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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

Marco Solmi,[1,2,3] Manu Suresh Sharma,[4] Emanuele F Osimo,[5,6,7] Michele Fornaro,[8] Beatrice Bortolato,[9] Giovanni Croatto,[1] Alessandro Miola,[1] Eduard Vieta,[10] Carmine M Pariante,[11] Lee Smith,[12] Paolo Fusar-Poli,[3,13,14] Jae Il Shin,[15] Michael Berk,[16,17,18,19] Andre F Carvalho[16,20,21]

1 Neurosciences Department, University of Padova, Italy

2 Padua Neuroscience Center, University of Padova, Italy

3 Early Psychosis: Interventions and Clinical-detection (EPIC) lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology& Neuroscience, King's College London, London, UK

4 Behavioural Health Network, Hartford Healthcare

5 MRC London Institute of Medical Sciences, Institute of Clinical Sciences, Imperial College, Hammersmith Campus, London, UK

6 Department of Psychiatry, University of Cambridge, Cambridge, UK

7 Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK

8 Department of Psychiatry, Federico II University, Naples, Italy

9 Psychiatry Department, Local Health Unit (ULSS) 6 Euganea, Padova, Italy

10 Bipolar and depressive disorders unit, Department of Psychiatry and Psychology, Institute of Neuroscience, Hospital Clínic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain

11 Stress, Psychiatry and Immunology Laboratory, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College, London, UK.

12 The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK

13 Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy;

14 OASIS Service, South London and Maudsley National Health Service (NHS) Foundation Trust, London, United Kingdom

15 Department of Pediatrics, Yonsei University College of Medicine, Seoul, South Korea

16 Deakin University, IMPACT - the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Barwon Health, 75 Pigdon's Road, Waurn Ponds, Geelong, VIC, 3216, Australia

17 School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, 3004, Australia.

18 Department of Psychiatry, University of Melbourne, Parkville, VIC, 3052, Australia.

19 Orygen Youth Health, 35 Poplar Road, Parkville, VIC, 3052, Australia

20 Centre for Addiction and Mental Health, Toronto, Ontario, Canada.

21 Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada.

Corresponding author:
Andre F. Carvalho, MD, PhD
E-mail: andrefc7@hotmail.com

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.

1. Introduction

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

Consistent and converging evidence has pointed toward a role of peripheral immune activation in the pathophysiology of BD and associated medical comorbidities (Maes and Carvalho, 2018; Modabbernia et al., 2013; Morris et al., 2019; Sayana et al., 2017). Differences in levels of inflammatory mediators have been reported both between subjects with BD and healthy controls(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, (Rosenblat et al., 2016) however the largest RCT conducted to date in participants with bipolar depression found no evidence of efficacy for either minocycline or celecoxib compared to placebo (Husain et al., 2020). These inconsistent findings may be at least in part due to the inclusion of participants with varying levels of peripheral immune activation (Berk et al., 2020). For example, it has been proposed that in major depressive disorder only a subset of subjects with BD may exhibit peripheral inflammation(Milaneschi et al., 2020; Miller and Raison, 2016). However, whether such a subgroup with peripheral inflammation exists

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

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

2. Methods

2.1 Search, inclusion criteria

We followed an a priori protocol (available upon request to the corresponding author). This was compliant with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols [PRISMA(-P)] (Moher et al., 2015, 2009) (eTable 1, supplementary 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 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 (supplementary material, page 6).

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). 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.

3. Results

3.1 Study selection

Out of the initial 729 references assessed at the title/abstract level, 125 were assessed at the full-text level. Of these, 72 were excluded, with specific reasons reported in eTable 3, Supplementary 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)

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 2. All mediators except IL-1 were elevated in BD compared to controls. Specifically, CRP (g=0.70, 95% CI 0.31-1.09, I^2=97.05%, k=37, BD=2,215 vs HC=3,750), IL-6 (g=0.81, 95% CI 0.46-1.16, I^2=96.12%,k=45, BD=1,956 vs HC=4,106), TNF-α (g=0.49, 95% CI 0.19-0.78, I^2=93.96%,

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

3.3 *Variability of levels of inflammatory mediators*

Results of meta-analyses of variability ratios are reported in Figures 4-5, and eFigures 7-8.

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 3, and eFigures 2-6. 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 material. The median study quality was 7 (IQR 6-9). Low quality emerged most frequently on item 5 ("Was a sample size justification, power description, or variance and effect estimates provided?"), with only two studies meeting this criterion (Jacoby et al., 2016; Mizuno et al., 2016).

4. Discussion

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

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

recurring affective episodes of BD (Berk et al., 2011; Carvalho et al., 2020). Peripheral immune activation is thought to contribute to neuroprogression in BD (Quevedo et al., 2021). Inflammation likely also drives the parallel process of 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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National Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Abbot, Astra Zeneca, Janssen and Janssen, Lundbeck and Merck and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Janssen and Janssen, Lundbeck Merck, Pfizer and Servier – all unrelated to this work. Other authors report no conflict of interest.

FIGURE CAPTIONS:

Figure 1. PRISMA study flow-chart.

Figure 2. Meta-analysis of levels of inflammatory markers in bipolar disorder vs healthy controls.

Figure 3. Sensitivity analysis of levels of inflammatory markers across disease states.

Figure 4. Meta-analysis of log coefficient of variation ratios of inflammatory markers in bipolar disorder vs healthy controls.

Figure 5. Meta-analysis of log coefficient of variation ratio of inflammatory markers in bipolar disorder vs healthy controls across disease state.

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Table 1. Characteristics of included studies

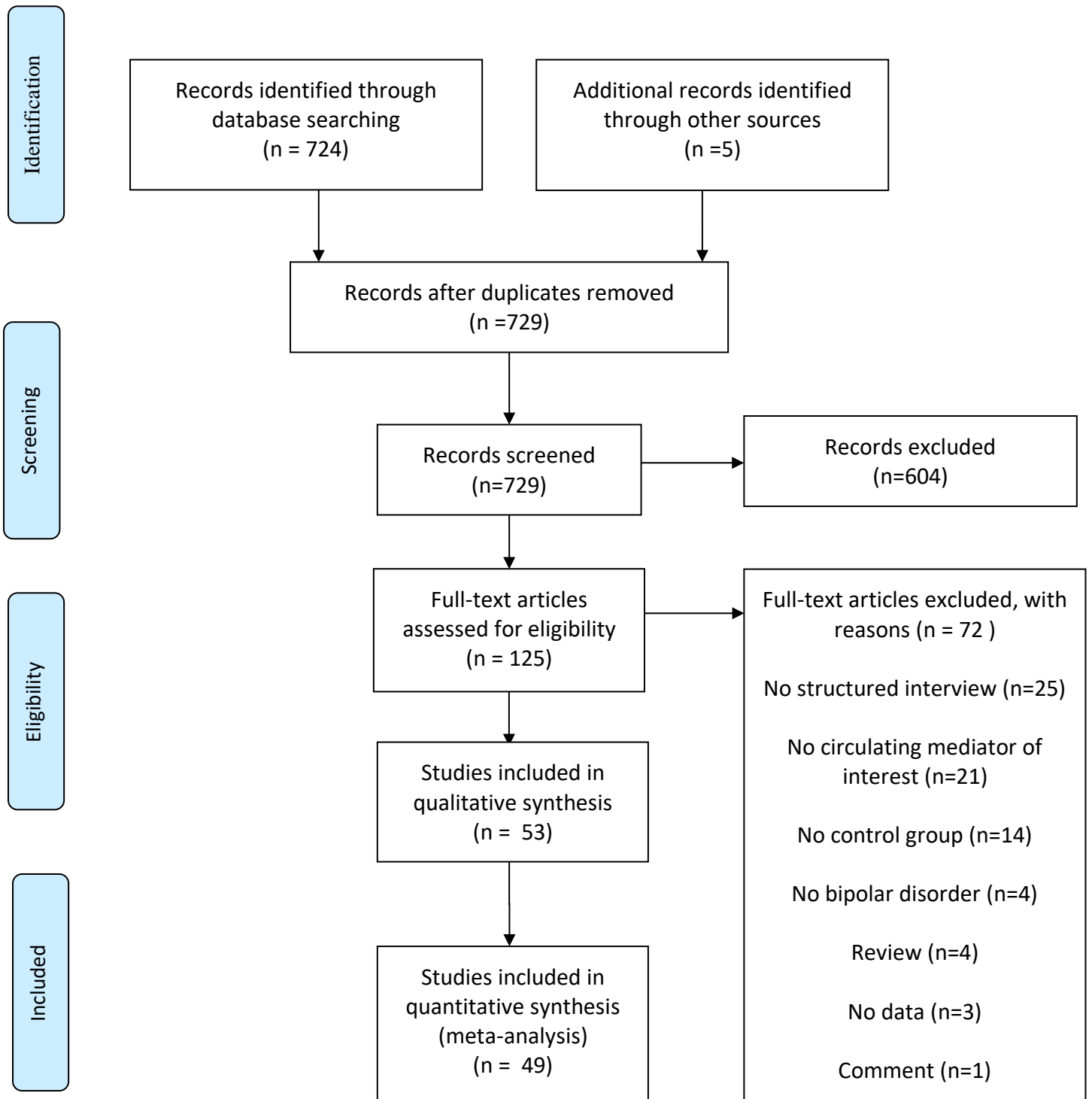| Author and year	N cases	N controls	Cytokine	BD states	Age case (mean)	Age ctrl (mean)	% female cases	% female ctrls	Treatment status	Country	Diagnosis criteria	Assay
Aas M. et al.,2017(Aas et al., 2017)	123	212	CRP	ns	32.3	30.9	59	86	ns	Norway	DSM-IV	ELISA
Bai Y-M et al.,2015(Bai et al., 2015)	130	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

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
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								

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
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					

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
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;

Figure 1