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# Meta-Analysis of Cytokines and Chemokines in Suicidality: Distinguishing Suicidal Versus Nonsuicidal Patients

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## ABSTRACT

**BACKGROUND:** Major psychiatric disorders are associated with inflammation. Aberrant cytokine and chemokine levels have been associated with psychiatric disorders and suicidal behavior. We performed a meta-analysis of cytokine and chemokine levels in patients with versus without suicidality and patients with suicidality versus healthy controls.

**METHODS:** We identified articles by searching MEDLINE, PsycINFO, and Thomson Reuters Web of Knowledge databases and the reference lists of identified studies.

**RESULTS:** Study inclusion criteria were met by 18 studies comprising 583 patients with suicidality, 315 patients without suicidality, and 845 healthy control subjects. Levels of interleukin (IL)-1β and IL-6 were significantly increased in blood and postmortem brain samples of patients with suicidality compared with both patients without suicidality and healthy control subjects ($p < .05$ for each). In vitro IL-2 production by peripheral blood mononuclear cells was significantly decreased in patients with suicidality compared with both patients without suicidality and healthy controls ($p < .01$ for each). Cerebrospinal fluid levels of IL-8 were significantly decreased in patients with suicidality versus control subjects ($p < .05$).

**CONCLUSIONS:** We found evidence for aberrant cytokine levels in blood, cerebrospinal fluid, and postmortem brain samples of patients with suicidality. Levels of IL-1β and IL-6 were most robustly associated with suicidality, and these cytokines may help distinguish suicidal from nonsuicidal patients. Rigorously designed longitudinal studies are needed to evaluate these associations further.

*Keywords:* Chemokines, Cytokines, Depression, Inflammation, Meta-analysis, Suicide

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The role of immunologic dysfunction, including cytokine and cytokine receptor or antagonist (referred to herein as "cytokine") levels and chemokine levels, in the pathophysiologic mechanism of many psychiatric disorders has been vigorously investigated. Aberrant levels of proinflammatory cytokines have been reported in major depressive disorder (MDD) (1), schizophrenia (2), bipolar disorder (3), alcohol use disorder (4), borderline personality disorder (5), eating disorders (6), and posttraumatic stress disorder (7). Similarly, a recent systematic review of chemokine levels across multiple psychiatric disorders reported significant alterations in chemokine levels observed in MDD, bipolar disorder, and schizophrenia (8).

There are also similarities in the pattern of cytokine alterations across several psychiatric disorders. Meta-analyses for MDD, schizophrenia, and bipolar disorder all found elevated blood levels of interleukin (IL)-1β, soluble interleukin-2 receptor (sIL-2R), and tumor necrosis factor (TNF)-α across all three disorders. Meta-analyses also found elevated blood levels of IL-6 in both MDD and schizophrenia (9). Potential mechanisms for associations between cytokines and psychiatric symptoms include direct effects of cytokines on dopaminergic neurotransmission and indirect effects on glutamatergic neurotransmissions through tryptophan catabolism (1–3).

Suicidal ideation, suicidal behavior, and completed suicide (referred to herein as "suicidality" or "suicide") are associated with many psychiatric disorders (10,11). Identifying risk factors for suicide in patients with psychiatric disorders is an area of increasing public health concern. Research efforts have investigated levels of cytokines and chemokines in patients with psychiatric disorders with and without suicidality. A qualitative review of inflammatory changes associated with suicidal behavior reported that IL-2, IL-6, IL-8, and TNF-α were the most commonly altered inflammatory markers (12).

Meta-analysis is one approach to bring increased clarity to an area of research with significant heterogeneity. We performed a meta-analysis of blood, cerebrospinal fluid (CSF), and postmortem brain cytokine and chemokine levels in patients with and without suicidality and healthy control subjects. The primary objective was to establish the characteristic cytokine or chemokine profile that emerges in patients with suicidality and whether cytokine or chemokine levels distinguish suicidal from nonsuicidal patients. We hypothesized an increase in

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proinflammatory cytokines, such as IL-6 and TNF-α, in patients with suicidality.

## METHODS AND MATERIALS

### Study Selection

Studies investigating cytokines and chemokines in suicide were systematically searched in MEDLINE (PubMed, National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda, Maryland), PsycINFO (via Ovid, American Psychological Association, Washington, DC), and Thomson Reuters (formerly ISI) Web of Knowledge (Science Citation Index and Social Sciences Citation Index, Thomson Reuters, Charlottesville, Virginia) in September 2014. The primary search strategy was "(inflammation OR cytokine OR chemokine OR interferon OR interleukin OR 'tumor necrosis factor' OR C-reactive protein) AND (suicide OR 'suicidal ideation' OR 'suicidal thoughts' OR 'suicide attempt' OR self-harm OR 'suicidal behavior')." These searches yielded 772 articles from PubMed, 30 from PsycINFO, and 275 from Web of Knowledge, and the resulting matches were screened. Of the preliminary results, matches were excluded if they 1) did not present quantitative data on cytokines, 2) did not measure cytokines within a population of patients with suicidality, 3) were review articles, 4) were genetic studies that did not quantify cytokine or chemokine levels, 5) were unavailable in English, or 6) were not performed in humans. From these sources and a manual review of reference lists, we identified 22 potential studies for inclusion. Demographic and study design information is presented in Table 1 (13–34).

Inclusion criteria were as follows: 1) cross-sectional or longitudinal studies; 2) measure cytokines or chemokines or both in blood, CSF, or postmortem brain; 3) possess a patient population who a) had active suicidal ideation, b) had a history of suicide attempt, or c) had completed suicide; and 4) possess a control population who were either a) patients with psychiatric disorders without suicidality or b) healthy controls. Studies were excluded if 1) they did not present mean and SD data for cytokines or chemokines or both (after attempting to contact the study authors) or 2) they possessed significant overlap in patient or control population sample.

After independent searches, review of study methods by both authors, and attempts to contact study authors, 18 of 22 identified studies met the inclusion criteria. Two studies (18,26) were not included because of lack of a control population. One study (13) was excluded because of a significant overlap in study population sample with a separate study (25). The fourth study (32) was excluded because the mean and SD data could not be obtained after attempting to contact the study author. Each of the 18 included studies was assessed and assigned a quality score by one author (CB), which was independently verified by the senior author (BJM). There was universal agreement between the authors on quality scores. Quality scores for studies of cytokines and chemokines in the blood or CSF were based on the sum of the presence or absence of eight factors (1 point for each): whether the study considered potential effects of age, sex, race, fasting status, socioeconomic status, body mass index (BMI), smoking, and medications by either 1) matching patients and controls or 2) controlling for these variables in the analysis. Quality scores for studies of cytokine levels in postmortem brain samples were based on the sum of the presence or absence of controlling for the potential effects of 12 factors (1 point for each): age, sex, race, socioeconomic status, BMI, smoking, postmortem hours, pH, cause of death, drug toxicology, premorbid psychiatric diagnosis, and medications by either 1) matching patients and controls or 2) controlling for these variables in the analysis. A flow chart summarizing the study selection process is presented in Figure 1.

### Data Extraction and Meta-analysis

Data were extracted (sample size, mean, and SD for patients and controls) for each cytokine or chemokine assessed in each study as well as data on demographic variables (including age, sex, BMI, and geographic location). One author (CB) extracted all data, which was independently verified by the senior author (BJM). We calculated effect size estimates (Hedges' *g*) for all cytokines and chemokines in each study. Random effects pooled effect size (ES) estimates and 95% confidence intervals (CIs) were calculated using the method of DerSimonian and Laird (35). Random effects models yield their actual first error rate, whereas fixed effect models tend to inflate their first error rate. The CIs obtained by fixed effect models are also biased, and their actual coverage rate is smaller than their nominal coverage rate (36). Meta-analysis could not be performed for cytokines or chemokines that were assessed in only a single study. In one study (21), patients with MDD were stratified based on atypical versus melancholic features. Data were extracted separately for both of these subgroups.

Separate meta-analyses were performed for each cytokine or chemokine by sample source (blood [in vivo and in vitro considered separately], CSF, or postmortem brain) and for comparison group (i.e., patients with psychiatric disorders with vs. without suicidality and patients with suicidality vs. healthy control subjects). The main statistical hypothesis was that the ES for the difference between patients and control subjects for each cytokine and chemokine equals zero. All tests were two-sided, and *p* values were considered statistically significant at the $\alpha = .05$ level.

The meta-analysis procedure also calculates a $\chi^2$ value for the heterogeneity in ES estimates, which is based on Cochran's *Q* test, and $I^2$, the proportion of the variation in ES attributable to between-study heterogeneity (37). Between-study heterogeneity $\chi^2$ was considered significant for $p < .10$ (38). We performed a sensitivity analysis for cytokines or chemokines measured in three or more studies for which the heterogeneity $\chi^2$ was significant. This analysis was done by removing one study at a time and repeating the meta-analysis procedure to examine its impact on the ES estimate and between-study heterogeneity (39). Given the significant heterogeneity in ES estimates, we also performed a series of meta-regressions to explore possible moderating variables to account for such heterogeneity. Meta-regressions were performed for IL-6 and TNF-α because these were the two cytokines measured in the largest number of studies. We conducted meta-regression analyses of age, sex, BMI, and geographic location (region). Potential for publication bias was