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A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression

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Abstract

Schizophrenia, bipolar disorder and major depressive disorder (MDD) have all been associated with aberrant blood cytokine levels; however, neither the pattern of cytokine alterations nor the impact of clinical status have been compared across disorders. We performed a meta-analysis of blood cytokines in acutely and chronically ill patients with these major psychiatric disorders. Articles were identified by searching the PubMed, PsycInfo and Web of Science, and the reference lists of these studies. Sixty-eight studies met the inclusion criteria (40 schizophrenia, 10 bipolar disorder and 18 MDD) for acutely ill patients. Forty-six studies met the inclusion criteria (18 schizophrenia, 16 bipolar disorder and 12 MDD) for chronically ill patients. Levels of two cytokines (interleukin- 6 (IL-6), tumor necrosis factor-α (TNF-α)), one soluble cytokine receptor (sIL-2R), and one cytokine receptor antagonist (IL-1RA) were significantly increased in acutely ill patients with schizophrenia, bipolar mania and MDD compared with controls ($P < 0.01$). Following treatment of the acute illness, IL-6 levels significantly decreased in both schizophrenia and MDD ($P < 0.01$); sIL-2R levels increased in schizophrenia; and IL-1RA levels in bipolar mania decreased. In chronically ill patients, the levels of IL-6 were significantly increased in schizophrenia, euthymic (but not depressed) bipolar disorder and MDD compared with controls ($P < 0.01$). The levels of IL-1β and sIL-2R were significantly increased in both chronic schizophrenia and euthymic bipolar disorder. Overall, there were similarities in the pattern of cytokine alterations in schizophrenia, bipolar disorder and MDD during acute and chronic phases of illness, raising the possibility of common underlying pathways for immune dysfunction. Effects of treatment on

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CONFLICT OF INTEREST

Dr Goldsmith has nothing to disclose relevant to the present work. Dr Rapaport has nothing to disclose relevant to the present work. Dr Miller has nothing to disclose relevant to present work.

AUTHOR CONTRIBUTIONS

Drs Goldsmith and Miller designed the study, managed the literature searches and the analyses. Drs Goldsmith, Rapaport and Miller wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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cytokines were more robust for schizophrenia and MDD, but were more frequently studied than for acute mania. These findings have important implications for our understanding of the pathophysiology and treatment of major psychiatric disorders.

INTRODUCTION

The investigation of immune system abnormalities in psychiatric disorders has become a popular area of research over the past decade. This interest has been at least partially stimulated by our increased understanding of the interactions that occur between the immune system and the brain in other chronic medical disorders. Advances in molecular biology and genetics have led to the identification of associations between genes involved in the regulation of the immune system and increased risk of schizophrenia, bipolar disorder and major depressive disorder (MDD).[1–3] These disorders are also associated with abnormalities in immune cell numbers, inflammatory markers and antibody titers.[4–9] There is mixed evidence in different psychiatric disorders, suggesting that adjunctive treatment with immunomodulatory agents may be associated with improvement in psychopathology.[10–13] Taken together, these findings suggest that we need to more extensively evaluate the hypothesis that immune dysfunction manifested by an increase in proinflammatory and decrease in anti-inflammatory biomarkers may be involved in the pathogenesis of major psychiatric disorders in some individuals.

Aberrant blood levels of components of the cytokine network have been reported in schizophrenia, bipolar disorder and MDD.[14–20] Cytokines are key signaling molecules of the immune system that exert effects in the periphery and brain. They are produced by immune and non-immune cells, and exert their effects by binding specific receptors on a variety of target cells. Cytokine receptors also exist in soluble forms, which can inhibit (e.g., soluble interleukin-2 receptor (sIL-2R)) or enhance (e.g., sIL-6R)) the biological activity of cytokines. And, there are endogenous cytokine receptor antagonists (e.g., interleukin-6 (IL-6) receptor antagonist (IL-1RA) that compete with cytokines for membrane receptors. Cytokines are key regulators of acute and chronic inflammation, a complex but vital biological response that impacts all organ systems. Cytokines help coordinate the function of both the innate and adaptive components of the immune system as well as a host of other physiological processes throughout the body.[21,22]

Previous meta-analyses in schizophrenia and bipolar disorder have found that blood levels of some components of the cytokine network may vary with clinical status,[16–18] but this has not been investigated in MDD. At this time, we do not know if or when changes in blood cytokine network proteins represent state or trait markers of these disorders.

Despite the evidence for cytokine network alterations in major psychiatric disorders, there is tremendous between-study heterogeneity with respect to: cytokine components studied; effects of clinical course and illness duration; effects of potential confounding factors (e.g., medications, smoking, body mass index (BMI), assay methodology, fasting status); and associations between cytokine component measurement and psychopathology. Meta-analysis is one approach that can bring increased clarity to an area of research with significant heterogeneity,[23] and thus is well suited to the study of the cytokine network in psychiatric

disorders. At this time, no one has used meta-analysis to compare and contrast the patterns of cytokine alterations across schizophrenia, bipolar disorder and MDD. This paper presents meta-analyses comparing and contrasting blood cytokine levels in acutely and chronically ill patients with these psychiatric disorders, and the effects of treatment of the acute episode on cytokine levels. In doing so, we investigate potential common underlying pathways for immune dysfunction across these disorders, identify important gaps in the literature and discuss implications for the research agenda in this field.

MATERIALS AND METHODS

Study selection

Studies of blood cytokine (and cytokine receptor or antagonist) levels in schizophrenia, bipolar disorder and MDD were identified from two sources. First, we identified studies from recent meta-analyses of cytokines in these disorders.[14–20] Second, studies were systematically searched using Medline (PubMed; National Center for Biotechnology Information, US National Library of Medicine, Bethesda, MD, USA), PsycInfo (via Ovid; American Psychological Association, Washington, DC, USA) and Thomson Reuters (formerly ISI) Web of Science (Science Citation Index and Social Sciences Citation Index; Thomson Reuters, Charlottesville, VA, USA) in July 2014 and again in March 2015. The primary search strategies were: (1) ‘(inflammation OR cytokine OR interleukin OR interferon OR ‘tumor necrosis factor’) AND (schizophrenia OR psychosis)’, (2) ‘(inflammation OR cytokine OR interleukin OR interferon OR ‘tumor necrosis factor’) AND (bipolar OR mania)’ and (3) ‘(inflammation OR cytokine OR interleukin OR interferon OR ‘tumor necrosis factor’) AND (depression OR ‘major depressive disorder’), limiting results to human studies in English. From all sources, we identified 164 potential studies for schizophrenia, 68 for bipolar disorder and 122 for MDD. The majority of initial matches were excluded because they were review articles, did not present cytokine data, measured only *in vitro* cytokine production or were genetic studies related to cytokines. We excluded studies of *in vitro* cytokine production because cytokine production in stimulated, separated mononuclear cells do not necessarily reflect endogenous immune system functioning.

The inclusion criteria were: (1a) studies assessing blood (plasma/serum) cytokine network component levels in acutely ill patients with schizophrenia, bipolar mania or MDD and healthy controls, (1b) studies assessing blood cytokine network component levels in acutely ill patients at baseline (i.e., first clinical contact for illness episode) and again following a period of treatment for the episode or (1c) studies assessing blood cytokine network component levels in chronically ill patients with schizophrenia, euthymic bipolar disorder, bipolar depression or MDD compared with healthy controls, (2) blood samples collected within 1 week of hospitalization and (3) studies in English. For patients with schizophrenia or bipolar disorder, we defined acutely ill as hospitalization for acute psychosis or acute mania. For patients with MDD, acutely ill was defined as either hospitalization for depression or outpatients with clinical data indicative of an acute depressive episode (i.e., mean Hamilton Rating Scale for Depression score >20 or mean Montgomery Asberg Depression Rating Scale score >25). For patients with schizophrenia, we defined chronically

ill as being treated as an outpatient. Patients with euthymic bipolar disorder and bipolar depression were chosen for the meta-analysis of chronically ill patients because subjects with mania usually require in-patient care. Finally, for patients with MDD, chronically ill was defined as outpatients with clinical data that did not indicate an acute depressive episode (i.e., mean Hamilton Rating Scale for Depression score <20 or mean Montgomery Asberg Depression Rating Scale score <25). If the acutely/chronically ill status of subjects was unclear, we attempted to contact study authors for clarification. Although we included studies with blood samples collected within 1 week of hospitalization, this was carried out at the time of admission/before initiation of psychotropic medications in a majority of studies, with the exception of acute mania (35/40 studies for acute schizophrenia; 2/10 for mania (most were hospitalized for acute mania despite already being on medication—all samples were drawn at the time of hospitalization); 16/17 studies for MDD). For studies of cytokine levels in schizophrenia, we further stratified subjects with first-episode psychosis and acute exacerbation of chronic schizophrenia, to investigate potential effects of antipsychotic medications and disease course. Insufficient data were available for stratified analyses of first-episode mania or MDD. There were only a few studies evaluating components of the cytokine network in treatment-resistant subjects and so these studies were excluded.

The exclusion criteria were: (1) studies without a control group (except for studies of treatment of the acute illness episode), (2) studies that did not present either mean and standard deviations or median and interquartile range for cytokine levels (after attempting to contact the study authors), (3) studies of clinically stable or treatment-resistant patients, (4) studies with significant overlap in study population and (5) genetic and gene expression studies related to cytokine network components. Owing to the potential for low concentrations of some cytokine network components, the methods of the potential studies were reviewed to evaluate assay sensitivity. An assay result was excluded if: (1) the mean concentration was less than the lower limit of assay detection, (2) concentrations were not detectable in >50% of subjects or (3) either the intra-assay coefficient of variation was >10% or the interassay coefficient of variation was >15%.

After independent searches, review of study methods by two authors (BJM and DRG) and attempts to contact other authors, 68 studies met the inclusion criteria (40 schizophrenia, 10 bipolar disorder and 18 MDD) for acutely ill patients, and 46 studies met the inclusion criteria (18 studies of schizophrenia, 16 studies of bipolar disorder and 12 studies of MDD) for chronically ill patients.[24–134] There was universal agreement on the included studies. There was no overlap in samples of acutely and chronically ill patients. All studies of outpatients with acute MDD measured cytokines before and after treatment of depression. A flow chart summarizing the study selection process is presented in Supplementary Material.

Data extraction and meta-analysis

Data were extracted (sample size, mean ± s.d. or median/interquartile range for patients and controls) for every cytokine network component assessed in each study for each disorder. If necessary, we estimated the mean ± s.d. from the median/interquartile range using the following formulas: (1) mean = $(2m+a+b)/4$, where m is the median and a and b are the 25th and 75th percentiles, respectively,[135] and (2) interquartile range = 1.35 × s.d.[136] One author

(DRG) extracted all data, which was independently verified by another author (BJM). We then calculated effect size (ES) estimates (Hedges' *g*) for every cytokine in each study for each disorder, and these data are included in Supplementary Material. Fixed-effects pooled ES estimates and 95% confidence intervals (95% CIs) were calculated using the Mantel and Haenszel method. Separate meta-analyses were performed for each individual cytokine network component for each disorder (versus controls), as well as for changes in cytokine levels following treatment of acute illness. Separate meta-analyses were performed for acutely and chronically ill patients. *P*-values were considered statistically significant at the $\alpha = 0.05$ level. The statistical analyses were performed in Stata 10.0 (StataCorp, College Station, TX, USA).

The meta-analysis procedure also calculates a χ^2 value for the heterogeneity in ES estimates, using Cochran's Q-statistic[137] and I^2, the proportion of the variation in ES attributable to between-study heterogeneity. χ^2 was considered significant for $P < 0.10$.[138] For many cytokine network components for each disorder, χ^2 was significant, so we performed a sensitivity analysis. This was carried out by removing one study at a time and repeating the meta-analysis procedure, to examine its impact on the odds ratio and between-study heterogeneity.[139]

Given the significant heterogeneity for many cytokine network components, we performed a series of meta-regressions for IL-6 and tumor necrosis factor-α (TNF-α) in acutely ill patients and IL-6 in chronically ill patients—the most frequently studied cytokines in each disorder—to explore possible moderating variables of age, sex, illness duration, smoking, body mass index and, for bipolar disorder, the proportion of subjects taking lithium and antipsychotic medications. We were not able to perform metaregression analyses for other cytokine network components because of the small number of available studies. The potential for publication bias was examined with Sterne's funnel plot analysis[140] and Egger's regression intercept[141] and can be found in Supplementary Materials.

RESULTS

To summarize our findings: the levels of IL-6 (medium-large ES, range 0.59–1.16), TNF-α (small ES, range 0.22–0.43), sIL-2R (medium-large ES, range 0.47–1.04) and IL-1RA (small-large ES, range 0.29–0.95) were significantly increased in acutely ill patients with schizophrenia, bipolar mania and MDD versus controls ($P < 0.01$ for each). Following treatment of acute illness, IL-6 (small ES, range − 0.13 to − 0.36) levels significantly decreased in both schizophrenia and MDD ($P < 0.01$ for each); there were no significant changes in TNF-α; sIL-2R (small ES = 0.30) levels increased in schizophrenia; and IL-1RA (medium ES = − 0.46) levels in bipolar mania decreased. In chronically ill patients, levels of IL-6 (small-to-medium ES, range 0.27–0.39) were significantly increased in patients with schizophrenia, euthymic bipolar disorder and MDD compared with controls ($P < 0.01$ for each). Levels of IL-1β and sIL-2R were significantly increased in chronically ill patients with schizophrenia and euthymic bipolar disorder. Findings for each disorder are presented in greater detail below.

Schizophrenia

Table 1 and Figures 1a–c present ES estimates with 95% CIs for cytokine alterations in schizophrenia.

First-episode psychosis versus controls—The ESs indicated that levels of interferon-γ (IFN-γ), IL-1RA, IL-1β, IL-6, IL-8, IL-10, IL-12, sIL-2R, TGF-β and TNF-α were all significantly increased ($P < 0.01$ for each), and levels of IL-4 were significantly decreased ($P < 0.01$), but IL-2, IL-17 and IL-18 levels did not differ in first-episode psychosis versus controls. Between-study heterogeneity was significant for all cytokines except for IL-1RA.

In sensitivity analyses, heterogeneity was no longer significant, but the ES remained significant, after removing one study for IFN-γ,[31] sIL-2R[37] and TGF-β.[47] For IL-12, the ES was no longer significant after removing one study.[28] Between-study heterogeneity remained significant in sensitivity analyses for IL-1β, IL-4, IL-6 and TNF-α. Sensitivity analysis was not possible for IL-8 because of the small number of studies.

A funnel plot and results of Egger's test showed no evidence for publication bias for IL-6 ($P = 0.624$). Egger's test showed significant evidence for publication bias for TNF-α ($P = 0.049$), but the funnel plot suggests that this may reflect true between-study heterogeneity (see Supplementary Material). In meta-regression analyses, age, sex, illness duration, smoking and BMI were all unrelated to IL-6 and TNF-α in first-episode psychosis ($P > 0.05$ for each).

Acute exacerbation of chronic schizophrenia versus controls—The ESs indicated that the levels of IFN-γ, IL-1RA, IL-1β, IL-6, IL-8, IL-12, sIL-2R, TGF-β and TNF-α were all significantly increased ($P < 0.04$ for each) and IL-4 and IL-10 levels were significantly decreased ($P < 0.01$ for each) in acutely ill patients with chronic schizophrenia versus controls. ES differences for IL-2 levels were not significantly different between patients and controls. ESs were similar in direction, although generally of smaller magnitude, than studies of first-episode psychosis versus controls. Between-study heterogeneity was significant for all cytokines (or receptors or antagonists) except for IFN-γ, IL-8, IL-12 and sIL-2R. In sensitivity analyses, the heterogeneity was no longer significant, but the ES estimate remained significant, after removing one study for IL-1β[32] and IL-6.[47] The heterogeneity remained significant in a sensitivity analysis for IL-4, TGF-β and TNF-α. Sensitivity analyses were not possible for IL-1RA, IL-8 and IL-10 because of the small number of studies.

A funnel plot and results of Egger's test showed no evidence for publication bias for IL-6 ($P = 0.752$) or TNF-α ($P = 0.993$). In metaregression analyses, age, sex, illness duration and BMI were all unrelated to IL-6; age, illness duration and smoking were all unrelated to TNF-α in schizophrenia ($P > 0.05$ for each). Sex ($P = 0.068$) and BMI ($P = 0.092$) showed a trend-level association, with a higher proportion of females and higher BMI associated with larger ESs for TNF-α.

Treatment of acute psychosis—Following treatment for acute psychosis (range 36–75 days), there were significant small ES decreases in levels of IL-1β ($P < 0.01$), IL-4 ($P = 0.01$) and IL-6 levels ($P = 0.04$). There were significant small ES increases in IL-12 ($P = 0.02$) and sIL-2R ($P = 0.04$) levels. Between-study heterogeneity was significant for IL-6, and remained significant in a sensitivity analysis. There were no significant ES changes in levels of IFN-γ, IL-2, TGF-β or TNF-α.

Chronically ill patients with schizophrenia versus controls—There were small-to-medium ESs for elevations of IL-6 (ES = 0.27), TNF-α (ES = 0.30) and sIL-2R (ES = 0.32), a large ES for elevation of IL-1β (ES = 0.89), and a large ES for decrease in IFN-γ (ES = − 1.07) for patients with schizophrenia versus controls. By contrast, there was not a significant ES difference in the levels of IL-2, IL-4 or IL-10 compared with controls. Between-study heterogeneity was significant for IL-1β, IL-6 and TNF-α, but not for sIL-2R. Between-study heterogeneity remained significant in sensitivity analyses for IFN-γ, IL-1β, IL-6 and TNF-α.

A funnel plot and results of Egger's test ($P = 0.069$) found no significant evidence for publication bias. The metaregression analyses for age, sex, illness duration, smoking and BMI were all unrelated to the association between IL-6 and schizophrenia ($P > 0.05$ for each).

Summary of findings for schizophrenia—After sensitivity analyses (where possible), IFN-γ, IL-1RA, IL-1β, IL-6, IL-8, IL-10, sIL-2R, TGF-β and TNF-α levels were significantly increased and IL-4 levels significantly decreased in first-episode psychosis versus controls ($P < 0.01$ for each). Levels of IFN-γ, IL-1RA, IL-1β, IL-6, IL-8, IL-12, sIL-2R, TGF-β and TNF-α were all significantly increased and the levels of IL-4 and IL-10 were significantly decreased in acutely ill patients with chronic schizophrenia versus controls ($P < 0.01$ for each). Following treatment of acute psychosis, there were significant decreases in IL-1β, IL-4 and IL-6, and increases in IL-12 and sIL-2R. In chronically ill patients, after sensitivity analyses (where possible) the levels of IL-1β, IL-6, sIL-2R and TNF-α were significantly increased and IFN-γ levels significantly decreased in chronically ill patients with schizophrenia compared with controls ($P < 0.01$ for each).

Bipolar disorder

Table 2 and Figures 1a–c present ES estimates with 95% CIs for cytokine alterations in bipolar disorder.

Bipolar mania versus controls—The ESs indicated that the levels of IL-1RA, IL-6, sIL-2R and TNF-α were all significantly increased in acute mania versus controls ($P < 0.01$ for each). Between-study heterogeneity was significant for IL-6 and TNF-α, but not for IL-1RA and sIL-2R. In a sensitivity analysis for TNF-α, the heterogeneity was no longer significant, but the ES estimate was also not significant after removal of one study.[69] Sensitivity analysis was not possible for IL-6 because of the small number of studies. By contrast, there was not a significant ES difference in levels of IL-10 or sIL-6R.

A funnel plot, Egger's test for potential publication bias and metaregression analyses were not performed because of a small number of studies for IL-6 and TNF-α.

Treatment of acute mania—Following treatment for acute mania, there was a significant ES decrease in IL-1RA levels ($P = 0.02$) and a trend toward a decrease in sIL-2R levels ($P = 0.08$). By contrast, there was not a significant change in ES for sIL-6R levels. Between-study heterogeneity was not significant for any cytokines.

Chronically ill patients with euthymic bipolar disorder versus controls—Blood levels in patients with euthymic bipolar disorder compared with controls indicated a small-to-medium ES for elevations of IL-10 (ES = 0.26), IL-6 (ES = 0.30), IL-1β (ES = 0.31) and sTNF-R1 (ES = 0.44), and medium-to-large ES for elevation of IL-4 (ES = 0.55), sIL-6R (ES = 0.78) and sIL-2R (ES = 0.80). Between-study heterogeneity was significant for IL-4, IL-6, IL-10, sIL-2R and sTNF-R1, but not sIL-6R or IL-1β. In sensitivity analyses, the heterogeneity was no longer significant, but the effect size estimate remained significant, after removing one study for sTNF-R1.[114] Between-study heterogeneity remained significant in sensitivity analyses for IL-4, IL-6, IL-10 and sIL-2R. Sensitivity analyses were not possible for either IL-1β or sIL-6R because of the small number of studies. By contrast, there was not a significant ES difference in levels of IFN-γ, IL-2 or TNF-α compared with controls.

A funnel plot and results of Egger's test ($P = 0.398$) showed no significant evidence for publication bias. The metaregression analyses for age, sex, illness duration, body mass index and the proportion of subjects taking lithium and antipsychotics were all unrelated to the association between IL-6 and bipolar disorder ($P > 0.05$ for each).

Chronically ill patients with bipolar depression versus controls—ES differences for IL-6, IL-10 and TNF-α levels were not significantly different between patients and controls. There was a trend for increased sTNF-R levels ($P = 0.052$).

Summary of findings for bipolar disorder—After sensitivity analyses, IL-1RA, IL-6 and sIL-2R levels were significantly increased in subjects with acute mania versus controls ($P < 0.01$ for each). Following treatment of acute mania, there was a significant decrease in IL-1RA levels ($P = 0.02$) and a trend for a decrease in sIL-2R. In chronically ill patients, after sensitivity analyses (where possible) levels of IL-1β, IL-4, IL-6, IL-10, sIL-2R, sIL-6R and sTNF-R1 were significantly increased in chronically ill patients with euthymic bipolar disorder compared with controls ($P \leq 0.01$ for each) but there were no differences between patients with bipolar depression and controls.

Major depressive disorder

Table 3 and Figures 1a–c present ES estimates with 95% CIs for cytokine alterations in MDD.

Acutely ill MDD versus controls—The ESs indicated that the levels of IL-1RA, IL-6, IL-10, IL-12, sIL-2R, sIL-6R and TNF-α were all significantly increased ($P < 0.01$) and levels of IFN-γ and IL-4 were significantly decreased ($P < 0.01$) in acutely ill patients with

MDD versus controls. There were not significant differences in ESs for levels of IL-1β and IL-2. Between-study heterogeneity was significant for IL-4, IL-6, IL-10, IL-12 sIL-2R and TNF-α, but not IL-1RA, IFN-γ or sIL-6R. In sensitivity analyses, heterogeneity was no longer significant and the ES remained significant, after removing one study for sIL-2R.[88] Between-study heterogeneity remained significant in sensitivity analyses for IL-6, IL-10, IL-12 and TNF-α. Sensitivity analysis was not possible for IL-4 because of the small number of studies.

A funnel plot and results of Egger's test showed no evidence for publication bias for IL-6 ($P = 0.118$) or TNF-α ($P = 0.166$). In metaregression analyses, age and sex were unrelated to IL-6; age, sex and BMI were unrelated to TNF-α in depression ($P > 0.05$).

Treatment of acute depression—Following treatment for acute depression (range 39–112 days), there were significant ES changes indicating a decrease in IL-6, IL-10 and IL-12 levels ($P < 0.02$ for each), and an increase in IL-4 ($P < 0.01$) and IL-1β ($P = 0.02$) levels. Between-study heterogeneity was significant for all of these cytokines. The heterogeneity remained significant in sensitivity analyses for IL-1β, IL-6 and IL-12. For IL-4, the heterogeneity was no longer significant, but neither was the ES estimate after removal of one study.[90] The small number of studies precluded a sensitivity analysis for IL-10.

Chronically ill patients with MDD versus controls—Blood levels in patients with MDD compared with controls indicated a small-to-medium ES for increase for IL-6 levels (ES = 0.39) and decrease for IL-12 levels (ES = − 0.44), and medium ES for decrease in IL-2 (ES = − 0.54). Between-study heterogeneity was significant for all of these cytokines. In sensitivity analysis, the heterogeneity was no longer significant and the ES estimate remained significant, after removing one study for IL-6.[112] The small number of studies precluded sensitivity analyses for IL-2 or IL-12. The ES differences were not significant for, IL-1β, IL-4, IL-8, IL-10, sIL-2R, sIL-6R or TNF-α.

Egger's test ($P = 0.037$) of the IL-6 data revealed significant evidence for publication bias, but the funnel plot suggests this may also reflect true between-study heterogeneity (see Supplementary Material). The metaregression analyses found that IL-6 levels were not effected by age, sex or smoking ($P > 0.05$).

Summary of findings for MDD—After sensitivity analyses, IL-1RA, IL-6, IL-10, IL-12, sIL-2R, sIL-6R and TNF-α levels were all significantly increased and IFN-γ and IL-4 levels were significantly decreased in subjects with MDD versus controls ($P < 0.01$). Following treatment of acute depression, there was a significant decrease in IL-6, IL-10 and IL-12 levels, and an increase in IL-4 and IL-1β levels ($P < 0.02$). In chronically ill patients, after sensitivity analyses (where possible) levels of IL-6 were significantly increased and levels of IL-2 and IL-12 significantly decreased in chronically ill patients with MDD compared with controls ($P < 0.01$) (Tables 1–3 and Figures 1a–c).

DISCUSSION

Overall, there are similarities in the ES direction and, to a lesser extent, magnitude of blood cytokine network component levels in schizophrenia, bipolar disorder and MDD during acute and chronic phases of illness, raising the possibility of common underlying pathways for immune dysfunction in these disorders (Figures 1a and c). The levels of two cytokines (IL-6 and TNF-α), one cytokine receptor antagonist (IL-1RA), thought to reflect increased IL-1 activity, and one soluble cytokine receptor (sIL-2R), thought to function in a counter-regulatory manner, were significantly elevated in all three syndromes during acute illness episodes. Following treatment of acute illness, there were similarities in the pattern of change of levels of these cytokine network components: IL-6 levels significantly decreased in both schizophrenia and MDD; there were no significant changes in TNF-α levels in either schizophrenia or MDD; sIL-2R levels increased in schizophrenia, but were not significantly changed in either bipolar mania or MDD; and IL-1RA levels in bipolar mania decreased, but were not significantly changed in MDD. In chronically ill patients, the levels of IL-6 were statistically significantly elevated in all three disorders, and the levels of sIL-2R and the cytokine IL-1β were significantly elevated in schizophrenia and bipolar disorder.

It is intriguing that all of the cytokines that were elevated in acutely ill patients with all three syndromes are modulated through the nuclear factor-κB, signaling pathway that is commonly activated in inflammatory and autoimmune disease.[142–144] This suggests that acutely symptomatic patients may share a profile of immune system activation that commonly is observed during an acute inflammatory state. Particularly in light of work demonstrating that acute stress increases IL-6 and other inflammatory markers, one may speculate that there may be a common stress-related phenomenon occurring in acutely ill patients across these disorders.[99,100] This hypothesis-generating observation requires more extensive investigation. In addition to the common cytokine network alterations across all three disorders, the pattern of other cytokine network alterations suggests that treatment of acute illness may lead to resolution of inflammation and an increase in anti-inflammatory biomarkers; this observation requires more extensive exploration (Figure 1b). Although speculative, the common findings in chronically ill patients also might reflect the influence of chronic stress on the immune system.[145,146] Chronic stress may lead to a dysregulation of the immune response with decreased glucocorticoid receptor sensitivity, impaired feedback of the HPA axis and subsequent increases in proinflammatory cytokines as well as suppression of anti-inflammatory cytokines and/or counter-regulatory mechanisms.[147–149] Elevations in the cytokines IL-1β and IL-6 suggest the possibility of monocyte/macrophage activation,[150,151] whereas elevations in sIL-2 R, which is constitutively produced by activated T cells, suggests a counter-regulatory response to T-cell activation.[152] Elevations in both IL-6 and sIL-2 R in chronically ill patients suggests a role for persistent immune activation for some patients with these disorders. Our findings suggest that it would be useful to compare and contrast inflammatory markers in the same subjects during both acute and chronic phases of illness.

The strengths of our study include comparisons of cytokine network alterations across three major psychiatric disorders, which has not been previously performed. We also investigated cytokine network component levels in both acute and chronic phases of illness, as well as

the effects of treatment of acute illness episodes on these biomarkers. There are always limitations to studies. Our findings should be interpreted with caution in light of relatively small number of studies meeting the inclusion criteria for this meta-analysis and small sample size available for many of the cytokine network comparisons. This limits our ability to make inferences regarding molecular mechanisms of similarities and differences across disorders. A second limitation is that one cannot account for either the type or the length of pharmacologic intervention used in the studies included in our meta-analysis. Furthermore, our classification of acute and chronic illness was limited by not having symptom measures for each patient in each study to make a determination of illness phase. Instead, we classified acute and chronic illness in a way that we felt most appropriately captured illness phase given the limitation of not having individual level data. A limitation of the field is the lack of agreement on a uniform panel of cytokine network components that are consistently studied. Consequently, the field may continue to focus on assays of individual cytokines, which, as observed in this meta-analysis, limits our ability to compare across studies. Furthermore, it may be less important to measure individual cytokines, but instead measure overall patterns of immune activation, for example, with a panel of relevant cytokines or with cytokine ratios (e.g. IFN/IL-4; TNF/IL-10). One also needs to acknowledge the problem of important potential confounding, and some potentially moderating, factors such as smoking, body mass index, medical comorbidities, level and type of psychopathology, genetic heterogeneity, sample collection and processing, time of day, whether plasma or serum were assayed, type of assay used and how and how long samples are stored before being analyzed.[153–155] Although we did not find evidence for moderating effects of age, sex, illness duration, BMI and medications on IL-6 levels in either acutely ill or chronically ill subjects, this does not preclude moderating effects between such clinical and demographic factors and other cytokine network components.[156–160] These factors should be carefully considered when one weighs the significance of meta-analytic findings in psychoneuroimmunology.

It is important to emphasize nuances in the interpretation of the ES estimates in the analyses of acutely ill patients. ESs for acutely ill subjects versus controls represent the magnitude of the difference in cytokine levels between two different subject groups. By contrast, ESs for treatment of acute illness reflect the change in cytokine levels in the same subjects before and after treatment, and thus tend to be smaller (see Figure 1). Another caveat is that analysis of impact of treatment on cytokine levels represents a subset of the analysis that contrasts patients with the three disorders with matched control samples. A final issue that must be taken into consideration when interpreting our findings is the understanding that many of the ES differences for statistically significant findings fall into the small ES category. This suggests that either the observed change is either relatively minor and may not be clinically significant, or, alternatively, immune disequilibrium occurs in only a minority of subjects with these syndromes.

Our findings raise many questions. What are the most useful set of cytokines to measure? Should we measure the same panel of cytokines across disorders? Should future studies preferentially measure cytokine network components where there is more robust evidence (to replicate findings), or those that have not been thoroughly investigated, or some combination of both? The creation of an agreed upon standard for assay methodology is critical to the advancement of the field: should we be using a multiplex system or an ELISA-

based system? What are the normal ranges for these measures? What are the most reasonable statistical approaches to employ with data that are frequently highly skewed? Another important question is whether measurement of peripheral levels of cytokine network components is sufficient? Evaluation of specific leukocyte populations via flow cytometry or coupling peripheral findings with brain imaging may be more informative. We need to determine whether traditional measures like demographic and clinical (e.g., psychopathology, cognition, medical comorbidities) features are associated with cytokine network alterations. We still need to more closely evaluate the effects of all aspects of treatment of the acute illness on cytokine levels through the serial measurement of intraindividual changes in cytokines across the course of illness. More studies in first-episode drug-naïve subjects would clarify which changes in the cytokine network are intrinsically associated with these disorders and which might be better attributed to medication effects. What are the effects of course of illness and treatment-resistant illness on cytokine levels? We excluded treatment-resistant schizophrenia because of preliminary evidence that these patients may represent a subset with unique cytokine alterations,[161–163] and there were insufficient number of studies in MDD and bipolar disorder to make meaningful comparisons. Future studies of the effects of treatment-resistant illness on immune function are needed.

In conclusion, acutely ill and chronically ill subjects with schizophrenia, bipolar disorder and MDD manifested alterations in blood cytokine levels most consistent with an inflammatory profile and T-cell activation. In general, treatment of these disorders led to a decrease in cytokines with proinflammatory functions and an increase in cytokines with anti-inflammatory functions. Despite between-study heterogeneity, there were remarkable similarities in these patterns that suggest that there may be common mechanisms at least partially responsible for these findings. The small to moderate effect sizes observed most likely reflects that immune system involvement occurs in only a subset of patients with each of these syndromes. This may explain why treatment studies that have targeted inflammation in these syndromes have yielded mixed results. Future studies of anti-inflammatory therapies may want to include only patients who clearly manifest signs of inflammation. The results from this meta-analysis reflect a need to more systematically evaluate how and what we measure in the immune system. Longitudinal data with a uniform sample of patients could clarify what role the cytokine network has in mediating the course of illness for these disorders. More extensive and systematic investigation is clearly warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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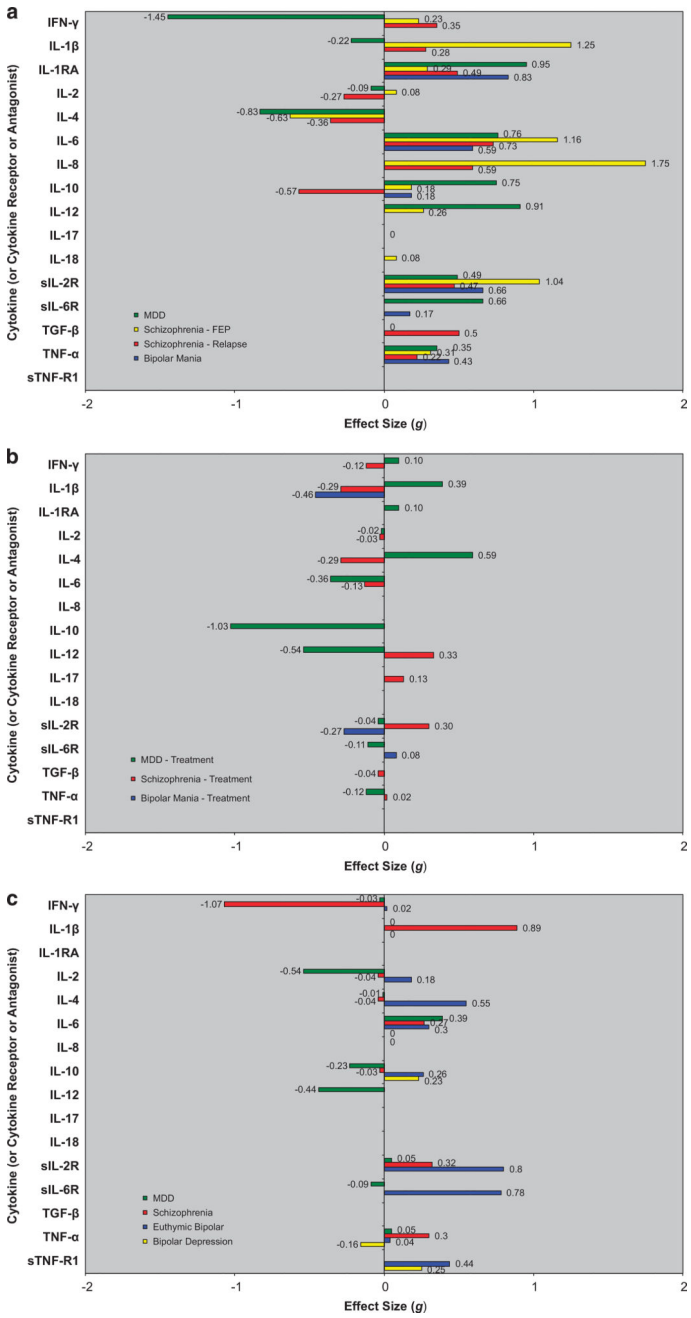

Figure 1.

Blood cytokine network alterations in studies of patients with schizophrenia, bipolar disorder and major depressive disorder (MDD) versus controls. (**a**) Acutely ill patients with schizophrenia, bipolar mania and MDD versus controls. (**b**) Changes in blood cytokine network levels following treatment of acute illness in schizophrenia, bipolar mania and MDD. (**c**) Chronically ill patients with schizophrenia, bipolar disorder and MDD versus control.

Table 1

Blood cytokine network alterations in schizophrenia

1a. Blood cytokine network levels in first-episode psychosis versus controls

Cytokine component	N			*Mean ES*	*95% CI*	P-*value*	*Heterogeneity*		I^2	*References*
	Studies	*Pt*	*Control*				χ^2	P-*value*		
IFN-γ	7	452	747	0.23	0.09–0.37	<***0.01***	37.28	<0.01	83.9	25,29–31,39,46,47
IL-1β	6	333	298	1.25	1.07–1.42	<***0.01***	78.36	<0.01	93.6	31,43,57–60
IL-1RA	2	194	376	0.29	0.10–0.48	<***0.01***	1.25	0.26	20.1	24,29
IL-2	5	140	300	0.08	−0.14 to 0.29	0.48	29.5	<0.01	86.4	31,39,43,47,60
IL-4	4	193	322	−0.63	−0.84 to −0.42	<***0.01***	74.95	<0.01	96.0	25,31,46,47
IL-6	11	506	577	1.16	1.03–1.30	<***0.01***	135.67	<0.01	92.6	24,25,30,31,35,41,43,47,48,58,59
IL-8	2	49	49	1.75	1.27–2.24	<***0.01***	12.43	<0.01	92.0	31,51
IL-10	4	357	461	0.18	0.04–0.31	***0.01***	38.52	<0.01	92.2	29,31,48,61
IL-12	3	258	463	0.26	0.05–0.47	***0.02***	69.17	<0.01	97.1	28,29,45
IL-17	2	157	96	0.00	−0.26 to 0.26	0.99	7.91	<0.01	87.4	25,30
IL-18	3	335	403	0.08	−0.07 to 0.23	0.28	0.87	0.65	0.0	29,62,63
sIL-2 R	3	30	97	1.04	0.55–1.52	<***0.01***	10.18	<0.01	80.3	24,37,54
sIL-6 R										
TGF-β	3	169	298	0.58	0.36–0.80	<***0.01***	11.86	<0.01	83.1	25,46,47
TNF-α	9	587	842	0.31	0.22–0.39	<***0.01***	238.22	<0.01	96.6	29,31,35,47,48,57–60
sTNF-R1										

1b. Blood cytokine network levels in acutely ill patients with schizophrenia versus controls

Cytokine component	N			*Mean ES*	*95% CI*	P-*value*	*Heterogeneity*		I^2	*References*
	Studies	*Pt*	*Control*				χ^2	P-*value*		
IFN-γ	4	162	266	0.35	0.13–0.57	<***0.01***	5.34	0.15	43.9	25,42,47
IL-1β	3	131	151	0.28	0.04–0.52	***0.02***	7.41	0.02	73.0	27,32,43
IL-1RA	2	32	94	0.49	0.07–0.90	***0.02***	8.19	<0.01	87.8	40,50

IL-2	2	43	199	−0.27	−0.61 to 0.07	0.12	14.08	<0.01	92.9	[43,47]
IL-4	5	169	350	−0.36	−0.56 to −0.16	<***0.01***	50.46	<0.01	92.1	[25,42,46,47,52]
IL-6	9	278	468	0.73	0.56–0.90	<***0.01***	134.19	<0.01	94.0	[25,33,36,38,42,43,47,49,52]
IL-8	2	46	52	0.59	0.19–1.00	<***0.01***	2.06	0.15	51.4	[42,52]
IL-10	2	46	52	−0.57	0.98 −0.17	<***0.01***	3.42	0.07	70.7	[42,52]
IL-12										
IL-17										
IL-18										
sIL-2 R	3	58	120	0.47	0.14–0.80	***0.01***	4.46	0.11	55.1	[32,30,50]
sIL-6 R										
TGF-β	6	243	382	0.50	0.32–0.68	<***0.01***	14.21	0.01	64.8	[25,32,46,47,49]
TNF-α	7	269	449	0.22	0.05–0.39	***0.01***	141.05	<0.01	95.7	[27,33,40,42,47,49,52]
sTNF-R1										

1c. Blood changes in cytokine network levels following treatment of acutely ill patients with schizophrenia

Cytokine component	*N*			*Mean duration*	*Mean ES Change*	*95% CI*	P-*value*	*Heterogeneity*		I^2	*References*
	Studies	*Pre*	*Post*					χ^2	P-*value*		
IFN-γ	4	265	265	36	−0.12	−0.29 to 0.05	0.16	1.57	0.81	0.0	[26,30,44,47]
IL-1β	4	189	189	75	−0.29	−0.49 to −0.09	<***0.01***	4.90	0.18	38.7	[43,44,57,59]
IL-1RA											
IL-2	4	132	132	49	−0.03	−0.27 to 0.22	0.84	8.27	0.04	63.7	[43,44,47,53]
IL-4	2	186	186	43	−0.29	−0.50 to −0.09	***0.01***	0.36	0.83	0.0	[26,47]
IL-6	11	521	500	56	−0.13	−0.25 to −0.01	***0.04***	20.55	0.04	46.5	[26,30,33,36,43,42,47,48,53,59]
IL-8											
IL-10											
IL-12	3	104	104	42	0.33	0.06–0.60	***0.02***	3.77	0.15	46.9	[28,44,45]
IL-17	2	193	193	29	0.13	−0.07 to 0.33	0.22	0.49	0.78	0.0	[26,30]
IL-18											
sIL-2 R	3	90	90	69	0.30	0.01 to 0.60	***0.04***	2.19	0.34	8.6	[51,55,56]
sIL-6 R											
TGF-β	4	286	286	43	−0.04	−0.21 to 0.12	0.61	22.63	<0.01	82.3	[26,46,47,49]

TNF-α	6	310	310	73	0.02	−0.14 to 0.18	0.84	15.53	0.01	67.8	33,47,53,57,59
sTNF-R1											

1d. Blood cytokine network alterations in chronically ill patients with schizophrenia versus controls

Cytokine component	N			*Mean ES*	*95% CI*	P-*value*	*Heterogeneity*		I^2	*References*
	Studies	*Pt*	*Control*				χ^2	P-*value*		
IFN-γ	4	198	132	−1.07	−1.35 to −0.80	<***0.01***	164.70	<0.01	98.2	75,77,80,91
IL-1β	4	330	303	0.89	0.73–1.05	<***0.01***	101.94	<0.01	96.1	75,78,81,91
IL-1RA										
IL-2	6	193	171	−0.04	−0.24 to 0.16	0.68	55.25	<0.01	91.0	76,80,84,88,90,91
IL-4	2	73	46	−0.04	−0.42 to 0.34	0.83	0.87	0.35	0.0	80,91
IL-6	12	711	674	0.27	0.17 to 0.38	<***0.01***	110.59	<0.01	88.2	75,78,80,81,83,85–91
IL-8										
IL-10	4	118	126	−0.03	−0.24 to 0.18	0.81	4.06	0.40	1.4	75,80,85,91
IL-12										
IL-17										
IL-18										
sIL-2 R	3	116	135	0.32	0.40–0.86	<***0.01***	1.42	0.70	0.0	78–80
sIL-6 R										
TGF-β										
TNF-α	9	508	509	0.30	0.18–0.43	<***0.01***	46.77	<0.01	80.8	75,78,80–83,85,90,91
sTNF-R1										

Abbreviations: ES, effect size; CI, confidence interval; IFN, interferon; IL, interleukin; IL-1RA, interleukin-2 receptor antagonist; Pt, patients; sIL, soluble interelukin; TGF, tumor growth factor; TNF, tumor necrosis factorr.

Bold and italicized values are statistically significant.

Table 2

Blood cytokine network alterations in bipolar disorder

2a. Blood cytokine network levels in acute ill patients with bipolar mania versus controls

Cytokine component	N			*Mean ES*	*95% CI*	P-*value*	*Heterogeneity*		I^2	*References*
	Studies	*Pt*	*Control*				χ^2	P-*value*		
IFN-γ										
IL-1β										
IL-1RA	2	46	53	0.83	0.42–1.25	<***0.01***	0.05	0.82	0.0	[67,73]
IL-2										
IL-4										
IL-6	2	44	160	0.59	0.25–0.93	<***0.01***	3.49	0.06	71.4	[64,68]
IL-8										
IL-10	2	61	116	0.18	−0.11 to 0.47	0.22	1.21	0.55	0.0	[64,66]
IL-12										
IL-17										
IL-18										
sIL-2 R	3	82	90	0.66	0.35–0.97	<***0.01***	1.81	0.41	0.0	[70–72]
sIL-6 R	3	82	90	0.17	−0.13 to 0.48	0.26	0.04	0.98	0.0	[70–72]
TGF-β										
TNF-α	3	73	137	0.43	0.12–0.74	<***0.01***	12.68	<0.01	84.2	[64,66,68]
sTNF-R1										

2b. Changes in blood cytokine network levels following treatment of acutely ill bipolar mania

Cytokine component	*N*			*Mean duration*	*Mean ES change*	*95% CI*	P-*value*	*Heterogeneity*		I^2	*References*
	Studies	*Pre*	*Post*					χ^2	P-*value*		
IFN-γ											
IL-1β	2	46	62	N/A	−0.46	−0.86 to −0.07	***0.02***	0.22	0.64	0.0	[67,73]
IL-1RA											
IL-2											

IL-4										
IL-6										
IL-8										
IL-10										
IL-12										
IL-17										
IL-18										
sIL-2 R	3	82	82	N/A	−0.27	−0.58 to 0.03	0.08	0.12	0.94	0.0	70–72
sIL-6 R	3	82	82	N/A	0.08	−0.23 to 0.39	0.60	0.15	0.93	0.0	70–72
TGF-β										
TNF-α										
sTNF-R1										

2c. Blood cytokine network alterations in chronically ill patients with euthymic bipolar disorder versus controls

Cytokine component	N			*Mean ES*	*95% CI*	P-*value*	*Heterogeneity*		I^2	*References*
	Studies	*Pt*	*Control*				χ^2	P-*value*		
IFN-γ	3	91	122	0.02	−0.26 to 0.30	0.89	3.20	0.36	6.2	95,101,108
IL-1β	2	125	158	0.31	0.07–0.55	***0.01***	0.01	0.92	0.0	105,108
IL-1RA										
IL-2	2	46	44	0.18	−0.24 to 0.60	0.40	2.87	0.24	30.3	95,100
IL-4	3			0.55	0.15–0.95	0.01	58.31	<0.01	94.9	95,96,100,95,96,101,103,104
IL-6	7	213	540	0.30	0.13–0.47	<***0.01***	27.57	<0.01	78.2	106,108
IL-8										
IL-10	7	166	273	0.26	0.06–0.46	0.01	27.74	<0.01	74.8	95,96,100,102–104,108
IL-12										
IL-17										
IL-18										
sIL-2 R	3	199	230	0.80	0.59–1.00	<***0.01***	24.63	<0.01	91.9	93,96,107
sIL-6 R	2	98	153	0.78	0.52–1.05	<***0.01***	2.14	0.14	53.4	93,98
TGF-β										
TNF-α	7	236	296	0.04	−0.14 to 0.22	0.66	19.08	0.01	58.1	94,95,99,100

sTNF-R1	4	133	310	0.44	0.19–0.69	<***0.01***	6.80	0.08	55.9	102–104,108

2d. Blood cytokine network alterations in chronically ill patients with bipolar depression versus controls

Cytokine component	N			*Mean ES*	*95% CI*	P-*value*	*Heterogeneity*		I^2	*References*
	Studies	*Pt*	*Control*				χ^2	P-*value*		
IFN-γ										
IL-1β										
IL-1RA										
IL-2										
IL-4										
IL-6	3	102	344	0.00	−0.23 to 0.23	0.98	6.94	0.03	71.2	95,101,103
IL-8										
IL-10	2	44	105	0.23	−0.14 to 0.60	0.22	0.80	0.37	0.0	95,103
IL-12										
IL-17										
IL-18										
sIL-2 R										
sIL-6 R										
TGF-β										
TNF-α	2	44	105	−0.16	−0.53 to 0.21	0.40	1.93	0.16	48.3	95,103
sTNF-R1	2	72	369	0.25	0.00–0.51	0.05	3.99	0.05	74.9	91,101

Abbreviations: ES, effect size; CI, confidence interval; IFN, interferon; IL, interleukin; IL-1RA, interleukin-2 receptor antagonist; N/A, not available; Pt, patients; sIL, soluble interelukin; TGF, tumor growth factor; TNF, tumor necrosis factor.

Bold and italicized values are statistically significant.

Table 3

Blood cytokine network alterations in MDD

3a. Blood cytokine network levels in acutely ill patients with MDD versus controls

Cytokine component	N			*Mean ES*	*95% CI*	P-*value*	*Heterogeneity*		I^2	*References*
	Studies	*Pt*	*Control*				χ^2	P-*value*		
IFN-γ	2	61	54	−1.45	−1.87 to −1.04	<***0.01***	1.06	0.30	5.7	78,79
IL-1β	4	116	112	−0.22	−0.49 to 0.06	0.13	80.87	<0.01	94.0	78,79,81,84
IL-1RA	2	44	25	0.95	0.42–1.48	<***0.01***	0.97	0.33	0.0	82,86
IL-2	3	84	79	−0.09	−0.47 to 0.29	0.64	108.92	<0.01	98.2	78,79,90
IL-4	2	53	57	−0.83	−1.26 to −0.40	<***0.01***	40.86	<0.01	97.6	78,90
IL-6	10	306	216	0.76	0.56–0.95	<***0.01***	96.09	<0.01	90.6	74,75,81,82,84–89
IL-8										
IL-10	4	112	103	0.75	0.46–1.04	<***0.01***	37.32	<0.01	92.0	78–80,82
IL-12	4	117	172	0.91	0.64–1.17	<***0.01***	44.69	<0.01	93.3	45,78,83,90
IL-17										
IL-18										
sIL-2 R	5	247	170	0.49	0.29–0.70	<***0.01***	11.04	0.05	54.7	77,81,85,87,88
sIL-6 R	3	145	68	0.66	0.36–0.96	<***0.01***	2.68	0.26	25.3	85,86,88
TGF-β										
TNF-α	8	296	281	0.35	0.17–0.53	<***0.01***	136.00	<0.01	94.1	77,78,80,81,84,86,88,90
sTNF-R1										

3b. Changes in blood cytokine network levels following treatment of acutely ill patients with MDD

Cytokine component	N		*Mean duration*	*Mean ES change*	*95% CI*	P-*value*	*Heterogeneity*		I^2	*References*
	Studies	*Pre*	*Post*				χ^2	P-*value*		
IFN-γ	2	54	61	112	0.10	−0.27 to 0.47	0.59	0.58	0.45	0.0	78,79
IL-1β	4	89	82	74	0.39	0.06–0.72	***0.02***	54.55	<0.01	92.7	78,79,81,84
IL-1RA	2	34	34	39	0.10	−0.38 to 0.58	0.70	2.30	0.13	56.5	82,86

IL-2	3	84	77	93	−0.02	−0.38 to 0.34	0.92	82.08	<0.01	97.6	78,79,90
IL-4	3	84	77	93	0.59	0.25–0.92	<***0.01***	38.97	<0.01	94.9	78,79,90
IL-6	7	116	116	45	−0.36	−0.62 to −0.09	***0.01***	17.95	0.01	61.0	74,81,82,84–87
IL-8											
IL-10	2	54	61	112	−1.03	−1.45 to −0.61	<***0.01***	30.41	<0.01	96.7	78,79
IL-12	4	86	86	60	−0.54	−0.86 to −0.23	<***0.01***	20.67	<0.01	85.5	45,78,83,90
IL-17											
IL-18											
sIL-2 R	4	139	139	60	−0.04	−0.28 to 0.19	0.72	3.33	0.50	0.0	77,81,85,87
sIL-6 R	2	42	42	63	−0.11	0.53–0.32	0.93	0.85	0.36	0.0	85,87
TGF-β											
TNF-α	6	205	205	54	−0.12	−0.32 to 0.08	0.22	45.66	<0.01	84.7	76–78,81,84,90
sTNF-R1											

3c. Blood cytokine network alterations in chronically ill patients with MDD versus controls

Cytokine component	N			*Mean ES*	*95% CI*	P-*value*	*Heterogeneity*		I^2	*References*
	Studies	*Pt*	*Control*				χ^2	P-*value*		
IFN-γ	4	195	226	−0.03	−0.24 to 0.16	0.82	158.68	<0.01	98.1	64,109,112,117
IL-1β	3	105	157	0.21	−0.04 to 0.47	0.10	17.32	<0.01	88.5	64,111,112
IL-1RA										
IL-2	2	82	82	−0.54	−0.90 to −0.17	<***0.01***	84.19	<0.01	98.8	64,117
IL-4	2	82	113	−0.01	−0.30 to 0.28	0.94	4.82	0.03	79.3	64,112
IL-6	7	205	211	0.39	0.20–0.59	<***0.01***	31.44	<0.01	77.7	64,110112,115,116,118,119
IL-8	3	126	137	0.08	−0.16 to 0.32	0.49	15.03	<0.01	80.0	64,112,116
IL-10	4	138	148	−0.23	−0.546 to 0.01	0.06	34.64	<0.01	88.5	64,110,112,116
IL-12	2	82	113	−0.44	−0.75 to −0.14	<***0.01***	30.32	<0.01	96.7	64,112
IL-17										
IL-18										
sIL-2 R	2	117	80	0.05	−0.20 to 0.30	0.68	10.84	0.01	72.3	113,118
sIL-6 R	2	66	42	−0.09	−0.43 to 0.26	0.63	0.94	0.63	0.0	115,116
TGF-β										

TNF-α sTNF-R1	7	346	351	0.05	−0.10 to 0.19	0.52	75.26	<0.01	86.7	64,109,111–114,116,109

Abbreviations: ES, effect size; CI, confidence interval; IFN, interferon; IL, interleukin; IL-1RA, interleukin-2 receptor antagonist; N/A, not available; Pt, patients; sIL, soluble interelukin; TGF, tumor growth factor; TNF, tumor necrosis factor.

Bold and italicized values are statistically significant.