

A Meta-Analysis of Cytokines in Major Depression

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Background: Major depression occurs in 4.4% to 20% of the general population. Studies suggest that major depression is accompanied by immune dysregulation and activation of the inflammatory response system (IRS). Our objective was to quantitatively summarize the data on concentrations of specific cytokines in patients diagnosed with a major depressive episode and controls.

Methods: We performed a meta-analysis of studies measuring cytokine concentration in patients with major depression, with a database search of the English literature (to August 2009) and a manual search of references.

Results: Twenty-four studies involving unstimulated measurements of cytokines in patients meeting DSM criteria for major depression were included in the meta-analysis; 13 for tumor necrosis factor (TNF)- α , 9 for interleukin (IL)-1 β , 16 for IL-6, 5 for IL-4, 5 for IL-2, 4 for IL-8, 6 for IL-10, and 4 for interferon (IFN)- γ . There were significantly higher concentrations of TNF- α ($p < .00001$), weighted mean difference (WMD) (95% confidence interval) 3.97 pg/mL (2.24 to 5.71), in depressed subjects compared with control subjects (438 depressed/350 nondepressed). Also, IL-6 concentrations were significantly higher ($p < .00001$) in depressed subjects compared with control subjects (492 depressed/400 nondepressed) with an overall WMD of 1.78 pg/mL (1.23 to 2.33). There were no significant differences among depressed and nondepressed subjects for the other cytokines studied.

Conclusions: This meta-analysis reports significantly higher concentrations of the proinflammatory cytokines TNF- α and IL-6 in depressed subjects compared with control subjects. While both positive and negative results have been reported in individual studies, this meta-analytic result strengthens evidence that depression is accompanied by activation of the IRS.

Key Words: Anti-inflammatory cytokines, depression, meta-analysis, proinflammatory cytokine

Major depression is an important public health issue (1) with a lifetime prevalence of 4.4% to 20% in the general population (2). The DSM-IV (3) stipulates that at least five of nine criteria depressive symptoms must be present, including either sadness or anhedonia, for at least 2 weeks to diagnose a major depressive episode. Depressive symptoms may also include fatigue, feelings of worthlessness or guilt, lack of ability to concentrate, suicidal ideation, or significant changes in weight or sleep. The impact of depression on quality of life is comparable with or greater than that of chronic medical illness (4,5), depending on the severity of symptoms (5), and depression is considered disabling to psychosocial function (6).

The monoamine hypothesis is the most extensively studied etiologic theory of depression (7,8) and virtually all available antidepressants act, at least in part, by increasing monoaminergic transmission. However, meta-analyses suggest that these agents are effective for only one half to one third of patients suffering from depression (9–13) and they often produce side effects that can sometimes limit their usefulness (11,12,14). Those studies underscore the urgent need for alternative or corollary hypotheses to help guide the development of more effective or adjunctive treatment strategies.

Numerous studies have suggested that major depression is accompanied by immune dysregulation. Specifically, activation of the inflammatory response system (IRS) has been demonstrated by increased production of proinflammatory cytokines

such as interleukin (IL)-1 β , IL-2, IL-6, interferon (IFN)- γ , tumor necrosis factor (TNF)- α , the soluble IL-6 receptor (IL-6R), and the IL-1 receptor antagonist (IL-1RA) (15–25). These findings may be clinically important because proinflammatory cytokines can contribute directly to the development of depressive symptoms (26). Proinflammatory cytokines have been shown to induce stress-reactive neuroendocrine and central neurotransmitter changes reminiscent of those in depression (26), and it has been demonstrated that immunotherapy with IFN- α can precipitate depression (27).

Although an association between IRS activation and depression has been documented in individual studies (17–26,28) of various cytokines, the association is not consistently significant in all studies or for all cytokines (29–31). Thus, a generalizable pattern of immune dysfunction in major depression remains to be defined. However, results from individual studies can be combined quantitatively using meta-analytical techniques to improve the strength of the evidence. Therefore, this study reports the results of a meta-analysis conducted to determine whether the concentrations of specific cytokines differ quantitatively between patients diagnosed with a major depressive episode and control subjects.

Methods and Materials

Only original studies that measured cytokine concentrations in depressed and nondepressed subjects were included in the meta-analysis. Studies were included if subjects met DSM-III-R or DSM-IV (3) criteria for major depression. Studies were included if they were published in English, if cytokine concentrations were measured in subjects free of major medical comorbidities (cancer, heart disease, etc.), if subjects were free of antidepressant medications for at least 1 week before the initiation of the study, if psychiatrically healthy subjects were used as control subjects, and if cytokine concentrations were measured in the unstimulated state and in the morning. Studies looking at stimulated levels of cytokines were excluded because they differ in

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that they reflect the consequences of immune challenge as opposed to basal immune activity.

This analysis was performed according to Quality of Reporting of Meta-Analyses (QUORUM) guidelines for conducting a meta-analysis (32). We searched English language literature using MEDLINE, EMBASE, PsycINFO, Cochrane Database of Systematic Reviews, AMED, and CINAHL from June 1960 to August 2009 using the key words depression, cytokine, interferon, interleukin, TNF- α , IL-1 β , IL-6, IL-4, IL-2, IL-8, IL-10, and IFN- γ . The reference lists of all the relevant studies were also searched for any additional trials.

Each article was separately examined by two independent raters and results were compared. Disagreements regarding inclusion were settled by consensus.

Two independent raters examined the Methods and Results sections of each relevant article, and data for mean (\pm SD) cytokine concentrations for each group of depressed and non-depressed subjects were extracted. We used Review Manager Version 5.0 (Cochrane Collaboration, Oxford, United Kingdom) for analysis. For our continuous outcomes data, a weighted mean difference and 95% confidence intervals (CIs) were calculated using a random effects model. This meta-analytic method includes both within-study variance and between-studies variation in the estimate of the uncertainty (confidence interval) around

results. Unlike a fixed effects model, a random effects model assumes that the underlying true effects vary from one study to another. Random effects models will give wider confidence intervals than fixed effect models, if there is significant heterogeneity among the results of the included studies. Thus, a random effects model is more conservative and is chosen if significant heterogeneity is expected.

Heterogeneity was tested for all combined results by means of a Q statistic (calculated using a chi-square analysis), and inconsistency was calculated using an I^2 index to determine the impact of heterogeneity (33). The presence of significant heterogeneity suggests diversity in characteristics of the trials. Likely sources of heterogeneity, such as severity of illness, diagnosis, age, gender, setting, and type of assay, were investigated. Publication bias was assessed where there were five or more studies using funnel plots and rank correlation tests between effect size and sample size (34,35). Altman's (36) method of describing CIs was used when the difference between groups was not statistically significant.

Results

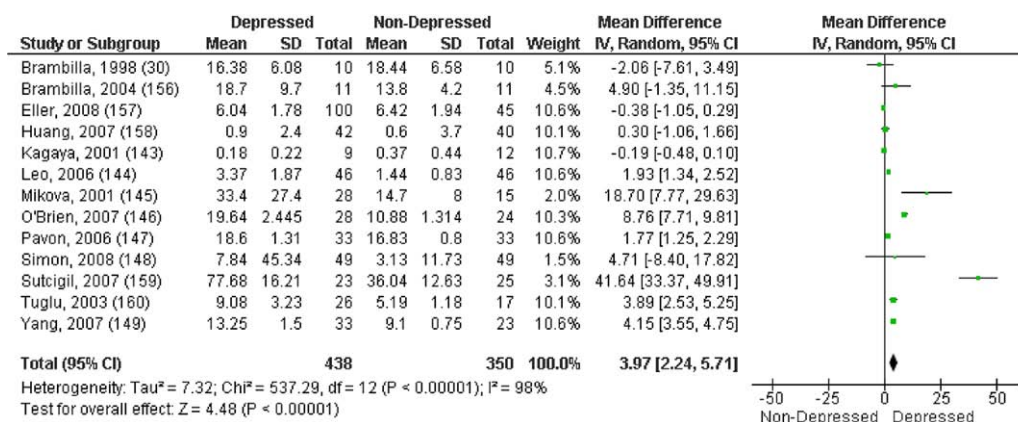
A total of 136 studies were identified for review. One hundred twelve studies did not meet inclusion criteria. Studies were

Table 1. Characteristics of Included Studies of Looking at Cytokine Concentrations in Depression

Study/Year	Cytokines Measured	N (D, ND)	Gender (% Male) (D, ND)	Age ^a (D, ND)	Depression Diagnosis (Scales)
Berk <i>et al.</i> , 1997 (29)	IL-6	28/21	36.3/NR	41.9/NR	DSM
Brambilla and Maggioni, 1998 (30)	TNF- α /IL-1 β /IL-6	10/10	0/0	72 \pm 4/71 \pm 3	DSM
Brambilla <i>et al.</i> , 2004 (156)	TNF- α /IL-1 β	11/11	81.8/72.7	12.2 \pm 1.7/11.4 \pm 2.4	DSM, Poznanski Rating Scale
Dhabhar <i>et al.</i> , 2009 (155)	IL-6, IL-10	12/11	41.7/45.5	38.4 \pm 11/38 \pm 13.3	DSM, HAM-D
Eller <i>et al.</i> , 2008 (157)	TNF- α /IL-8	100/45	35.0/42.2	23.1 \pm 11.9/32.9 \pm 14.1	DSM, MADRS
Hernandez <i>et al.</i> , 2008 (161)	IL-2/IFN- γ /IL-4/IL-10/ IL-1 β	31/22	29.0/31.2	32.0 \pm 9.4/30.8 \pm 6.3	DSM, HAM-D, BDI
Huang <i>et al.</i> , 2007 (158)	TNF- α /IL-1 β /IL-10	42/40	28.6/37.5	38 \pm 8.2/31.4 \pm 3.9	DSM, HAM-D
Jozuka <i>et al.</i> , 2003 (162)	IL-2	17/10	47.1/40.0	40.3 \pm 15.3/39.9 \pm 9.8	DSM, ZDS
Kagaya <i>et al.</i> , 2001 (143)	TNF- α /IL-1 β /IL-6	12/12	75.0/75.0	31.1 \pm 8.2/30.9 \pm 7	DSM, HAM-D, POMS
Kubera <i>et al.</i> , 2000 (150)	IL-6/IL-10	9/10			DSM, HAM-D
Leo <i>et al.</i> , 2006 (144)	TNF- α /IL-1 β /IL-6	46/46	43.5/41.3	34.9 \pm 5.9/34.1 \pm 5.2	DSM, HAM-D
Maes <i>et al.</i> , 1995 (151)	IL-6	61/38	59.0/55.3	36.6 \pm 1.3/33.8 \pm 1.5	DSM, HAM-D
Maes <i>et al.</i> , 1995 (152)	IL-6	13/28	53.8/64.3	35.2 \pm 12.2/36.1 \pm 4.9	DSM, HAM-D
Maes <i>et al.</i> , 1997 (17)	IL-6	35/15	54.3/66.7	50.3 \pm 13.9/47.5 \pm 15.0	DSM, HAM-D
Mikova <i>et al.</i> , 2001 (145)	TNF- α /IL-6/IL-8	28/15	17.9/46.7	47.3 \pm 11.3/42 \pm 10.9	DSM, HAM-D
Myint <i>et al.</i> , 2005 (163)	IL-4/IFN- γ	18/3	32.5/32.5	40.7 \pm 15.5/40.3 \pm 13.1	DSM, HAM-D, BPRS
O'Brien <i>et al.</i> , 2007 (146)	TNF- α /IL-6/IL-8/IL-10	TNF- α , IL-6 28/24; IL-8, IL-10 28/68	32.1/41.6 (n = 24)	44.2 \pm 13.2/35.6 \pm 9 (n = 24)	DSM, HAM-D
Pavon <i>et al.</i> , 2006 (147)	TNF- α /IL-1 β /IL-6/IL-4/ IFN- γ /IL-2	33/33	15.2/15.2	33.6 \pm 10.2/32.3 \pm 10.8	DSM, HAM-D
Pike and Irwin, 2006 (153)	IL-6	25/25	100/100	42.5 \pm 9.2/42.7 \pm 12	DSM, HAM-D
Simon <i>et al.</i> , 2008 (148)	TNF- α /IL-1 β /IL-6/IL-4/ IFN- γ /IL-2/IL-8/IL-10	49/49	59.2/57.1	41.7 \pm 11.1/41.7 \pm 11.3	DSM
Sluzewska <i>et al.</i> , 1996 (154)	IL-6	49/15	18.4/NR	42.3 \pm 6.5/NR	DSM, HAM-D
Sutcgil <i>et al.</i> , 2007 (159)	TNF- α /IL-4/IL-2	23/25	52.2/52.0	34.8 \pm 7.4/34.3 \pm 7.8	DSM, HAM-D
Tuglu <i>et al.</i> , 2003 (160)	TNF- α	26/17	57.7/64.7	39.4 \pm 14.6/37.1 \pm 11.1	DSM, HAM-D, BDI
Yang <i>et al.</i> , 2007 (149)	TNF- α /IL-1 β /IL-6	33/23	27.3/30.4	42.1 \pm 2.3/38.4 \pm 1.8	DSM, HAM-D

BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; D, depressed; DSM, Diagnostic and Statistical Manual of Mental Disorders; HAM-D, Hamilton Depression Rating Scale; IFN- γ , interferon γ ; IL, interleukin; MADRS, Montgomery-Åsberg Depression Rating Scale; ND, nondepressed; NR, not reported; POMS, Profile of Mood States; TNF- α , tumor necrosis factor α ; ZDS, Zung Depression Scale.

^aValues reflect mean \pm SD in each group.

Figure 1. Tumor necrosis factor- α .

excluded based on the presence of comorbid medical diseases (23,25,37–86) ($n = 52$), use of concomitant medications (87–118) ($n = 32$), lack of specific diagnosis of major depression (24,119,120) ($n = 3$), lack of healthy control groups (121,122) ($n = 2$), use of diagnostic criteria other than the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (22,123–125) ($n = 4$), reporting of only stimulated cytokines (31,96,126–131) ($n = 8$), and publication type being a review rather than a clinical study (132–142) ($n = 11$). In total, 24 cross-sectional studies satisfied inclusion and exclusion criteria (Table 1): 16 studies for IL-6 (17,29,30,143–155), 12 for TNF- α (30,143–149,156–160), 9 for IL-1 β (30,143,144,147–149,156,158,161), 5 for IL-2 (147, 148,159,161,162), 5 for IL-4 (147,148,159,161,163), 4 for IFN- γ (147,148,161,163), 4 for IL-8 (145,146,148,157), and 6 for IL-10 (146,148,150,155,158,161). Cytokine concentrations were all reported in pg/mL.

Studies of TNF- α

Tumor necrosis factor- α measurements were made in 438 depressed and 350 nondepressed subjects extracted from 13 studies. There were significantly higher concentrations of TNF- α in depressed subjects compared with control subjects with an overall weighted mean difference (WMD) of 3.97 pg/mL (95% CI: 2.24 to 5.71, $p < .00001$) (Figure 1).

Studies of IL-1 β

Measurements for IL-1 β were extracted from nine studies that included 267 depressed and 246 nondepressed subjects. The overall WMD for IL-1 β (-1.58) was not significant (95% CI: -3.59 to .43, $p = .39$) (Figure 2).

Studies of IL-6

Interleukin-6 measurements were made in 492 depressed and 400 nondepressed subjects extracted from 16 studies. Depressed patients had significantly higher concentrations of IL-6 ($p < .00001$) with an overall WMD of 1.78 pg/mL (95% CI: 1.23 to 2.33) (Figure 3).

Studies of IL-4

Concentrations of IL-4 were extracted from five studies for 154 depressed and 132 nondepressed subjects. There was no significant difference in concentrations of IL-4 between depressed and nondepressed patients and the overall WMD was 7.86 pg/mL (95% CI: -11.03 to 26.75, $p = .41$) (Figure 4).

Studies of IFN- γ

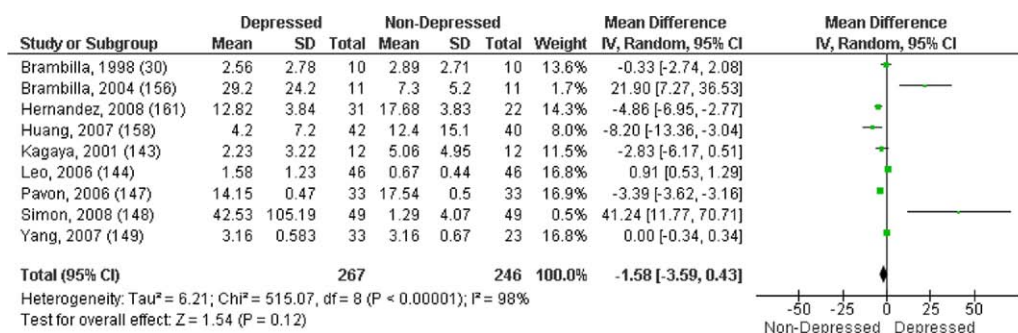
Measurements for IFN- γ were extracted from four studies for 131 depressed and 107 nondepressed subjects. Concentrations of IFN- γ did not differ between groups. The overall WMD for IFN- γ was -6.63 pg/mL (95% CI: -25.91 to 12.65, $p = .50$) (Figure 5).

Studies of IL-2

There were 153 depressed and 139 nondepressed subjects extracted from five studies for whom IL-2 was measured. Concentrations of IL-2 did not differ between groups. The overall WMD for IL-2 was -5.75 pg/mL (95% CI: -100.45 to 88.96, $p = .91$) (Figure 6).

Studies of IL-8

Measurements for IL-8 were extracted from four studies for 205 depressed and 177 nondepressed subjects. Concentrations of

Figure 2. Interleukin-1 β .

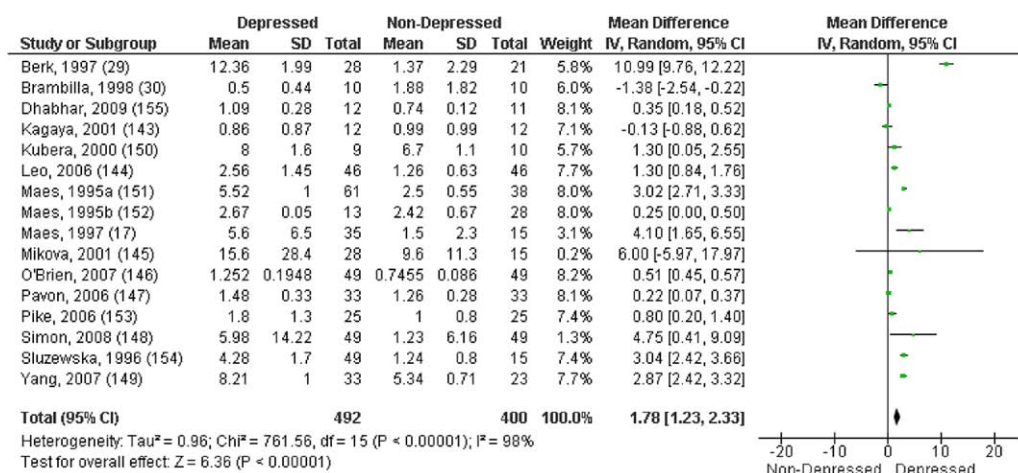


Figure 3. Interleukin-6.

IL-8 did not differ between groups. The overall WMD for IL-8 was -0.39 (95% CI: -2.13 to 1.35 , $p = .66$) (Figure 7).

Studies of IL-10

Interleukin-10 measurements were made in 171 depressed and 200 nondepressed subjects extracted from six studies. Concentrations of IL-10 did not differ between groups. The overall WMD for IL-10 was 1.13 (95% CI: -0.37 to 2.63) (Figure 8).

Heterogeneity and Publication Bias

Significant heterogeneity was found in all comparisons (Table 2), justifying the use of random effects models. Publication bias was not identified among the studies, as demonstrated by funnel plots, and no significant correlations between effect size and sample size were detected (TNF- α : Spearman $\rho = -.071$, $p = .82$) (IL-1 β : Spearman $\rho = .133$, $p = .69$) (IL-6: Spearman $\rho = .351$, $p = .18$) (IL-4: Spearman $\rho = .700$, $p = .19$) (IL-2: Spearman $\rho = -.300$, $p = .62$) (IL-10: Spearman $\rho = .200$, $p = .07$).

Methodological Differences

For IL-6 and TNF- α determinations, different studies used enzyme-linked immunosorbent assay (ELISA) kits from at least 6 and 10 different suppliers, respectively. Most studies included in this meta-analysis used noncompetitive sandwich ELISA techniques, while some used competitive assays or solid phase reverse ELISA techniques. Removing all studies but those using noncompetitive sandwich assays did not significantly improve the heterogeneity of the results. Interplate variability was not consistently reported in the included studies, though when reported it varied between 2.8% and 10%.

Discussion

This study reports significantly higher concentrations of the proinflammatory cytokines TNF- α and IL-6 in depressed subjects compared with control subjects. While both positive and negative results have been reported in individual studies, this meta-analytic result strengthens the evidence that depression is accompanied by activation of the IRS.

Both TNF- α and IL-6 are acute-phase proteins secreted into the bloodstream in response to immunologic challenge and elevations of these cytokines in the absence of infection or tissue injury are considered abnormal (164,165). Peripherally, IL-6 is secreted by macrophages and monocytes to stimulate differentiation and proliferation of B cells (166,167). Tumor necrosis factor- α is secreted by macrophages, mast cells, and natural killer cells, with the effect of stimulating the release of proinflammatory cytokines and prostaglandin inflammatory mediators from macrophages (168).

This article did not find support for the involvement IL-1 β , a third proinflammatory acute-phase response protein (164). Similarly, there were no significant differences in the concentrations of other proinflammatory cytokines investigated (IL-2, IL-8, and IFN- γ). Fewer studies assessed concentrations of these cytokines, resulting in considerably smaller population sizes, which may have made it more difficult to observe associations.

There were no significant differences detected between depressed and nondepressed in the concentrations of the anti-inflammatory cytokines IL-10 and IL-4. The balance between anti-inflammatory cytokines and proinflammatory cytokines determines the extent of an inflammatory response. Interleukin-4 and IL-10 play similar roles in stimulating B cells to fight

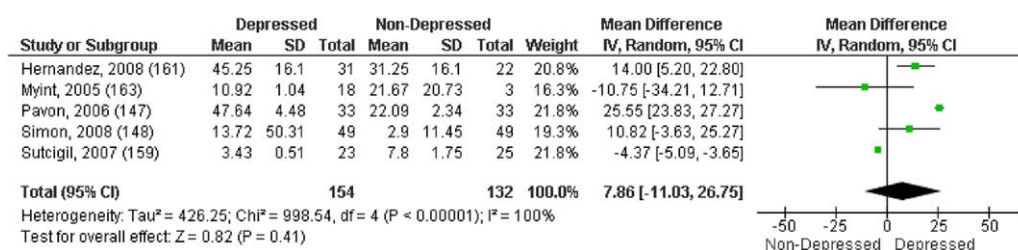


Figure 4. Interleukin-4.

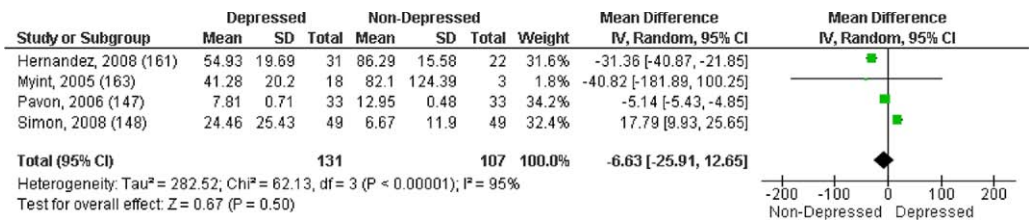


Figure 5. Interferon-γ.

pathogens and in inhibiting secretion of IFN-γ (169), though they differ in their secretory patterns and activities (170,171). Functionally, IL-4 stimulates differentiation of naive T cells down the extracellular pathogen-fighting arm of the immune system, which can compromise differentiation into helper T cells directed against intracellular pathogens, whereas IL-10 is secreted by regulatory T cells without pronounced effects on intracellular immunity (171–174). The lack of detectable elevation in IL-10 and IL-4 may be due to smaller sample sizes and more difficulty in detection. However, if true, lack of activation may suggest that proinflammatory cytokine activation is unopposed.

The presence of peripheral acute phase proteins may be related to an inflammatory state within the central nervous system (CNS). Proinflammatory cytokines produced peripherally can sometimes cross the blood-brain barrier (175,176) and peripheral proinflammatory signals can be actively propagated across the blood-brain barrier by cross-talk between the peripheral and central immune systems (177–179). Within the CNS, proinflammatory cytokines play crucial roles in the stress response system and in the regulation of adult neurogenesis.

Elevated cytokines may be important in depression for several reasons. One candidate mechanism for the detrimental effects of proinflammatory cytokines on mood is their ability to modulate hippocampal neurogenesis. Neurogenesis has been implicated as a key contributing mechanism in the pathophysiology and treatment of depression (180,181). Specifically, the selective serotonin reuptake inhibitors (SSRIs) can upregulate the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus, which promotes the proliferation and survival of neural progenitor cells (180,182–185). Conversely, the influence of inflammatory activity on hippocampal neurogenesis is considered largely inhibitory (186). The inflammatory system of the CNS is composed largely of the microglia (187), which may be overactivated in major depression (188). Activated microglia employ IL-6 as a key antineurogenic signal (189), which can interact directly with neural progenitor cells via IL-6 receptors (190). Similarly, TNF-α has appreciable antiproliferative activity on neuronal progenitor cells via TNF receptor 1 (TNF-R1) receptors (191–193). Congruently, this meta-analysis supports the involvement of IL-6 and TNF-α in major depression. Over time, a decrease in neurogenesis could contribute to the reductions in hippocampal volume seen in major depression (194)

because higher IL-6 levels have been associated with reduced hippocampal gray matter volume (195). Antineurogenic properties of IL-1β and IFN-γ have also been established (196,197), though some studies demonstrate less consistent detrimental effects on the proliferation of neural progenitor cells (189,198). We could not find evidence to support the involvement of IL-1β and IFN-γ in major depression. Meta-analytic support for the involvement of IL-6 and TNF-α in major depression may parallel their inhibitory roles on adult hippocampal neurogenesis.

Neurogenesis may be further affected by activation of the hypothalamic-pituitary-adrenal (HPA) axis due to the antineurogenic properties of glucocorticoids (199). The stress response system is intricately linked with proinflammatory signaling. The stress response involves the release of TNF-α and IL-6, which increase the release of corticotropin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH), and cortisol by acting directly on hypothalamic and pituitary cells (200–204). Dysregulation of the HPA axis is an important finding associated with depressive behavior (205,206), underscoring the potential for direct clinical significance of elevations in proinflammatory cytokines.

Another mechanism relating proinflammatory cytokines to mood is their capacity to induce the indoleamine-2,3-dioxygenase (IDO) enzyme, which catalyzes the rate-limiting step in the synthesis of kynurenine from dietary tryptophan (207–209). Proinflammatory cytokines, including IFN-γ, IL-6, and TNF-α, have been shown to increase the expression of IDO in both central and peripheral immune-competent cell types (179,210). Thus, activation of these cell types can degrade tryptophan, which may contribute to depressive symptoms by reducing the availability of the requisite precursor for the synthesis of serotonin and melatonin (208,209). Perhaps even more importantly, kynurenine gives rise to metabolites such as quinolinic acid, an endogenous N-methyl-D-aspartate (NMDA) agonist that could perturb neurotransmission along glutamatergic pathways (211,212). As a potent NMDA receptor agonist, quinolinic acid may lead to hippocampal neuron damage and apoptosis (213,214). This excitotoxic mechanism may also contribute to the symptoms of major depression and to hippocampal volume loss. The clinical significance of the kynurenine pathway is suggested by studies finding increased concentrations of kynurenine and its metabolites in patients with major depression (215–217) and by

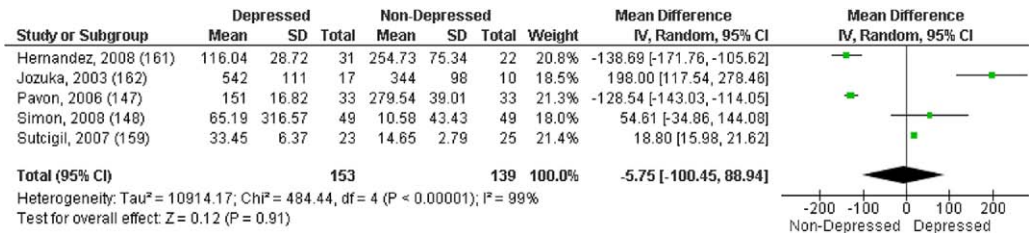


Figure 6. Interleukin-2.

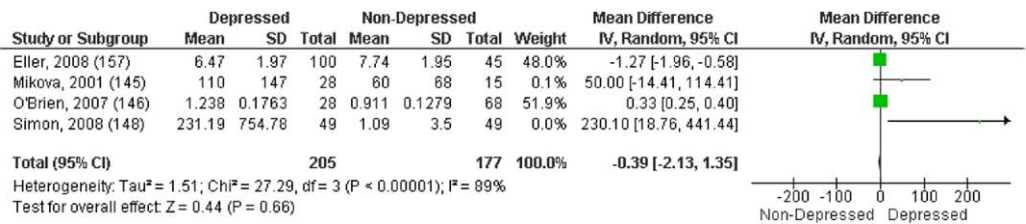


Figure 7. Interleukin-6.

the correlation of these concentrations with depressive symptoms and the remission of these symptoms following therapy (218).

This meta-analysis benefited from including only studies of unmedicated, medically healthy, and currently depressed patients who had blood extracted in the morning. As limitations, many clinical variables that may have affected the relationship between cytokines and depression remain to be clarified. Some studies suggest that inflammatory markers can be associated with the severity of depressive symptoms, and differences in symptom severity may account for some of the observed heterogeneity between studies. Because depressive symptoms were not quantified in each study, a meta-regression with symptom severity was not feasible, and this study relied entirely on the use of a categorical diagnosis of depression. Similarly, age, gender, race, and whether in the acute phase of the illness may have an impact. In addition, it is not known whether IL-6 and TNF- α are elevated over prolonged periods in depressed patients or if the associations found in clinical studies reflect transient elevations. These patterns may differ in their implications for long-term health effects. Large standard deviations are noted in most studies, suggesting that substantial interindividual variation exists. The wider confidence intervals are also expected with the choice of a random effects model, justified here due to the heterogeneity. As a further limitation, many trials comparing cytokines are not registered with clinical trials databases, so the scope of the unpublished literature cannot be ascertained and an effect of publication bias cannot be ruled out. However, funnel plots generated for each cytokine of interest did not support the presence of publication bias.

A significant portion of the observed heterogeneity may be attributable to variability in assay procedures both within and between laboratories. Nonetheless, removing all studies but those using noncompetitive ELISA assays did not eliminate heterogeneity. Between noncompetitive ELISA assays, some factors contributing to uncertainty in cytokine values have been examined previously. In one study, the same cytokine preparation was analyzed by 11 expert laboratories, which returned concentrations varying between 67% and 136% of the reported

mean value (219). Within laboratories, the interplate uncertainties reflecting day-to-day operational differences varied considerably, ranging between 5% and 30%. Interplate variability varied between 2.8% and 10% in the included studies, though it was not consistently reported. Thus, a relatively large sample size may be required to obtain significant results in any individual study. Noble *et al.* (219) observed considerable differences in assay performance parameters, such as signal-to-noise ratio and quantitative range between laboratories, suggesting that within the range of expected clinical cytokine values, there is likely to be considerable concentration-dependent variation in the ability of a given laboratory to make accurate determinations. Thus, appreciable heterogeneity is expected when combining assay results obtained from different laboratories. These methodological limitations and variations in laboratory practices may contribute substantially to the observed heterogeneity in the present study, independent of clinical confounders.

The substantial heterogeneity observed between studies, likely due to both technical considerations and clinical confounders, suggests a limited potential for the utility of cytokines as predictive measures in major depression. However, the general pattern of inflammatory involvement suggests that anti-inflammatory agents may be useful in clinical management. Preliminary evidence suggests that patients treated with rofecoxib for other indications showed improvement in depressive symptoms (220), though placebo-controlled studies are lacking. Thus, in patients with inflammatory activation, anti-inflammatory agents may have beneficial effect on mood. In medically healthy, major depressed patients treated with reboxetine, one randomized, placebo-controlled, double-blind trial showed that patients treated with celecoxib showed significantly better improvement than those receiving reboxetine alone (221). More research into the potential utility of anti-inflammatory agents is warranted.

In conclusion, this meta-analysis confirms the association between elevations of two proinflammatory cytokines, IL-6 and TNF- α , and major depression. These proteins are normally involved in the acute phase response and their presence is likely to be of pathological significance. It remains to be identified

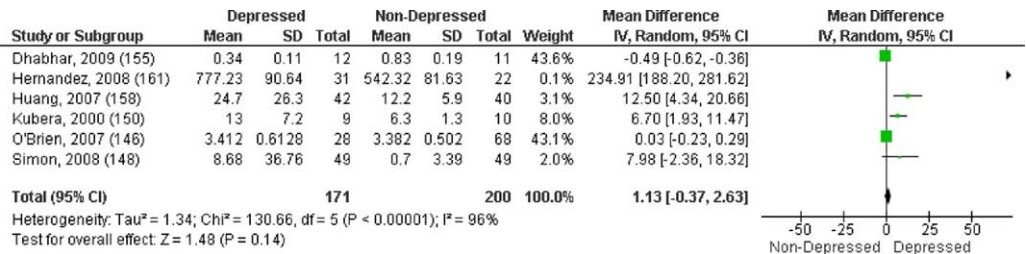


Figure 8. Interleukin-10.

Table 2. Summary of Comparative Outcomes

Outcome	N (depressed, nondepressed)	Effect Estimate (95% CI)	Heterogeneity χ^2 (p value)	Inconsistency I^2 (%)
TNF- α	788 (438, 350)	WMD 3.97 (2.24–5.71)	537.29 (<.0005)	98
IL-1 β	513 (267, 246)	WMD –1.58 (–3.59–.43)	515.07 (<.0005)	98
IL-6	892 (492, 400)	WMD 1.78 (1.23–2.33)	761.56 (<.0005)	98
IL-4	286 (154, 132)	WMD 7.86 (–11.03–26.75)	998.54 (<.0005)	100
IFN- γ	238 (131, 107)	WMD –6.63 (–25.91–12.65)	62.13 (<.0005)	95
IL-2	292 (153, 139)	WMD –5.75 (–100.45–88.94)	484.44 (<.0005)	99
IL-8	382 (205, 177)	WMD –.39 (–2.13–1.35)	27.29 (<.0005)	89
IL-10	371 (171, 200)	WMD 1.13 (–.37–2.63)	130.66 (<.0005)	96

Data extracted from included studies and pooled.

CI, confidence interval; IL, interleukin; IFN- γ , interferon γ ; TNF- α , tumor necrosis factor α ; WMD, weighted mean difference.

whether their presence may be a cause or consequence of major depression.

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