Associations of Depression With C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis

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Objective: To assess the magnitude and direction of associations of depression with C-reactive protein (CRP), interleukin (IL)-1, and IL-6 in community and clinical samples. **Methods:** Systematic review of articles published between January 1967 and January 2008 in the PubMed and PsycINFO electronic databases was performed. Effect sizes were calculated as *stat d* and meta-analyzed, using random-effects models. **Results:** Each inflammatory marker was positively associated with depression; CRP, $d = 0.15$ (95% CI = 0.10, 0.21), $p < .001$; IL-6, $d = 0.25$ (95% CI = 0.18, 0.31), $p < .001$; IL-1, $d = 0.35$ (95% CI = 0.03, 0.67), $p = .03$; IL-1ra, $d = 0.25$ (95% CI = 0.04, 0.46), $p = .02$. Associations were strongest in clinically depressed patient samples—but were also significant in community-based samples—and when clinical interviews were used. Studies adjusting for body mass index (BMI) had smaller associations, albeit significant. Relationships were inconsistent with respect to age, medication, and sex. Depression was related to CRP and IL-6 among patients with cardiac disease or cancer. **Conclusions:** Depression and CRP, IL-1, and IL-6 are positively associated in clinical and community samples and BMI is implicated as a mediating/moderating factor. Continuity in clinic- and community-based samples suggests there is a dose-response relationship between depression and these inflammatory markers, lending strength to the contention that the cardiac (or cancer) risk conferred by depression is not exclusive to patient populations. Available evidence is consistent with three causal pathways: depression to inflammation, inflammation to depression, and bidirectional relationships. **Key words:** depression, inflammation, C-reactive protein, interleukin-1, interleukin-6, meta-analysis.

ANS = autonomic nervous system; **BDI** = Beck Depression Inventory; **BMI** = body mass index; **CAD** = coronary artery disease; **CES-D** = Center for Epidemiological Studies-Depression Scale; **CI** = confidence interval; **CNS** = central nervous system; **CRH** = corticotrophin-releasing hormone; **CRP** = C-reactive protein; **DSM** = Diagnostic and Statistical Manual of Mental Disorders; **HPA** = hypothalamic-pituitary-adrenal; **IL** = interleukin; **IL-1ra** = interleukin-1 receptor antagonist; **LPS** = lipopolysaccharide; **MI** = myocardial infarction; **OTC** = over-the-counter; **PBMC** = Peripheral Blood Mononuclear Cells; **PHQ-9** = Depression Module of the Patient Health Questionnaire; **SE** = Standard Error.

INTRODUCTION

Depression is a prevalent condition (1) that is related to all-cause, cardiovascular, and cancer morbidity and mortality (2–10). The mechanisms responsible for these associations have yet to be elucidated but inflammatory processes are implicated. An early theory proposed that proinflammatory cytokines secreted by activated macrophages, such as interleukin (IL)-6 and IL-1, can cause depression (11). Sickness behaviors (e.g., inactivity, negative mood), which share features with depression, are also associated with cytokine activation (12). A mutual connection with coronary artery disease (CAD) is suggested by the discovery that cardiac risk is associated with higher levels of C-reactive protein (CRP) (13–16), a nonspecific acute-phase protein synthesized in the liver in response to stimulation from IL-6 (17–19) and IL-1 (18,20). Additionally, IL-6 can promote some types of cancer by blocking apoptosis of transformed cells during cancer initiation and by facilitating angiogenesis in solid tumors during cancer progression (21,22).

These converging theories and evidence suggest that CRP, and its precursors IL-6 and IL-1, should be positively associated with the incidence and severity of depression. Earlier meta-analyses (23,24) assessed some of these relationships and found positive associations between IL-6 and intensity of depression but did not include outcomes for CRP. A third review (25), including CRP, was restricted to a small set of community-based samples and the results were inconclusive.

The present series of meta-analyses were conducted to provide estimates of the magnitude and generalizability of associations of depression with CRP, IL-6, and IL-1 in both community and clinic/hospital samples. Comparisons of population-based and patient samples evaluated whether inflammation only emerges once a person crosses the threshold of clinical depression or increases in a dose-response fashion with affective symptoms in the general population. In addition, we examined how size of the association varied as a function of the type of depression assessment, age, sex, and adjustment for covariates, such as BMI and medication use. The latter two features are particularly important because several studies reported significant associations between BMI and inflammation (26,27) whereas medications (e.g., antidepressants, statins) potentially reduce or otherwise alter the inflammatory response (28–31). Sex differences are also critical as inflammatory markers may fluctuate with the menstrual cycle (32). Age is considered as a factor because, as people age, rates of depression and inflammation tend to increase (33,34). Finally, although other inflammatory markers in peripheral circulation—besides CRP, IL-6, and IL-1—have been studied in relation to depression, the number of relevant studies is small; thus, we restricted our searches and analyses to these specific inflammatory markers.

METHODS

Search Strategy and Inclusion Criteria

We conducted a systematic review of the PubMed and PsycINFO electronic databases for English language studies reporting the relationship between CRP, IL-6, and/or IL-1 and depression published between January 1967 and January 2008.[1] In addition, the functionally distinct molecule, IL-1 receptor antagonist (IL-1ra), was also included in the review. IL-1ra acts to counterregulate the effects of IL-1 and, thus, is highly correlated with IL-1 (35). Because of this association and the fact that IL-1ra is easier to detect in circulation than IL-1, it is often examined as a surrogate marker for IL-1.

[1]The form of IL-1 in all included studies is interleukin-1β.

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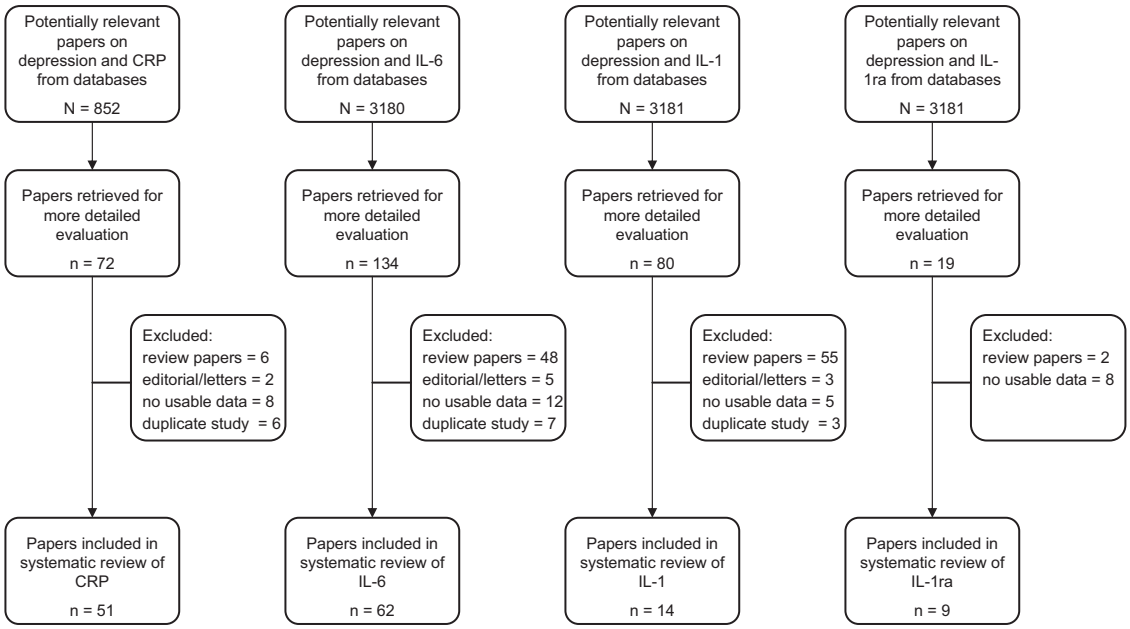

Figure 1. Flow chart representing the literature search. IL = interleukin.

Separate searches were conducted for the following keywords: *depression, major depression, minor depression, melancholia, dysthymia, depressed mood,* and *depressive symptoms* combined with *C-reactive protein, CRP, acute-phase proteins, IL-6, IL-1, IL-1ra, interleukins, cytokines, inflammation,* and *inflammatory markers*. Additional studies were identified by reviewing the reference sections of retrieved articles.

Eligibility for inclusion was independently determined by two of the authors. Studies reporting cross-sectional data/analyses for depression and CRP, IL-6, and/or IL-1 in either clinical or community adult populations were included. Additionally, samples of depressed patients (versus nondepressed patient controls) suffering from comorbid CAD-related disease or cancer were included. Other chronic disease populations were excluded (e.g., end-stage renal disease). Major depression could be assessed by standardized clinical interviews (e.g., *Structured Clinical Interview for DSM*) (36) and depressive symptoms with standardized psychometric instruments (e.g., Beck Depression Inventory (BDI)) (37).

Although depression may be examined in relation to inflammatory markers in various compartments (e.g., cerebral spinal fluid (CSF) and saliva) or contexts (e.g., as a measure of immune competence via stimulated production of cytokines from peripheral blood mononuclear cells (PBMC)), the review was restricted to studies that measured systemic inflammation (38). Thus, only those studies in which inflammatory markers were assessed in circulating peripheral blood were included.[2]

[2]Measures of proinflammatory cytokines (IL-1, IL-6, TNF-α) from other compartments, such as CSF, saliva, and in vitro supernatant of spontaneously expressing PBMC tend to be uncorrelated with systemic levels of these same cytokines in depressed patients (39,40). There are studies of stimulated production of cytokines from PBMC by mitogens, such as lipopolysaccharide (LPS), but even if one assumed that cytokines from PBMC in vitro are representative of systemic inflammation, these studies do not provide a measure of the association between current depressive symptoms and current inflammation. Such studies provide a specific, functional measure of the immune system's active response to antigen stimulation (41). Polyclonally stimulated PBMC often serve as a positive control in immune system experiments as mitogens induce a maximum immune response (42). Thus, they provide a relative measure of the highest potential inflammation in the body. As in the case of the compartments noted above, multiple studies have consistently found systemic, circulating levels of IL-6 are uncorrelated with stimulated production of IL-6 from PBMC in vitro in persons with depression or chronic stress (38,40,43). Thus, we decided the meta-analytic grouping of studies of circulating cytokines with studies examining the same cytokine(s) from other compartments was inappropriate.

Study Selection and Data Extraction

A flow diagram of the literature search is shown in Figure 1. Studies that provided sufficient information about the relationship between depression and inflammatory markers to calculate effect sizes were included in the final analyses. There were 51 studies for CRP, 62 for IL-6, 14 for IL-1, and 9 for IL-1ra (See Appendix online with this article for a full listing of studies, Supplemental Digital Content1. http://links.lww.com/A734).

A standardized data coding form was developed to extract the following information from each study: (a) authors and citation; (b) study design; (c) characteristics of the study sample (age, sex, size, subgroups); (d) method used to measure depression; (e) outcomes of interest; (f) adjusted covariates; and (g) brief results.[3] When data for both men and women were reported separately, these were treated as separate samples in the analyses. One author conducted and another verified data extraction for each inflammatory outcome. Disagreements were resolved through group discussion. Fewer than 5% of all studies required discussion.

Calculation and Aggregation of Study Effect Sizes

The Comprehensive Meta-Analysis software package version 2.0 was used to compute and aggregate effect sizes (46). This program utilizes Hedge's and Olkin's (47) methods for combining effect sizes by computing (sample-size) weighted means of the effects for all included outcomes. Correlations or standardized difference in means (*stat d*) may be calculated under both the fixed-effect and random-effects models.

Fixed-effect models assume that a common population effect size underlies each of the included studies and that any variation in the observed effects is due only to sampling error within each study. In other words, it is assumed that the true effect size is the same, or "fixed," for every study. Further, it is assumed that the set of observed studies have been conducted under similar conditions with similar subjects. Consequently, fixed-effect models limit inferences concerning effect sizes to the set of observed studies only (48).

In contrast, random-effects models assume there is a distribution of population effect sizes across studies. Random-effects models account for both the within- and between-study variation and therefore permit generalization beyond the set of observed studies to ones not identical to those in the observed sample. Random-effects models also generally produce wider confidence intervals (CI) and are considered to be more conservative than

[3]The "adjusted covariates" category includes both statistically adjusted and matched variables. Groups were considered matched on a variable if the *p* value for difference was ≥.50 (44,45).

fixed-effect models (48, 49). Random-effects models were more appropriate for our purposes and were used in all analyses.

All effect sizes were calculated such that positive values represent higher levels of inflammatory markers in depression. Negative values indicate the opposite. In those cases when a statistical test was reported as nonsignificant and no additional information provided, the effect size coefficient was set to $d = 0.00$ ($n = 7$) and weighted according to sample size to yield the most conservative effect size estimate.

The heterogeneity among study effect sizes was assessed by calculating the Q statistic.[4] This value is distributed as χ^2 and reflects whether the variability among study outcomes is sufficiently large to reject the hypothesis that they were drawn from a common population.

Subgroup analyses based on study features were conducted if there was evidence of significant heterogeneity.[5] Categorical moderators were entered as grouping variables in the effect size calculations. Continuous moderators (i.e., age and percent of each sample that is female) were evaluated using meta-regression. Categorical moderators included: (a) participant sex; (b) method of depression assessment (i.e., clinical interviews, self-reports); (c) community-based versus clinical sample; (d) statistical/experimental adjustment for body mass index (BMI); and (e) statistical/experimental adjustment for medication use.

To address the problem of publication bias (i.e., the existence of possible unpublished and unidentified studies with null results), a fail-safe N was computed for each of the aggregated effect sizes and funnel plots were constructed (50). The fail-safe N value represents the number of additional null studies that, on average, would be required to reduce the combined effect size to the point of nonsignificance. A funnel plot portrays the distribution of effect sizes in the analysis and indicates possible bias when the distribution is asymmetrical (i.e., when there is an overrepresentation of positive results in the published literature).

RESULTS

CRP

Overall Analysis

The vast majority of studies reported a positive association between CRP and depression (Figure 2).[6] The standardized mean difference was small yet highly significant, $d = 0.22$ (95% CI = 0.15, 0.28), $p < .001$. Removal of two studies with unusually large effect sizes (51,52) (*stat* $d = 4.10$, 6.09, respectively) had a small effect on the overall analysis, $d = 0.15$ (95% CI = 0.10, 0.21), $p < .001$.[7] The funnel plot was approximately symmetrical, suggesting evidence of publication bias (Figure 6); In addition, the fail-safe N was large (Table 1). There was considerable heterogeneity among study outcomes (Table 1), so several subgroup analyses were conducted.

Age and Sex

As individuals get older, rates of both depression and inflammation increase dramatically (33,34). However, meta-regression analyses revealed no significant relationship between CRP and depression as a function of the sample's mean age ($\beta = -0.002$, standard error (SE) = 0.002, $p = .33$).

Very few studies provided data partitioned by sex. For those samples comprised only of men ($n = 14$), the relationship was significant, $d = 0.17$, (95% CI = 0.04, 0.30), $p = .009$. In women ($n = 15$), however, the relationship was not significant by conventional standards, $d = 0.14$, (95% CI = −0.02, 0.30), $p = .08$. Additionally, meta-regression was used to evaluate whether the percent of each sample comprised of female subjects moderated the CRP-depression association. Greater female representation in the sample was not significantly related to the magnitude of this association, $\beta = -0.0004$, SE = 0.001, $p = .68$.

Clinical Versus Community Samples

In studies with clinically depressed patients (versus controls; $n = 16$), the association was moderate in size, $d = 0.40$ (95% CI = 0.15, 0.64), $p = .001$. For the subset of studies with depressed patients who also had CAD-related disease ($n = 9$), the effect size was smaller, but also significant, $d = 0.18$ (95% CI = 0.03, 0.33), $p = .02$. No studies were identified that evaluated this relationship in cancer patients. In community-based samples, a much smaller association was obtained, $d = 0.11$ (95% CI = 0.05, 0.17), $p < .001$. Partitioning by type of sample did not yield homogeneous subsets.

Depression Assessment

For studies using clinical interviews, there was a moderate-sized association, $d = 0.26$ (95% CI = 0.11, 0.40), $p = .001$. For those studies utilizing self-report measures of depression (BDI, Center for Epidemiological Studies-Depression Scale (CES-D), Depression Module of the Patient Health Questionnaire (PHQ-9)) (37,53,54), the association was smaller, $d = 0.12$ (95% CI = 0.06, 0.18), $p < .001$.

Adjustment for Covariates

Separate analyses were conducted for studies that adjusted for BMI and medication use. For the subset of studies controlling for BMI, the association was small, albeit significant, $d = 0.11$ (95% CI = 0.06, 0.17), $p < .001$. Those studies not adjusting for BMI yielded an effect size nearly three times as large, $d = 0.32$ (95% CI = 0.16, 0.49), $p < .001$. Clearly, BMI influences the association between CRP and depression.

The results for subgroup analyses with respect to medication use were ambiguous. When adjustments were made, the effect size was modest but significant, $d = 0.23$ (95% CI = 0.12, 0.33), $p < .001$. If medication use was uncontrolled, the association was smaller, $d = 0.12$ (95% CI = 0.05, 0.19), $p = .001$. However, subgroup analyses based on classes of medication known to alter inflammatory processes (e.g., statins, antidepressants, anti-inflammatory agents) yielded inconsistent results (Table 1).

IL-6

Overall Analysis

The effect size based on aggregation of all 61 studies was highly significant, $d = 0.25$ (95% CI = 0.18, 0.31), $p < .001$. Like CRP, IL-6 was positively associated with depression. The funnel plot (Figure 7) was less symmetrical than for CRP, suggesting that some publication bias may exist. However, the fail-safe N was substantial (Table 2). Significant heterogeneity was also present, Q (64) = 281.02, $p < .001$, so several subgroup analyses were conducted.

[4] Q values are reported for all analyses in Tables 1–4.

[5] An aggregated effect size was computed for a subgroup if at least five separate studies were identified that represented the subgrouping factor in question.

[6] See also figures 3,4, and 5 for forest plots of the individual study effect sizes for IL-6, IL-1, and IL-1ra, respectively.

[7] All values for CRP and IL-6 reported in the text reflect the removal of these outliers, if relevant.

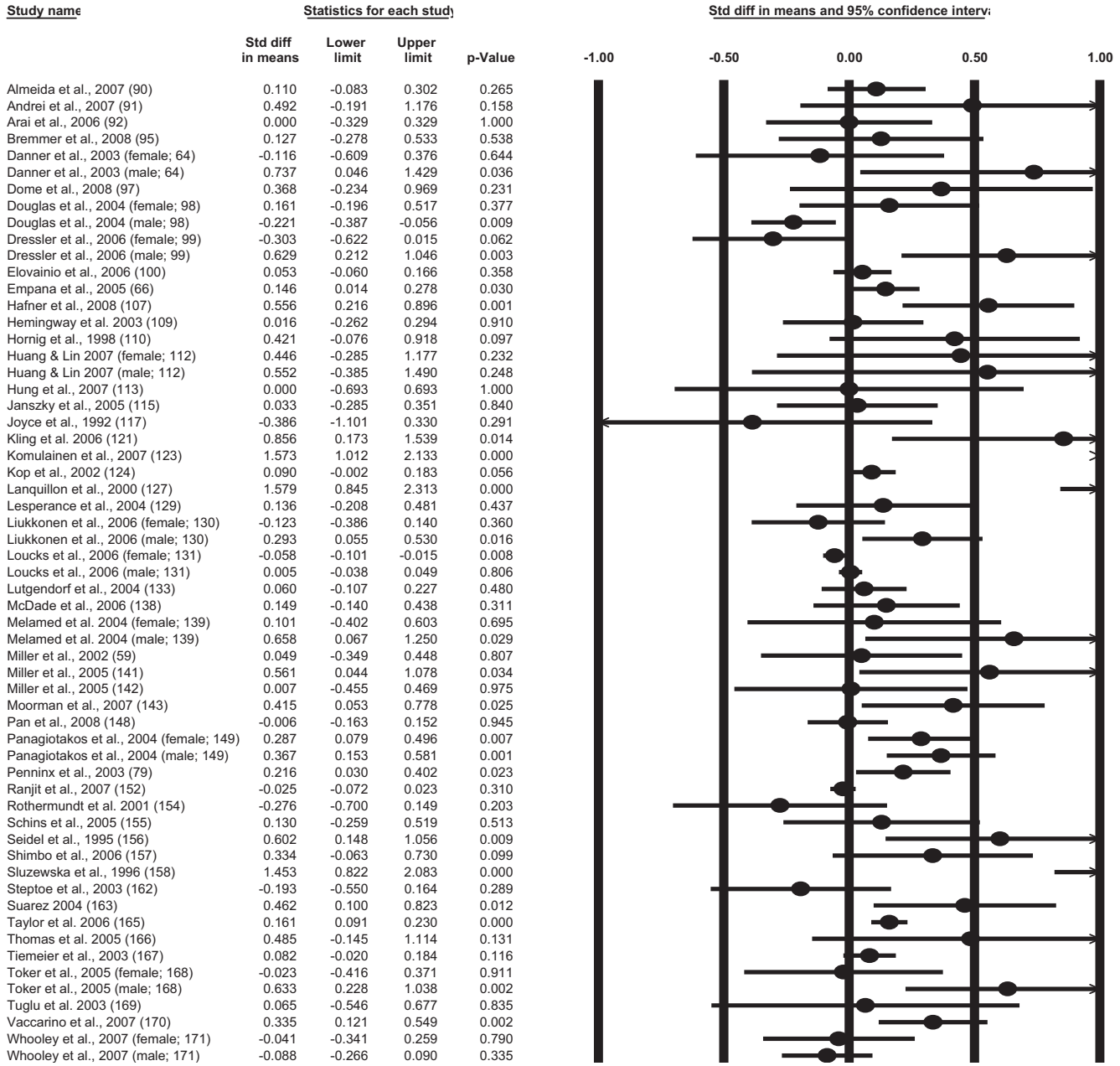

Figure 2. CRP articles included in systematic review. CRP = C-reactive protein. Corresponding reference numbers appear in parentheses.

Age and Sex

In contrast to CRP, meta-regression revealed that the association between IL-6 and depression became smaller as the mean age of the sample increased ($\beta = -0.013$, SE = 0.003, $p < .001$). Again, very few studies provided data partitioned by sex. For those samples comprised only of women ($n = 13$), the relationship was significant, $d = 0.26$, (95% CI = 0.08, 0.44), $p = .004$. In men ($n = 8$), the relationship was not significant, $d = 0.08$, (95% CI = −0.05, 0.22), $p = .24$. Meta-regression testing the moderating effect of sex on this relationship was also not significant, $\beta = 0.002$, SE = 0.002, $p = .14$.

Clinical Versus Community Samples

For studies with clinically depressed patients (versus controls; $n = 25$), the average effect size was large, $d = 0.71$ (95% CI = 0.46, 0.97), $p < .001$. If patients also had CAD-related disease ($n = 12$), the association was small but remained significant, $d = 0.10$ (95% CI = 0.00, 0.20), $p = .05$. For depressed patients who also had cancer ($n = 7$), the effect size was moderate, $d = 0.36$ (95% CI = 0.02, 0.70), $p = .04$. Studies with community-based samples also yielded a significant, positive association, $d = 0.09$ (95% CI = 0.04, 0.15), $p = .001$. Except for the subset of studies evaluating the relationship between depression and IL-6 in

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Ai et al., 2005 (88)	0.310	0.050	0.570	0.020
Alesci et al., 2005 (87)	0.576	-0.366	1.519	0.231
Allen-Mersh et al., 1998 (89)	0.000	-0.620	0.620	1.000
Andrei et al., 2007 (91)	-0.172	-0.847	0.503	0.617
Basterzi et al., 2005 (93)	0.540	-0.049	1.128	0.072
Brambilla & Maggioni, 1998 (94)	-1.074	-2.011	-0.136	0.025
Bremmer et al., 2008 (95)	0.503	0.037	0.969	0.034
Costanzo et al., 2005 (96)	0.435	-0.092	0.962	0.105
Cyranowski et al., 2007 (38)	0.242	-0.211	0.695	0.295
Empana et al., 2005 (66)	0.118	-0.014	0.250	0.080
Eskandari et al., 2007 (101)	1.890	1.040	2.739	0.000
Ferketich et al., 2005 (102)	0.112	-0.617	0.841	0.763
Ferruci et al., 2002 (103)	0.174	-0.019	0.367	0.077
Frommberger et al., 1997 (104)	2.580	1.138	4.022	0.000
Glaser et al., 2003 (105)	0.000	-0.364	0.364	1.000
Haack et al., 1999 (106)	0.150	-0.116	0.416	0.270
Hekler et al., 2007 (108)	0.374	-0.207	0.956	0.207
Hemingway et al., 2003 (109)	0.147	-0.131	0.425	0.300
Hung et al., 2007 (113)	0.000	-0.693	0.693	1.000
Jacobson et al., 2008 (114)	1.855	-0.328	4.037	0.096
Janszky et al., 2005 (115)	0.076	-0.243	0.395	0.641
Jehn et al., 2006 (116)	0.053	0.002	0.103	0.040
Kagaya et al., 2001 (118)	-0.139	-1.065	0.786	0.768
Kahl et al., 2005 (119)	0.548	-0.101	1.196	0.098
Kiecolt-Glaser et al., 2007 (120)	0.889	0.006	1.772	0.048
Koenig et al., 1997 (122)	0.120	0.025	0.215	0.013
Kubera et al., 2000 (125)	0.957	0.006	1.908	0.048
Kudoh et al., 2001 (126)	0.000	-0.572	0.572	1.000
Leo et al., 2006 (128)	1.190	0.746	1.633	0.000
Lesperance et al., 2004 (129)	0.078	-0.266	0.422	0.656
Loucks et al., 2006 (female; 131)	-0.034	-0.081	0.013	0.155
Loucks et al., 2006 (male; 131)	0.016	-0.029	0.062	0.482
Lutgendorf et al., 1999 (132)	0.484	-0.009	0.977	0.054
Lutgendorf et al., 2004 (133)	0.080	-0.100	0.260	0.384
Maes et al., 1995 (136)	1.093	0.661	1.526	0.000
Maes et al., 1997 (135)	0.889	0.260	1.519	0.006
Mikova et al., 2001 (140)	0.250	-0.379	0.880	0.436
Miller et al., 2002 (59)	0.200	-0.200	0.600	0.327
Miller et al., 2005 (141)	0.100	-0.398	0.599	0.694
Miller et al., 2005 (142)	-0.113	-0.575	0.350	0.633
Moorman et al., 2007 (143)	0.330	-0.031	0.691	0.073
Motivala et al., 2005 (144)	0.605	-0.068	1.278	0.078
Musselman et al., 2001 (cancer patients; 145)	0.990	0.060	1.920	0.037
Musselman et al., 2001 (controls; 145)	1.011	0.120	1.902	0.026
Pace et al., 2006 (147)	0.793	0.009	1.577	0.047
Pan et al., 2008 (148)	0.005	-0.147	0.158	0.944
Parissis et al., 2004 (150)	0.236	-0.435	0.908	0.490
Penninx et al., 2003 (79)	0.283	0.087	0.478	0.005
Pike & Irwin, 2006 (151)	0.681	0.110	1.251	0.019
Ranjit et al., 2007 (152)	0.001	-0.048	0.049	0.980
Rief et al., 2001 (153)	0.131	-0.329	0.590	0.577
Schins et al., 2005 (155)	0.112	-0.277	0.501	0.573
Sjogren et al., 2006 (40)	0.723	0.166	1.280	0.011
Sluzewska et al., 1995 (159)	3.128	2.083	4.174	0.000
Sluzewska et al., 1996 (158)	1.970	1.298	2.641	0.000
Song et al., 1998 (160)	1.078	0.065	2.091	0.037
Soygur et al., 2007 (cancer patients; 161)	0.895	0.364	1.426	0.001
Soygur et al., 2007 (controls; 161)	0.709	0.188	1.231	0.008
Steptoe et al., 2003 (162)	-0.059	-0.419	0.301	0.750
Suarez et al., 2003 (164)	0.000	-0.420	0.420	1.000
Tiemeier et al., 2003 (167)	0.209	0.078	0.340	0.002
Vaccarino et al., 2007 (170)	0.206	-0.006	0.418	0.057
Whooley et al., 2007 (female; 171)	0.000	-0.300	0.300	1.000
Whooley et al., 2007 (male; 171)	-0.140	-0.318	0.038	0.123
Yang et al., 2007 (172)	0.631	0.086	1.176	0.023

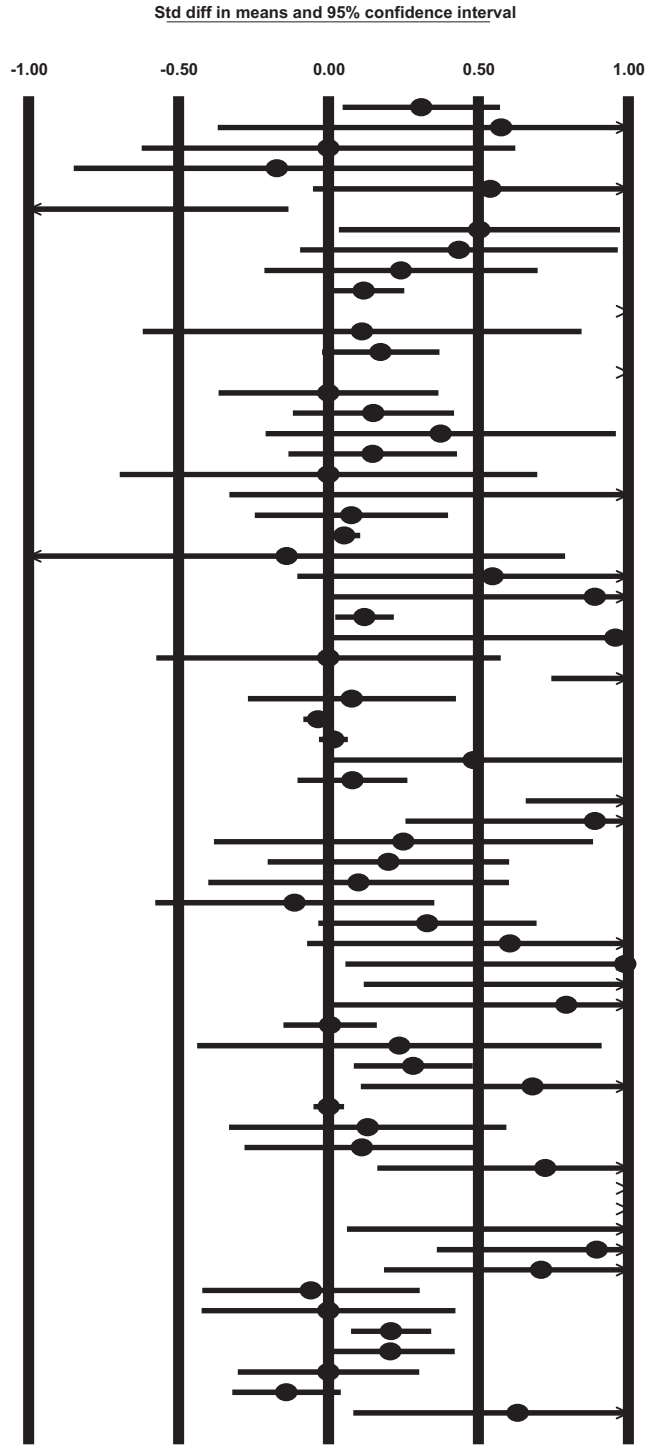

Figure 3. IL-6 articles included in systematic review. IL = interleukin. Corresponding reference numbers appear in parentheses.

those with CAD-related disease, variability among study outcomes remained even after partitioning by type of sample.

Depression Assessment

For those studies using clinical interviews to assess depression, the aggregated effect size was moderate, d = 0.52 (95% CI = 0.36, 0.67), $p < .001$. In contrast, the association for those studies using self-report instruments was much smaller, d = 0.08 (95% CI = 0.03, 0.12), p = .001.

Adjustment for Covariates

As with CRP, adjusting for BMI was consequential. Without such adjustment, the *stat d* was 0.50 (95% CI = 0.37, 0.63), $p < .001$, but with adjustment, d = 0.08 (95%

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Brambilla & Maggioni, 1998 (94)	-0.109	-0.986	0.768	0.807
Eskandari et al., 2007 (101)	1.795	0.958	2.631	0.000
Ferketich et al., 2005 (102)	-0.081	-0.809	0.648	0.828
Hekler et al., 2007 (108)	0.226	-0.349	0.802	0.441
Huang & Lee 2007 (111)	0.241	-0.194	0.675	0.277
Kagaya et al., 2001 (118)	-0.678	-1.501	0.145	0.106
Leo et al., 2006 (128)	0.985	0.552	1.418	0.000
Levine et al., 1999 (39)	1.870	0.173	3.567	0.031
Lyness et al., 2001 (134)	-0.442	-1.130	0.247	0.209
Miller et al., 2002 (59)	0.576	0.162	0.990	0.006
Moorman et al., 2007 (143)	-0.197	-0.556	0.163	0.284
Owen et al., 2001 (146)	0.768	0.126	1.410	0.019
Thomas et al., 2005 (166)	0.882	0.232	1.532	0.008
Yang et al., 2007 (172)	-0.010	-0.542	0.522	0.971

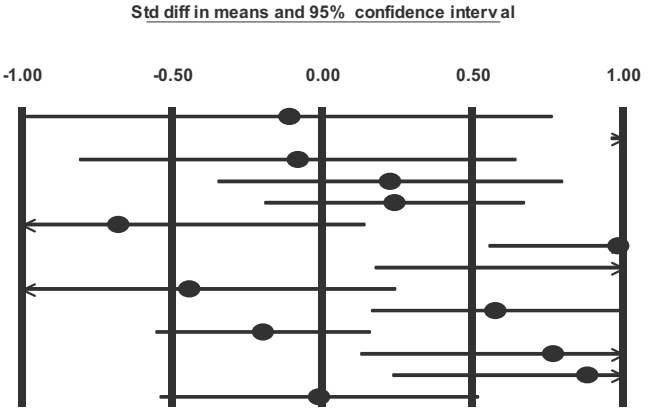

Figure 4. IL-1 articles included in systematic review. IL = interleukin. Corresponding reference numbers appear in parentheses.

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Haack et al., 1999 (106)	0.150	-0.116	0.416	0.270
Janszky et al., 2005 (115)	0.076	-0.243	0.395	0.641
Kubera et al., 2000 (125)	0.957	0.006	1.908	0.048
Maes et al., 1995 (137)	0.352	-0.225	0.930	0.232
Maes et al., 1997 (135)	0.889	0.260	1.519	0.006
Moorman et al., 2007 (143)	0.109	-0.250	0.468	0.553
Rief et al., 2001 (153)	0.131	-0.329	0.590	0.577
Song et al., 1998 (160)	1.408	0.357	2.459	0.009
Steptoe et al., 2003 (162)	-0.059	-0.419	0.301	0.750

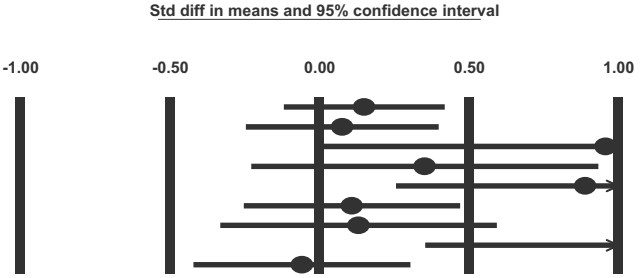

Figure 5. IL-1ra articles included in systematic review. IL-1ra = interleukin-1 receptor antagonist. Corresponding reference numbers appear in parentheses.

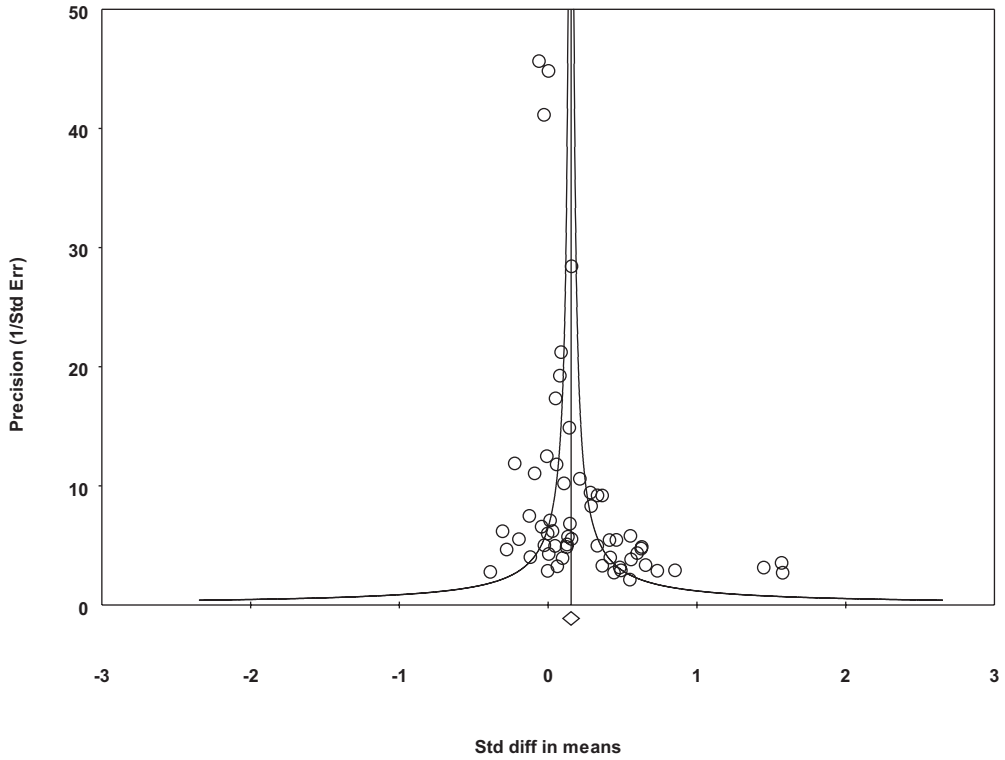

Figure 6. Funnel plot for CRP articles included in systematic review. CRP = C-reactive protein.

CI = 0.02, 0.13), $p = .007$. Analyses stratified according to control for medication use were more consistent for IL-6 than for CRP. Studies adjusting for medication use yielded a d of 0.35 (95% CI = 0.24, 0.46), $p < .001$, whereas those studies failing to control for medication use yielded a smaller effect, $d = 0.15$ (95% CI = 0.08, 0.23), $p < .001$. Subgroup analyses for antidepressants, anti-inflammatory agents, and statins followed the same pattern (Table 2).

TABLE 1. Random Effects Models for All CRP Analyses

Analysis	Number of Studies	Effect Size (*d*)	*p*	95% CI	*Q* (*df*)	Fail-Safe *N*
All Studies[a]	49[b]	0.15	<.001	0.10–0.21	234.79 (58)**	1119
Men	14	0.17	.009	0.04–0.30	56.71 (13)**	54
Women	15	0.14	.078	−0.02–0.30	65.93 (14)**	N/A
BMI adjusted	30	0.11	<.001	0.06–0.17	132.01 (38)**	321
BMI unadjusted	19	0.32	<.001	0.16–0.49	74.56 (19)**	216
Meds adjusted	24	0.23	<.001	0.12–0.33	103.05 (25)**	289
Meds unadjusted	25	0.12	.001	0.05–0.19	130.76 (31)**	242
Antidepressants adjusted	18	0.28	<.001	0.13–0.44	63.73 (19)**	154
Antidepressants unadjusted	31	0.12	<.001	0.07–0.18	160.80 (38)**	409
Anti-inflammatories adjusted	16	0.15	.015	0.03–0.27	52.77 (17)**	43
Anti-inflammatories unadjusted	33	0.16	<.001	0.10–0.23	179.68 (40)**	662
Statins adjusted	13	0.22	.005	0.07–0.37	62.89 (14)**	67
Statins unadjusted	36	0.14	<.001	0.08–0.21	171.51 (43)**	595
HRT/contraceptive adjusted	11	0.25	.010	0.06–0.44	65.92 (10)**	37
HRT/contraceptive unadjusted	34	0.15	<.001	0.08–0.22	109.13 (33)**	335
Clinical interview methods	21	0.26	.001	0.11–0.40	69.37 (23)**	154
Self-report methods	25	0.12	<.001	0.06–0.18	148.33 (31)**	298
Community sample	24	0.11	<.001	0.05–0.17	143.79 (31)**	278
Clinical sample (MDD Only)	16	0.40	.001	0.15–0.64	46.22 (15)**	109
Clinical sample (comorbid CAD-related illness)	9	0.18	.017	0.03–0.33	17.99 (9)*	21

CRP = C-reactive protein; CI = confidence interval; BMI = body mass index; Meds = medications; HRT = hormone replacement therapy; MDD = major depressive disorder; CAD = coronary artery disease.

[a] Total $N = 51{,}234$.

[b] Reflects the removal of two outliers (51,52).

* $p < .05$; ** $p \leq .001$.

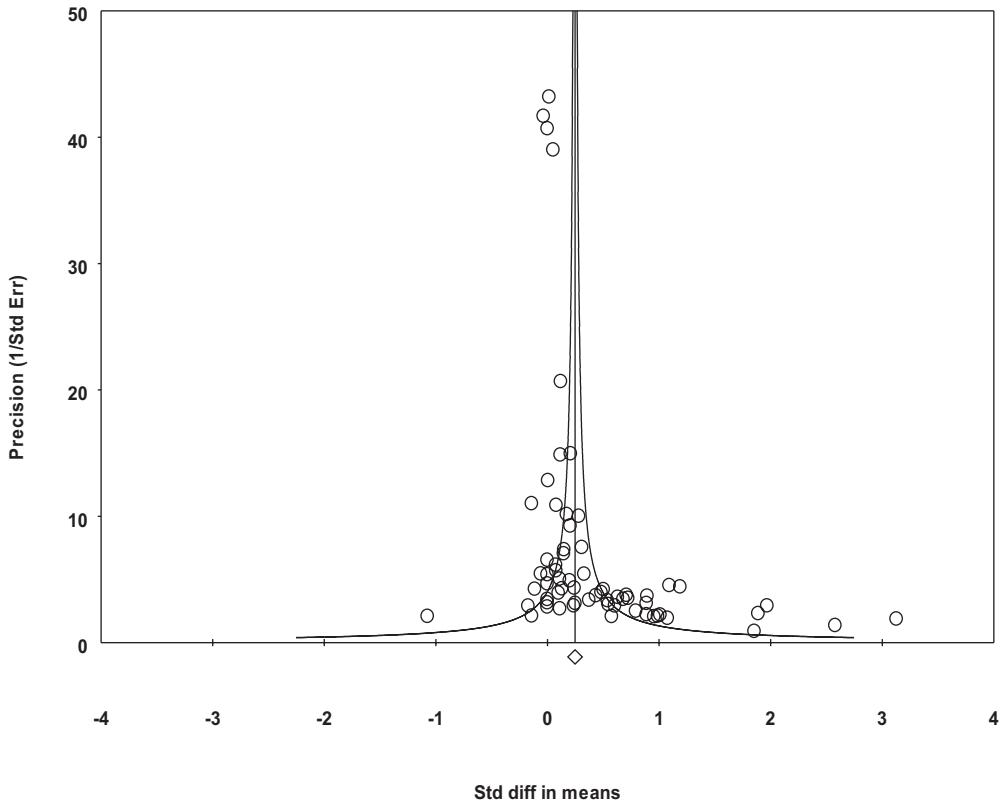

Figure 7. Funnel plot for IL-6 articles included in systematic review.

TABLE 2. Random Effects Models for All IL-6 Analyses

Analysis	Number of Studies	Effect Size (*d*)	*p*	95% CI	*Q* (*df*)	Fail-Safe *N*
All Studies[a]	61[b]	0.25	<.001	0.18–0.31	281.02 (64)**	2343
Men	8	0.08	.239	−0.05–0.22	16.97 (7)*	N/A
Women	13	0.26	.004	0.08–0.44	61.08 (13)**	58
BMI adjusted	22	0.08	.007	0.02–0.13	53.10 (23)**	56
BMI unadjusted	39	0.50	<.001	0.37–0.63	198.89 (40)**	1571
Meds adjusted	39	0.35	<.001	0.24–0.46	212.11 (41)**	1065
Meds unadjusted	22	0.15	<.001	0.08–0.23	65.32 (22)**	227
Antidepressants adjusted	31	0.46	<.001	0.31–0.61	189.75 (33)**	891
Antidepressants unadjusted	30	0.12	<.001	0.06–0.18	73.37 (30)**	318
Anti-inflammatories adjusted	28	0.34	<.001	0.22–0.46	171.24 (28)**	601
Anti-inflammatories unadjusted	33	0.20	<.001	0.12–0.28	109.55 (35)**	539
Statins adjusted	14	0.33	.003	0.11–0.55	103.87 (14)**	92
Statins unadjusted	47	0.24	<.001	0.17–0.31	175.24 (49)**	1452
HRT/contraceptive adjusted	8	0.88	.001	0.36–1.40	100.83 (7)**	116
HRT/contraceptive unadjusted	48	0.24	<.001	0.17–0.32	162.01 (49)**	1202
Clinical interview methods	34	0.52	<.001	0.36–0.67	209.93 (36)**	1129
Self-report methods	22	0.08	.001	0.03–0.12	39.19 (22)*	96
Community sample	18	0.09	.001	0.04–0.15	47.80 (18)**	111
Clinical sample (MDD only)	25	0.71	<.001	0.46–0.97	116.44 (25)**	762
Clinical sample (comorbid CAD-related illness)	12	0.10	.049	0.00–0.20	14.05 (12)***	5
Clinical sample (comorbid cancer)	7	0.36	.038	0.02–0.70	17.99 (6)*	23

IL = interleukin; CI = confidence interval; BMI = body mass index; Meds = medications; HRT = hormone replacement therapy; MDD = major depressive disorder; CAD = coronary artery disease.
[a] Total $N = 24{,}873$.
[b] Reflects the removal of one outlier (51).
* $p < .05$; ** $p \leq .001$; *** $p = .30$.

TABLE 3. Random Effects Models for All IL-1 Analyses

Analysis	Number of Studies	Effect Size (*d*)	*p*	95% CI	*Q* (*df*)	Fail-Safe *N*
All Studies[a]	14	0.35	.033	0.03–0.67	52.49 (13)**	53
BMI adjusted	6	0.39	.022	0.06–0.72	11.30 (5)*	14
BMI unadjusted	8	0.38	.169	−0.16–0.93	37.82 (7)**	N/A
Meds adjusted	7	0.28	.251	−0.20–0.76	22.43 (6)**	N/A
Meds unadjusted	7	0.42	.081	−0.05–0.89	29.04 (6)**	N/A
Clinical interview methods	10	0.41	.034	0.03–0.80	37.75 (9)**	44

IL = interleukin; CI = confidence interval; BMI = body mass index; Meds = medications.
[a] Total $N = 756$.
* $p < .05$; ** $p \leq .001$.

IL-1

Overall Analysis

Aggregating across studies, there was a moderate-sized, positive association between IL-1 and depression, $d = 0.35$ (95% CI = 0.03, 0.67), $p = .03$ (Table 3). The funnel plot for IL-1 showed little evidence of publication bias (Figure 8). In light of significant heterogeneity, subgroup analyses were conducted, but because of the small number of studies meeting inclusion criteria, some subgroup analyses were infeasible.

Age and Sex

Only one study looked solely at females; none evaluated males only. The percent of each sample comprised of female subjects and mean sample age were used as predictors of the association between depression and IL-1, but neither age nor sex emerged as moderators.

Type of Cohort

All studies utilized clinical samples (see Overall Analysis for *stat d*). As only four samples included patients with comorbid CAD-related disease, subgroup analyses were not conducted.

Depression Assessment

Ten of 14 studies utilized structured clinical interview assessments. In those studies, the aggregated effect size was significant, $d = 0.41$ (95% CI = 0.03, 0.08), $p = .03$.

Adjustment for Covariates

In studies adjusting for BMI, the *stat d* was 0.39 (95% CI = 0.06, 0.72), $p = .02$; however, without adjustment, the effect was not significant, $d = 0.38$ (95% CI = −0.16, 0.93), $p = .17$. The effect size for studies adjusting for medication use was nonsignificant (Table 3), and when no adjustment occurred, the effect

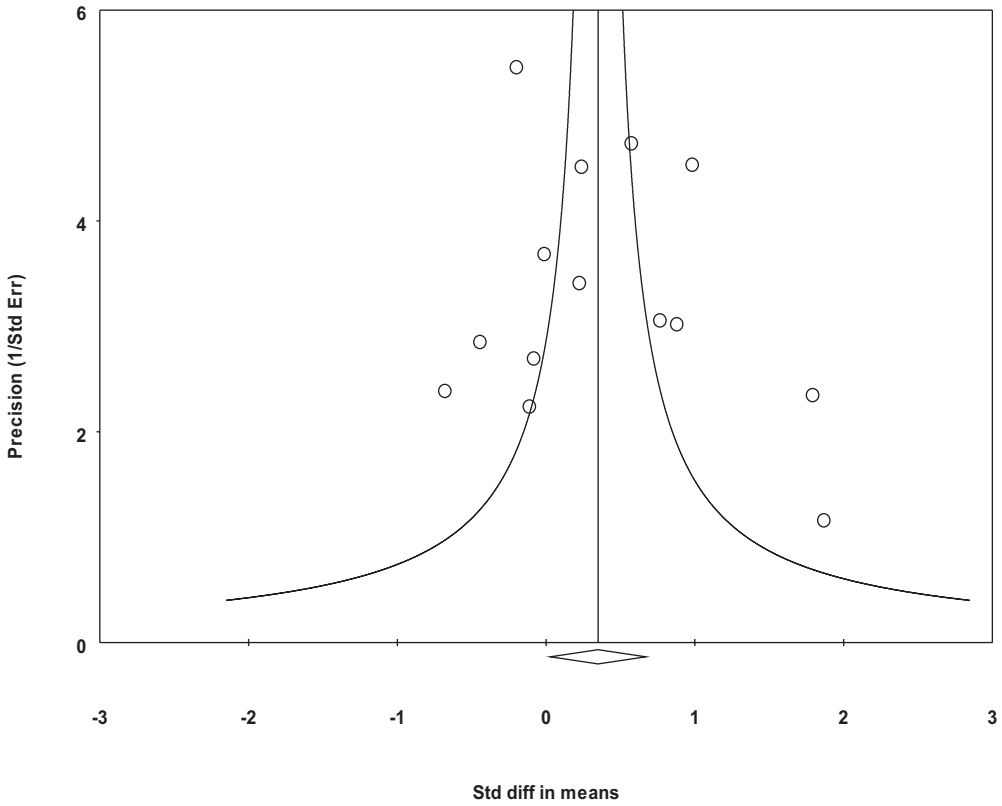

Figure 8. Funnel plot for IL-1 articles included in systematic review.

size was only marginally significant, $d = 0.42$ (95% CI = −0.05, 0.89), $p = .08$. These results may be limited by the small number of studies included in these analyses.

IL-1ra

Overall Analysis

The effect-size for IL-1ra was also significant, $d = 0.25$ (95% CI = 0.04, 0.46), $p = .019$. The funnel plot for IL-1ra, however, showed some evidence of publication bias (Figure 9). Due to significant heterogeneity, subgroup analyses were conducted. However, because of the few studies meeting inclusion criteria, only one subgroup analysis was possible for IL-1ra (Table 4).

Age and Sex

As with IL-1, only one study looked solely at females and none evaluated males only. Once again, neither age nor sex emerged as moderators of this association.

Type of Cohort

For IL-1ra, eight of nine studies evaluated clinical samples yielding a *stat d* of 0.31 (95% CI = 0.08, 0.54), $p = .009$, a larger value than for the overall analysis. As only two samples included individuals with comorbid CAD, subgroup analyses were not conducted.

DISCUSSION

To date, this is the largest quantitative review of the relationship between depression and prominent inflammatory markers and confirms that CRP, IL-6, and IL-1 (and its surrogate, IL-1ra) are positively associated with depression. This pattern is present in both clinic- and community-based samples as well as those studies using clinical interviews or self-report measures of depression. The continuity in clinic- and community-based samples suggests there is a dose-response relationship between depression and these inflammatory markers, lending strength to the contention that the cardiac (or cancer) risk conferred by depression is probably not exclusive to patient populations. The magnitude of the depression-inflammation associations, however, was substantially larger in clinical samples and when standard clinical interviews were used to evaluate depression.

Although statistically significant, the magnitude of these associations was attenuated when adjusted for BMI, specifically for CRP and IL-6. Overall, no consistent pattern emerged regarding medication use. This is likely due to the wide degree of experimental control across studies with respect to the samples' medication usage. The moderating effects of age and sex were also inconsistent. Finally, among patients with cardiac disease or cancer, depression and inflammation were positively associated. This result is consistent with evidence that CRP influences the initiation and progression of atherosclerosis (14–16) and IL-6 promotes several cancers (21,22).

Depression Assessment

Type of depression assessment makes a substantive difference in these relationships. This may partly reflect the greater

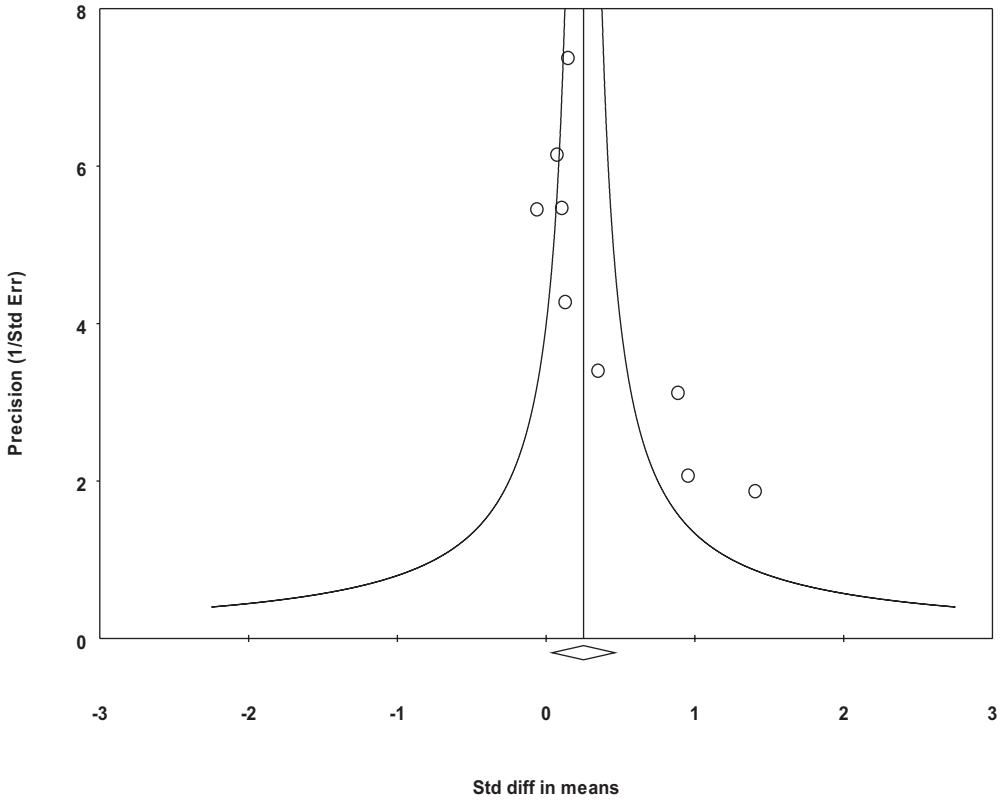

Figure 9. Funnel plot for IL-1ra articles included in systematic review.

TABLE 4. Random Effects Models for All IL-1ra Analyses

Analysis	Number of Studies	Effect Size (*d*)	*p*	95% CI	*Q* (*df*)	Fail-Safe *N*
All Studies[a]	9	0.25	.019	0.04–0.46	15.37 (8)*	23
Clinical sample (MDD only)	8	0.31	.009	0.08–0.54	13.32 (7)**	26

IL = interleukin; CI = confidence interval; MDD = major depressive disorder.
[a] Total $N = 1214$.
* $p = .05$; ** $p = .07$

sensitivity of standardized clinical interviews to detect depression and/or greater range of depressive symptomatology in clinical samples. However, because clinical interviews are more frequently used in clinic samples, it is not possible to distinguish between these two explanations with presently available evidence.

Age

The relationship between IL-6 and depression weakened as the sample's mean age increased. This may reflect the fact that, as individuals age, they exhibit greater inflammation, irrespective of whether they also manifest depressive symptoms (34,55). Experimental evidence suggests this may be a result of feedback mechanisms responsible for inhibiting inflammatory processes becoming dysregulated in aged populations (56). Overall, however, the moderating effect of age on effect size differences between depressed and nondepressed samples was inconsistent; no other inflammatory markers were significantly related to age in meta-regression analyses.

BMI

Associations of depression with both CRP and IL-6 were substantially smaller in studies that adjusted for BMI versus those that did not. The results for IL-1 were inconclusive, which may reflect the smaller number of studies assessing IL-1. In general, however, these findings likely reflect the fact that adipose tissue is an important source of IL-1, IL-6, and, thus, CRP (26,27,57,58). Miller and colleagues (59,60) proposed that depressive symptoms facilitate weight gain over time as a result of sedentary behavior (61), which in turn promotes inflammation. Additionally, they identified leptin, a neurotransmitter produced by fat cells and involved in the regulation of appetite (62), as a mediating factor. Leptin upregulates the expression of IL-6, further promoting the release of CRP. Others have speculated that depression and fat

mass affect chronic low level inflammation independently as both conditions are associated with a hypersensitive hypothalamic-pituitary-adrenal (HPA) axis (63). Because associations between CRP, IL-6, and depression remained positive and statistically significant even after adjusting for BMI, fat mass seems to play a complementary role rather than simply confounding these relationships.

Medication

Overall, no clear pattern emerged with respect to medication use. However, for both CRP and IL-6, the magnitude of associations was larger in studies that controlled for the use of medication. Several subgroup analyses based on specific classes of medication showed similar results. The overall inconsistency may be due to the wide range of medications present, including several types of statins, antidepressants, anti-inflammatory agents, several over-the-counter (OTC) and prescription medications, and oral contraceptives, all with varying degrees of immunomodulatory effects. Some studies only controlled for the use of one class of medication whereas others controlled for several; still other studies excluded participants using any form of medication. It is important that future research control for these different medications given that their anti-inflammatory effects can vary substantially (e.g., antidepressants and statins) (28–31).

Sex

Based on the few studies reporting results separately for men and women (e.g., 64–66), the role of sex differences is unclear. Depression and IL-6 were more strongly related in females than in males, but the reverse pattern was observed for CRP. As an additional complication, studies that combined data from men and women showed no (significant) relationships between depression and inflammation as the number of females in each sample increased. More research comparing men and women is needed. Additionally, studies that systematically compare pre- and postmenopausal women are warranted because of the potential confounding effects of the menstrual cycle (32,67), hormonal contraceptives (68,69), and estrogen (64,70) on CRP and IL-6 levels.

Causal Pathways

With respect to the causal direction between depression and increased inflammation, depression may lead to increased inflammation, a view recently supported by prospective, longitudinal research (71). In this literature, depression gives rise to several mediators associated with increased inflammation, including elevated sympathetic and decreased parasympathetic nervous activity as well as sedentary behavior, all of which contribute to the release of IL-6 and CRP (57,72).

A second body of research, largely articulated by Dantzer and colleagues, supports an inflammation to depression causal pathway (73). Administration of inflammatory cytokines or other inflammatory agents (e.g., experimentally induced pathology in the body) can cause a collection of sickness behaviors, such as anhedonia and sleep and appetite changes, that resemble depression (74,75). Although empirical support for the "sickness behavior model" of depression is more extensive in the animal literature, similar effects have been demonstrated in humans (76,77). In a prospective design, van den Biggelaar and colleagues (78) tested whether inflammation (i.e., CRP, IL-6, and IL-1) preceded depression and cognitive decline in older adults.[8] Notably, higher circulating levels of CRP and IL-1 at baseline predicted an accelerated increase of depressive symptoms over a 5-year follow-up period.

The positive association between depression and inflammation may also be the result of a complex, bidirectional process in which central nervous system (CNS) correlates of depression alter immunity and vice versa. For example, depression is associated with decreased parasympathetic activity in the autonomic nervous system (ANS), which results in increased inflammation in the body (72). In turn, these inflammatory processes directly influence the CNS via heightened HPA activity because proinflammatory cytokines, such as IL-6, stimulate the release of corticotrophin-releasing hormone (CRH) (79). Increased HPA activity can lead to elevated cortisol levels, which are known to initiate and/or worsen symptoms of depression (80). Much evidence supports this reciprocal hypothesis (12,81); most recently, it has also been supported longitudinally (82). Given the apparent role of BMI found in the current results, a potential tridirectional relationship among adiposity, inflammation, and depression should not be ruled out. However, elucidation of these and other causal pathways is currently hindered by the scarcity of prospective studies.

Limitations

There was marked heterogeneity across studies, the sources of which subgroup analyses were unsuccessful in identifying. The use of random-effects models, for reasons described earlier, alleviate that concern to some extent.

Second, we relied primarily on cross-sectional studies as very few prospective studies are currently available. Because combining cross-sectional and prospective data is inappropriate, we used cross-sectional data from all of the relevant studies. The present results underscore the need for investigations that track changes in depression and CRP, IL-6, and IL-1 levels over time, and experimentally control or statistically adjust for BMI and medication use.

Third, the positive effects for depression and both IL-1 and IL-1ra, albeit significant, were based on relatively few studies. The paucity of IL-1 studies, relative to IL-6 and CRP, probably results from IL-1 being difficult to detect in plasma since it works primarily at the local site of inflammation (83–85). The lack of studies assessing IL-1ra may also reflect the relatively recent discovery of this marker (i.e., 1987 versus the 1940s for IL-1) (86). Despite these limitations, however, the fact that we

[8]This study was not included in our review because it failed to provide usable cross-sectional data for depression and inflammation to compute an effect size.

observed significant effect sizes between depression and two separate indices of this inflammatory marker further reinforces our general conclusions.

Conclusions and Future Directions

The associations between depression and CRP, IL-6, and, to a lesser extent, IL-1 seem to be reliable and valid. We recommend that future investigators explore the roles of fat mass, sex-specific variables, and the use of specific classes of medications. Additionally, as the circadian pattern of IL-6 in depressed individuals has been shown to fluctuate sharply throughout the day (87), future studies should rely on multiple assessments to account for temporal variation.

It also is imperative that prospective studies of both community-based and clinical samples be undertaken to test the directionality of the relationship between depression and inflammation and to further elucidate mediating and confounding factors. Such knowledge will help inform interventions to increase the quality of life in patients with pathological inflammatory conditions, such as cardiovascular disease and cancer, and to decrease the risk of such diseases in individuals who are otherwise healthy but suffer from depression.

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