipe, T.A., Thacker, S.B., 2000. Meta-analysis of observational studies in epidemiology: A proposal for reporting. J. Am. Med. Assoc. 283, 2008–2012. https://doi.org/10.1001/jama.283.15.2008

Su, S.-C., Sun, M.-T., Wen, M.-J., Lin, C.-J., Chen, Y.-C., Hung, Y.-J., 2011. Brain-Derived Neurotrophic Factor, Adiponectin, and Proinflammatory Markers in Various Subtypes of Depression in Young Men. Int. J. Psychiatry Med. 42, 211–226. https://doi.org/10.2190/PM.42.3.a

Tanaka, T., Matsuda, T., Hayes, L.N., Yang, S., Rodriguez, K., Severance, E.G., Yolken, R.H., Sawa, A., Eaton, W.W., 2017. Infection and inflammation in schizophrenia and bipolar disorder. Neurosci. Res. 115, 59–63. https://doi.org/10.1016/j.neures.2016.11.002

Tatay-Manteiga, A., Balanzá-Martínez, V., Bristot, G., Tabarés-Seisdedos, R., Kapczinski, F., Cauli, O., 2017. Clinical staging and serum cytokines in bipolar patients during euthymia. Prog. Neuro-Psychopharmacology Biol. Psychiatry 77, 194–201. https://doi.org/10.1016/j.pnpbp.2017.04.028

Teixeira, A.L., de Souza, R.T., Zanetti, M. V., Brunoni, A.R., Busatto, G.F., Zarate, C.A., Gattaz, W.F., Machado-Vieira, R., 2015. Increased plasma levels of soluble TNF receptors 1 and 2 in bipolar depression and impact of lithium treatment. Hum. Psychopharmacol. Clin. Exp. 30, 52–56. https://doi.org/10.1002/hup.2450

Tsai, S.-Y., Chen, K.-P., Yang, Y.-Y., Chen, C.-C., Lee, J.-C., Singh, V.K., Leu, S.-J.C., 1999. Activation of indices of cell-mediated immunity in bipolar mania. Biol. Psychiatry 45, 989–994. https://doi.org/10.1016/S0006-3223(98)00159-0

Tsai, S.-Y., Chung, K.-H., Chen, P.-H., 2017. Levels of interleukin-6 and high-sensitivity C-reactive protein reflecting mania severity in bipolar disorder. Bipolar Disord. 19, 708–709. https://doi.org/10.1111/bdi.12570

Tsai, S.-Y., Chung, K.-H., Huang, S.-H., Chen, P.-H., Lee, H.-C., Kuo, C.-J., 2014. Persistent inflammation and its relationship to leptin and insulin in phases of bipolar disorder from acute depression to full remission. Bipolar Disord. 16, 800–808. https://doi.org/10.1111/bdi.12240

Tsai, S.-Y.M., Yang, Y.-Y., Kuo, C.-J., Chen, C.-C., Leu, S.-J.C., 2001. Effects of symptomatic severity on elevation of plasma soluble interleukin-2 receptor in bipolar mania. J. Affect. Disord. 64, 185–193. https://doi.org/10.1016/S0165-0327(00)00252-4

Tsai, S.Y., Chung, K.H., Wu, J.Y., Kuo, C.J., Lee, H.C., Huang, S.H., 2012. Inflammatory markers and their relationships with leptin and insulin from acute mania to full remission in bipolar disorder. J. Affect. Disord. 136, 110–116. https://doi.org/10.1016/j.jad.2011.08.022

Tunç, S., Atagün, M.İ., Başbuğ, H.S., Erel, Ö., 2019. Serum ceruloplasmin-ferroxidase activity in bipolar disorder is elevated compared to major depressive disorder and schizophrenia: a controlled study. Psychiatry Clin. Psychopharmacol. 29, 307–314. https://doi.org/10.1080/24750573.2019.1584489

Uyanik, V., Tuglu, C., Gorgulu, Y., Kunduracilar, H., Uyanik, M.S., 2015. Assessment of cytokine levels and hs-CRP in bipolar I disorder before and after treatment. Psychiatry Res. 228, 386–392. https://doi.org/10.1016/j.psychres.2015.05.078

van den Ameele, S., Fuchs, D., Coppens, V., de Boer, P., Timmers, M., Sabbe, B., Morrens, M., 2018. Markers of inflammation and monoamine metabolism indicate accelerated aging in bipolar disorder. Front. Psychiatry 9. https://doi.org/10.3389/fpsyt.2018.00250

Vasconcelos-Moreno, M.P., Fries, G.R., Gubert, C., Dos Santos, B.T.M.Q., Fijtman, A., Sartori, J., Ferrari, P., Grun, L.K., Parisi, M.M., Guma, F.T.C.R., Barbé-Tuana, F.M., Kapczinski, F., Rosa, A.R., Yatham, L.N., Kauer-Sant’Anna, M., 2017. Telomere Length, Oxidative Stress, Inflammation and BDNF Levels in Siblings of Patients with Bipolar Disorder: Implications for Accelerated Cellular Aging. Int. J. Neuropsychopharmacol. 20, 445–454. https://doi.org/10.1093/ijnp/pyx001

Wadee, A.A., Kuschke, R.H., Wood, L.A., Berk, M., Ichim, L., Maes, M., 2002. Serological observations in patients suffering from acute manic episodes. Hum. Psychopharmacol. 17, 175–179. https://doi.org/10.1002/hup.390

Wang, T.Y., Lee, S.Y., Chen, S.L., Chung, Y.L., Li, C.L., Chang, Y.H., Wang, L.J., Chen, P.S., Chen, S.H., Chu, C.H., Huang, S.Y., Tzeng, N.S., Hsieh, T.H., Chiu, Y.C., Lee, I.H., Chen, K.C., Yang, Y.K., Hong, J.S., Lu, R.B., 2016. The differential levels of inflammatory cytokines and bdnf among bipolar spectrum disorders. Int. J. Neuropsychopharmacol. 19, 1–8. https://doi.org/10.1093/ijnp/pyw012

Wieck, A., Grassi-Oliveira, R., do Prado, C.H., Rizzo, L.B., de Oliveira, A.S., Kommers-Molina, J., Viola, T.W., Marciano Vieira, É.L., Teixeira, A.Ô.L., Bauer, M.E., 2014. Pro-inflammatory cytokines and soluble receptors in response to acute psychosocial stress: Differential reactivity in bipolar disorder. Neurosci. Lett. https://doi.org/10.1016/j.neulet.2014.07.040

Wieck, A., Grassi-Oliveira, R., do Prado, C.H., Viola, T.W., Petersen, L.E., Porto, B., Teixeira, A.L., Bauer, M.E., 2016. Toll-like receptor expression and function in type I bipolar disorder. Brain. Behav. Immun. 54, 110–121. https://doi.org/10.1016/j.bbi.2016.01.011

Wiener, C.D., Moreira, F.P., Cardoso, T.A., Mondin, T.C., da Silva Magalhães, P.V., Kapczinski, F., de Mattos Souza, L.D., da Silva, R.A., Oses, J.P., Jansen, K., 2017. Inflammatory cytokines and functional impairment in drug-free subjects with mood disorder. J. Neuroimmunol. 307, 33–36. https://doi.org/10.1016/j.jneuroim.2017.03.003

Wiener, C.D., Moreira, F.P., Portela, L.V., Strogulski, N.R., Lara, D.R., da Silva, R.A., Souza, L.D. de M., Jansen, K., Oses, J.P., 2019. Interleukin-6 and Interleukin-10 in mood disorders: A population-based study. Psychiatry Res. https://doi.org/10.1016/j.psychres.2019.01.100

Wollenhaupt-Aguiar, B., Librenza-Garcia, D., Bristot, G., Przybylski, L., Stertz, L., Kubiachi Burque, R., Ceresér, K.M., Spanemberg, L., Caldieraro, M.A., Frey, B.N., Fleck, M.P., Kauer-Sant’Anna, M., Passos, I.C., Kapczinski, F., 2020. Differential biomarker signatures in unipolar and bipolar depression: A machine learning approach. Aust. New Zeal. J. Psychiatry 54, 393–401. https://doi.org/10.1177/0004867419888027

Wu, W., Zheng, Y.L., Tian, L.P., Lai, J.B., Hu, C.C., Zhang, P., Chen, J.K., Hu, J.B., Huang, M.L., Wei, N., Xu, W.J., Zhou, W.H., Lu, S.J., Lu, J., Qi, H.L., Wang, D.D., Zhou, X.Y., Duan, J.F., Xu, Y., Hu, S.H., 2017. Circulating T lymphocyte subsets, cytokines, and immune checkpoint inhibitors in patients with bipolar II or major depression: A preliminary study. Sci. Rep. 7. https://doi.org/10.1038/srep40530