A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: Exploring the causes of heterogeneity

Sarah A. Hiles[1]; Amanda L. Baker, PhD[1]; Theo de Malmanche, MB.ChB[2]; John Attia, MD, PhD[3,4]

---

[1] Priority Research Centre for Translational Neuroscience and Mental Health, Faculty of Health, University of Newcastle, New South Wales, Australia

[2] Immunology, Hunter Area Pathology Service, John Hunter Hospital, New South Wales, Australia

[3] Centre for Clinical Epidemiology and Biostatistics, Faculty of Health, University of Newcastle, New South Wales, Australia

[4] Hunter Medical Research Institute, John Hunter Hospital, New South Wales, Australia

Short Running Title: Inflammatory markers and depression

Corresponding Author: Sarah Hiles, Priority Research Centre for Translational Neuroscience and Mental Health, University of Newcastle, Level 5, McAuley Centre, Calvary Mater Hospital, Waratah, NSW, 2308, Australia.

Phone: +61 2 40335713; Fax: +61 2 40335692

Email: Sarah.Hiles@uon.edu.au

Word count: abstract 275; article text 4312 (excluding references and tables).

Abstract

Epidemiological evidence for the inflammatory hypothesis of depression is largely cross-sectional; people with depression have elevated levels of circulating pro-inflammatory markers compared to people without depression. The limitation of cross sectional research is the potential for extraneous factors to influence observed effects. The purpose of this meta-analysis of cross-sectional studies of interleukin(IL)-6 and IL-10 in people with and without depression is to provide a targeted analysis of potential moderator factors relating to the diagnosis of depression and to physical and psychiatric comorbidity. Electronic searches of Embase and Medline databases were conducted using subject headings “interleukin-6” or “interleukin-10” and those relating to depression. Studies were included if they measured circulating marker levels in serum or plasma in a group of people with and without depressive symptoms (99 studies for IL-6, 19 studies for IL-10). IL-6 was elevated in depressed compared to non-depressed groups (d = 0.46, 99% CI 0.34 to 0.58, I^2 = 85.9%). This effect was larger in subgroups where depressive disorders were diagnosed compared to those with only depressive symptoms via standardized inventory, and those who were recruited from inpatient or outpatient settings compared to the general community. The effect was also larger in those who were not selected for a particular comorbidity compared to those selected for cardiovascular disease. IL-10 effect size was not significant (d = -0.31, 99% CI -0.95 to 0.32, I^2 = 94.1%) which was not accounted for in subgroup analyses or meta-regression, indicating there is not a global elevation in cytokines. These data highlight that comorbidity and behavioral aspects of depression need to be measured and controlled in future prospective and experimental research testing the inflammatory hypothesis of depression.

Keywords: major depressive disorder, dysthymia, inflammation, interleukin-6, interleukin-10, comorbidity, meta-analysis, systematic review.

Introduction

Depressive disorders are common and contribute substantially to disease burden (Kessler et al., 2003; Üstün et al., 2004). The key to understanding their origins may be inflammation. The theory that inflammation causes depression relies on the idea that cytokines exert central and peripheral effects which cause the psychological and physiological experience of depression (Miller et al., 2009). Inflammation is thought to cause clinical depressive disorders by inducing sickness behaviours which are akin to neurovegetative symptoms of depression (e.g., lethargy, changed appetite, changed sleep), activating the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, altering serotonin and dopamine synthesis and reuptake and causing neurodegenerative processes which lead to the phenomenology of depression (for reviews, see Dantzer et al., 2008; Irwin and Miller, 2007; Maes et al., 2009; Miller et al., 2009). Likely sources of depression-inducing cytokines include internal stressors (e.g., organic disease, adipose tissue) and external stressors (e.g., psychological distress, diet).

Animal models and some experimental human studies support the causal nature of this theory, where administration of cytokines or immune stimulants cause depression-like behaviour and symptoms, and also evidence that medical illness and inflammation-based treatments (i.e., interleukin[IL]-2 or interferon alpha treatments for hepatitis C and cancer) are linked to incidence of depressed mood or depressive disorders (Capuron et al., 2009; Dantzer et al., 2008). However, the bulk of human literature is cross sectional; people with depression or depressive symptoms have elevated levels of circulating inflammatory markers compared to those without (Dowlati et al., 2010; Howren et al., 2009). It is impossible to infer causality in this context, but these studies do permit examination of the strength of association between inflammatory markers and depressive symptoms/disorder.

Several recent meta-analyses have verified that people with depression show elevated levels of the cytokine IL-6 compared to people without depression in circulating serum or plasma (Dowlati et al., 2010; Howren et al., 2009; Liu et al., in press). IL-6 is a pleiotropic cytokine associated with inflammation, both acute and chronic, and also produced by adipose cells. Elevations in IL-6 have been associated with increases in several "trait" factors such as advancing age, high body mass index (BMI), smoking and physical comorbidity as well as "state" factors such as fat consumption, acute physical activity, and psychological stress (see O'Connor et al., 2009 for review). As people with depressive disorders frequently exhibit these lifestyle factors, there is a possibility that one or more of these is driving the observed elevations in circulating levels of inflammatory markers. This is supported in prospective studies which show that once BMI, smoking and physical activity are controlled for, the relationship between depression and IL-6 is no longer significant (Duivis et al., 2011). It is important to assess the contribution of lifestyle factors to the observed associations between depression and IL-6 to more accurately define the role of peripheral, circulating inflammatory markers as markers of an inflammatory depressive state. A second interleukin of potential interest is IL-10, a cytokine with anti-inflammatory effects which is in part stimulated by IL-6 among other factors. IL-10 is also elevated in response to acute immune challenge (Henry et al., 2009) and may be implicated in depression (Mesquita et al., 2008; Roque et al., 2009).

The current meta-analysis compares IL-6 and IL-10 in people with and without depression and is the most extensive to date. It includes a broad range of studies with different degrees of "depression" (diagnosed disorder vs. depressive symptoms), different recruitment sources and instances where depressed and control groups are matched for particular physical disease. The aim was to pool the evidence of a cross sectional association between depression and IL-6 and IL-10 in light of moderating factors to investigate whether

the elevations in inflammatory markers are attributable to the physical and psychiatric comorbidities of depressive disorders.

Methods

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) primary study comparing adult participants with non-perinatal depression (either diagnosed with major depression/dysthymia or endorsing high depressive symptoms on a standardized inventory) and a control group of people without depressive symptoms; (2) reported mean or median circulating plasma or serum IL-6 or IL-10 for both groups; (3) publication in English in a peer reviewed journal since 1990; (4) provided sufficient information to calculate an effect size, namely the means or medians of the interleukin for the depressed and non-depressed groups, sample size for each, either the standard deviations or range of interleukin levels for each group or at least an exact *p* value. Studies which measured inflammatory markers via *ex vivo* stimulation were excluded from this meta-analysis to minimize measurement error. Studies which sampled from people with a particular physical or psychiatric comorbidity (e.g., heart disease, post-traumatic stress disorder) were eligible for inclusion in this meta-analysis providing the comorbidity was present in both the depressed and non-depressed groups.

Search strategies

A computerized search of Embase and Medline databases was completed in January 2011 using the key words mapped to subject headings for depression (depression, depressive disorder, major depressive disorder, dysthymic disorder) and “interleukin-6” or “interleukin-10”, limited to human and English language literature. The abstract of each article identified in the search was screened for relevance. Full text articles were extracted and assessed for eligibility when the abstracts described measurement of inflammatory markers or when

abstracts lacked detail or were ambiguous in methods (Figure 1 shows the article extraction process; Online Supplement 1 contains references the 102 included studies).

Coding procedures

Eligible studies were coded for the outcome variable of mean or median circulating IL-6 or IL-10 and the reported dispersion measure (standard deviation, standard error, range), number of participants and, if appropriate, *p* value. Interleukin measures reported graphically were converted to numerical values using Data Thief III, version 1.6 (Tummers et al., 2008). Potential moderator variables were also coded including participant characteristics (diagnosis, depressive symptom ratings, age, gender ratio, inpatient or outpatient status, BMI, smoking status, presence of physical and psychiatric comorbidities, antidepressant use, whether the participants were matched) and assay procedure characteristics (assay brand, mood assessment and blood collection on the same day, blood samples frozen and thawed once, time of day of blood sampling, intra- and inter-assay variation). Data were extracted and re-checked by a single author (SH).

Statistical methods

Statistical analyses were completed using Comprehensive Meta-Analysis II (Biostat, Inc., USA) for study effect size calculations and Stata/SE 11.1 (StataCorp LP, USA) for meta-analysis and meta-regression. Study effect sizes were calculated as Cohen's *d* standardized mean difference of IL-6 or IL-10 between depressed and non-depressed groups. A positive effect size indicates the depressed group reported elevated interleukin compared to the non-depressed group. If required, the mean was estimated using the median when sample sizes were large ($n > 25$), or estimated using the median and range when sample sizes were small (Pudar Hozo et al., 2005). If required, standard deviation was estimated using range (Pudar Hozo et al., 2005), and if a study did not report standard deviation or range but

otherwise met selection criteria, the study effect size was estimated using the difference in means, sample size and *p* value.

Most studies only contributed one effect size to the meta-analysis. In studies where participants were followed up or underwent experimental procedure (e.g., stress test, exercise test, antidepressant treatment), the baseline measurement for that study was coded for analysis. In studies where levels of inflammatory markers were reported separately for groups with Major Depressive Disorder (MDD), elevated depressive symptoms and non-depressed controls, only the comparison between MDD and non-depressed controls was coded. For studies which reported inflammatory markers for subgroups of participants with depression, whole sample effect sizes were imputed by collapsing subgroup means. The three studies which contributed two effect sizes to the meta-analysis reported effect sizes for a depressed and non-depressed group with a particular comorbid condition and without that condition.

Individual study effect sizes were synthesized to generate an overall effect size using a random effects model, weighted by the inverse of variance. We also completed a sensitivity analysis to identify potential outliers by removing each study one by one to examine the individual influence of each study on the overall effect size. To assess publication bias, we computed a funnel plot of effect size versus study standard error and the Egger test of funnel plot asymmetry (Egger et al., 1997) and the fail-safe N (Rosenthal, 1979).

Heterogeneity was assessed using Cochrane's Q and I^2, which calculates the proportion of variation attributed to heterogeneity (Higgins et al., 2003). To explore sources of heterogeneity, moderator analysis was undertaken via subgroup analysis and residual maximum likelihood meta-regression. Subgroup analysis was completed for categorical variables, comparing pooled random effect size with separate estimates of tau for each subgroup using Z test (Borenstein et al., 2009). Meta-regression included the average magnitude and standardized mean differences of continuous variables between depressed and

non-depressed groups. To control for family-wise error, criterion for significance was set to α = .01 in all analyses.

Results

Interleukin-6

There were 99 comparisons of IL-6 in depressed and non-depressed groups from 96 publications. The majority of these studies used a diagnostic interview to diagnose depressive disorders, typically a current Major Depressive Episode (n = 67). Recruitment source of patients was mixed (inpatient n = 28; outpatient n = 39; inpatients or outpatients n = 4; community sources including cohort studies n = 19). In addition to depression, in 35 studies participants were selected for general medical or psychiatric comorbidity including cardiovascular disease (n = 15), other DSM-IV Axis I and II disorders (n = 7) and renal disease (n = 6).

Overall, IL-6 was significantly elevated in the depressed group compared to the non-depressed group, recording a moderate effect size, d = 0.46 (99% CI 0.34, 0.58), Figure 2. There was evidence of publication bias using Egger's test with a slight positive bias, b = 2.19, SE = 0.399, t (97) = 5.49, p < .001, although the fail safe-N was 9145. No outliers were found. There was significantly high heterogeneity, $Q(98) = 693.51$, $p < .001$, $I^2 = 85.9\%$.

We completed meta-analysis on more homogenous subgroups to explore sources of heterogeneity (Tables 1-3). Many subgroups provided significant effect sizes which differed in magnitude to the overall effect size and differed from other subgroups within their category, although the only subgroups to substantially decrease heterogeneity according to I^2 values (<50%) were subgroups of participants where both depressed and non-depressed groups had cardiovascular disease or cancer.

Effect of depressive disorder

First, we looked at subgroups relating to the measurement of “depression”, specifically the extent to which the “depressed” group represented depressive disorder rather than depressive symptoms and the severity of the depressive condition (Table 1). When participants in the depression group were diagnosed with a depressive disorder via a diagnostic interview, the effect size was significantly larger than when participants only endorsed high depressive symptoms on a standardized inventory. In terms of specific diagnoses, there were no significant differences in effect size between samples diagnosed with MDD only and samples which included people with a diagnosis of lifetime MDD, people with bipolar disorder in a current depressive phase and other depressive disorders (e.g., minor depression, dysthymia). Furthermore, there was no significant difference in effect sizes between participants recruited from inpatient versus outpatient sources, although a significantly smaller effect size was recorded from those recruited from community samples (e.g., cohort studies) compared with inpatient settings, indicative of some degree of variation in effect size according to severity of illness. There was also a significantly larger effect size in studies where the depressed group did not include antidepressant users compared with those that included antidepressant users, consistent with evidence that antidepressants may reduce pro-inflammatory markers (Hiles et al., in press). Finally, there was a significantly smaller effect size when the control group included participants who used antidepressants, indicating the potential presence of people in the control group with a depressive disorder without current depressive symptoms who may be diluting the difference in inflammatory markers between depressed and “non-depressed” groups. Meta-regressions on the minority of studies that reported depressive symptom inventory scores were not significant between IL-6 effect size and Hamilton Depression Rating Scale (Hamilton, 1960) score in the depressed group (36 studies) or the standardized difference in depression inventory score between depressed and non-depressed groups (32 studies).

Effect of lifestyle factors

Second, we examined subgroups related to comorbidity (Table 2). The only significant differences were smaller effect sizes in studies where all participants had cardiovascular disease or "other" comorbidity (e.g., Parkinson's disease, fibromyalgia), compared to those with participants not selected for a particular comorbidity. Studies that did not select for a particular comorbidity were not significantly different in effect size to those that selected for renal disease, psychiatric comorbidity (e.g., post-traumatic stress disorder, borderline personality disorder) or cancer. Effect size did not significantly differ depending on whether participants were normal weight or overweight/obese, or studies included or excluded smokers, and meta-regression of these as continuous variables were also not significant. However, in a restricted sample of studies where participants were not selected for particular comorbidities, there was a trend association between BMI and IL-6, where higher BMI in the depressed than the non-depressed group was associated with larger differences in IL-6 between groups, $b = 0.23$, $SE = 0.11$, $a = 0.35$, $t(19) = 2.12$, $p = .048$, $R^2 = 18.36\%$. In the entire sample, meta-regression between IL-6 effect size and the variables percentage males or average age across groups were not significant. However, there was a significant positive relationship between IL-6 effect size and the standardized difference of ages, where IL-6 effect size increased as the age in the depressed group became larger than the age in the control group; $b = 0.39$, $SE = 0.16$, $a = 0.42$, $t(80) = 2.47$, $p = .016$, $R^2 = 10.82\%$.

Sensitivity analyses

Finally, we examined the sensitivity of our analyses (Table 3). Compared with the overall analysis with broad inclusion criteria, the effect size was significantly larger for studies where participants were diagnosed with MDD and not selected for comorbid conditions (similar sample to previous meta-analyses; Dowlati et al., 2010; Liu et al., in

press). There was a significantly smaller effect size in those studies which did not match for any variables compared with those that matched for age and gender and studies where effect size was estimated from the median compared to the mean. There were no significant differences in several other factors related to the sensitivity of measurement, including whether the study collected mood and blood measures on the same day, reported freezing and thawing blood samples once, or sampling blood in the morning. There was also no significant difference in effect size between two common assay suppliers. No meta-regression related to IL-6 measurement sensitivity was significant.

Interleukin-10

19 studies of IL-10 were available. As with IL-6, most of these studies diagnosed depressive disorder via diagnostic interview (n = 13), although these studies tended to recruit patients from outpatient sources (*n* = 14; inpatient *n* = 3; mixed inpatients and outpatients *n* = 1; community *n* = 1). Few studies selected for comorbidities (cardiovascular *n* = 2; renal *n* = 2; other *n* = 2). Blood was sampled in the morning. The effect size between depressed and non-depressed groups was non-significant, *d* = -0.31 (99% CI -0.95, 0.32), Figure 3. However, there was no evidence of publication bias via Egger's test, $t(18) = 0.23$, $p = .82$. There was significant heterogeneity, $Q(18) = 306.02$, $p < .001$, $I^2 = 94.1\%$. In the subgroup analyses, there were some subgroups with no statistical heterogeneity according to I^2, although these had only 2-3 studies; these included studies which reported whether they included or excluded people with anxiety disorders and those studies where we used the median to estimate the effect size (subgroup data not shown). The only significant subgroup at $\alpha = .01$ level was the overweight/obese subgroup where this effect was negative (*d* = -2.15 [99% CI -4.17, -0.14]), and significantly different to the positive effect size for the normal weight subgroup (normal weight subgroup *d* = 1.07 [99% CI -0.80, 2.94]; effect size difference = 3.22 [99% CI 0.47, 5.97]). No meta-regression was significant.

Discussion

In this updated literature search we found a moderate and significant effect size with IL-6 elevated in depressed compared to non-depressed groups, consistent with the magnitude and direction of IL-6 effect size in previous meta-analyses (Dowlati et al., 2010; Howren et al., 2009; Liu et al., in press). However, there was high heterogeneity, such that interpretation of the overall effect size is done with caution, and this heterogeneity was only partly explained by subgroup analyses. Effect size was larger in the subgroup of studies with diagnosed MDD and no known comorbid conditions (similar to criteria of Dowlati et al., 2010; Liu et al., in press) than for the broader inclusion criteria. We expanded on subgroup analyses reported previously (Howren et al., 2009), demonstrating that aspects related to the operational definition of depression and comorbid conditions affected the magnitude of the effect size. The findings of the subgroup analyses not only help explain past discrepancies between individual study results but also have implications for the design and interpretation of future studies into depression and inflammation.

First, differences in IL-6 between depressed and non-depressed groups appear to be magnified when studies more closely approximate the complexity of the DSM-IV criteria for depression through a diagnostic interview (i.e., verification that behavioral and cognitive criteria are met, differential diagnoses examined) or more severe experiences of depression obtained through inpatient or outpatient rather than community recruitment settings. This is not unlike studies which show that patients with melancholic features (emphasis on somatic symptoms, often regarded as a more severe form of depression) have different immune profiles to those with non-melancholic features (Maes et al., 2012; Rothermundt et al., 2001). However, these relationships are not always apparent (Marques-Deak et al., 2007). Furthermore, modest relationships have been observed between acute psychological stress or negative mood induction (possibly mediated via neuroendocrine stress and sympathetic

nervous system activity) and increased pro-inflammatory markers, and between acute immune challenge and temporary depressive mood (Reichenberg et al., 2001; Steptoe et al., 2007). Subgroup analysis also showed that effect size is smaller when there is evidence that the "non-depressed" control groups contains participants who may have recent/current experience of a depressive disorder, but are currently not reporting depressive symptoms due to antidepressant treatment. Furthermore, effect size is smaller when the depressed group contains antidepressant users, who may be subject to the anti-inflammatory properties of antidepressants or have fewer emotional and behavioral aspects of depression which would otherwise be contributing to their pro-inflammatory state (Hiles et al., in press; Tynan et al., 2012). These findings are consistent with the expectation that "loose" definitions of case and control would tend to bias towards the null, indicating the need to get "tight" case and control definitions in order to best identify any differences. Consistent reporting of depressive symptom inventory scores and perhaps separate reporting of neurovegetative and cognitive-emotional may lead to a clearer relationship between symptom severity and effect size particularly in a more homogenous sample of studies.

Second, depression is substantially comorbid with physical and psychiatric conditions (Evans et al., 2005; Rush et al., 2005; Van der Kooy et al., 2007), most of which also have pro-inflammatory associations. For instance, adiposity is thought to considerably contribute to levels of circulating IL-6, vascular inflammation is thought to cause atherosclerosis, and anxiety is associated with increased levels of pro-inflammatory markers most likely via neuroendocrine and nervous system stress activation (O'Donovan et al., 2010; Pitsavos et al., 2006; Rocha and Libby, 2009; Shelton and Miller, 2010). Compared to studies that did not select for a particular comorbidity, presence of cardiovascular disease, renal disease, cancer and other psychiatric conditions reduced the effect size between depressed and non-depressed groups, significantly so for cardiovascular disease. These results suggest that inflammatory

cytokines are influenced by many disease processes and these obscure the association of cytokines with depression. Studies that match for age and gender had a significantly and substantially larger effect size than those that did not. Age matching is important, as highlighted through the meta-regression where IL-6 effect size increases as the difference in age between the depressed group and control group increases. This is again consistent with the expectation that removing confounding influences on cytokine levels from other factors, such as age, allows the association with depression to be more clearly detected. However, there is also some preliminary evidence that as BMI becomes higher in the depressed group compared to the non-depressed group, IL-6 effect size increases; this raises the possibility that there may be some synergy or interaction between depression and other disease processes in raising cytokine levels.

One final issue examined in our subgroup analyses was sensitivity of IL-6 measurement. As expected, we observed a smaller effect size when effect size was estimated from the median, rather than the mean, but importantly, each effect size was positive and significant. No significant differences in effect size were observed in any other sensitivity analyses or meta-regression (regarding mood assessed the same day as blood collection, samples frozen and thawed once, time of blood collection, assay supplier, intra- and inter-assay variation). These may reflect genuine indifferences of effect size to these measurement issues, or perhaps that they require routine description in this literature to more accurately identify their role and ensure that effect sizes are more likely to represent genuine between-group differences.

Despite clear evidence that the pro-inflammatory marker IL-6 is elevated across most studies, to date, IL-10 has given conflicting signals in people with and without depression. There was no significant effect size for IL-10 which could not be accounted for in subgroup analyses or meta-regression. At this stage, the reason for disparity across human studies is

unclear. Generally, IL-10 and IL-6 have some association, with IL-6 alone or with other cytokines increasing production of IL-10 (for instance, via STAT3 in Th17 cells which are pathogenic in several autoimmune disorders) and IL-10 regulating and inhibiting pro-inflammatory responses in various cells (Dantzer et al., 2008; Ouyang et al., 2011; Saraiva and O'Garra, 2010). Animal research indicates there may be a relationship between IL-10 and depressive behavior such as helplessness and changes in sleep patterns (Mesquita et al., 2008; Toth and Opp, 2001) and research in human populations has indicated that in MDD there may be a deregulation of the association between IL-6 and IL-10 as shown via lack of correlation between these cytokines in depressed but not non-depressed samples (Dhabhar et al., 2009). Absolute levels of cytokines may therefore be less important than relative levels (Dantzer et al., 2008). Perhaps a greater number of homogenous studies are required for a clear pattern to emerge or relative levels, or ratios of cytokines might be more relevant in future meta-analyses.

Heterogeneity was not substantially reduced or explained in any of our subgroup analyses or meta-regression, including those related to measurement considerations. While this high heterogeneity caused by the non-restrictive inclusion criteria means the size of the effect size estimates may be unreliable, the criteria has helped satisfy our aim of developing a set of exploratory subgroup analyses and meta-regression to explore the circumstances under which effects are strongest and weakest. It is possible that combinations of factors or other untested factors may explain the high heterogeneity.

There are other behavioral aspects of depression that we could not capture in this meta-analysis, but are important to consider for the primary researcher. One feature of DSM-IV-TR criteria for Major Depressive Episode missed in this meta-analysis is sleep. Pro-inflammatory cytokines generally help regulate the sleep-wake cycle, although in high levels can promote somnolence as would occur during acute inflammation and deprivation of sleep

can also increase some pro-inflammatory markers (Kapsimalis et al., 2008). A relationship between difficulty initiating sleep and elevated IL-6 in people with MDD has been observed (Motivala et al., 2005). Pro-inflammatory cytokines have been independently associated with other behaviors related to DSM-IV-TR criteria such as fatigue (Raison et al., 2009), suicidal behavior (Janelidze et al., 2011; Kim et al., 2008), transient guilt (Dickerson et al., 2004), and cognitive problems and psychomotor slowing (Brydon et al., 2008; Reichenberg et al., 2001). Understanding the role of each is important for developing a comprehensive inflammation-based theory of depression.

The pooled effect seen in this meta-analysis of cross-sectional studies does not shed light on the directionality of causation between depression and inflammation. It is consistent with the idea that cytokines influence a variety of behavioral aspects including appetite, sleep and fatigue let alone mood symptoms and concentration difficulties; therefore a larger pro-inflammatory cytokine response would provide a broader depressive symptom profile. It is also consistent with the idea that the behavioral aspects of depression occur prior to (or simultaneously with) and cause the observed elevated pro-inflammatory markers. This is impossible to verify in the cross sectional context, but it highlights that the pattern of depressive symptoms is important. Prospective research has focused on depressive symptoms as the operational definition of depression, demonstrating that elevations in pro-inflammatory markers both precede and follow depressive symptoms (Hamer et al., 2009; Matthews et al., 2010). The few which have been completed using diagnosis have shown that levels of inflammatory markers can predict *de novo* depressive disorder (Pasco et al., 2010). Additionally, often in the context of general medical illness, randomized controlled trials have indicated that psychological or antidepressant treatment for depression may reduce pro-inflammatory markers and improve immune functioning, administration of antidepressants can reduce depression induced by treatment with pro-inflammatory cytokines such as

interferon, and administration of anti-inflammatory medications such as etanercept and celecoxib can reduce depressive symptoms (Andersen et al., 2004; Kraus et al., 2008; Muller et al., 2006; Pizzi et al., 2009; Tyring et al., 2006). This meta-analysis informs the design of future necessary prospective and human experimental literature in how to operationally define depression, recruit patients and control for comorbidity, in the context of methodological and measurement rigor.

References

Andersen, B.L., Farrar, W.B., Golden-Kreutz, D.M., Glaser, R., Emery, C.F., Crespin, T.R., Shapiro, C.L., Carson, W.E., 2004. Psychological, behavioral, and immune changes after a psychological intervention: A clinical trial. J. Clin. Oncol. 22, 3570-3580.

Borenstein, M., Hedges, L.V., Higgins, J.P.T., Rothstein, H.R., 2009. Introduction to Meta-analysis. John Wiley & Sons, Ltd., Chichester.

Brydon, L., Harrison, N.A., Walker, C., Steptoe, A., Critchley, H.D., 2008. Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans. Biol. Psychiatry 63, 1022-1029.

Capuron, L., Fornwalt, F.B., Knight, B.T., Harvey, P.D., Ninan, P.T., Miller, A.H., 2009. Does cytokine-induced depression differ from idiopathic major depression in medically healthy individuals? J. Affect. Disord. 119, 181-185.

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: When the immune system subjugates the brain. Nat. Rev. Neurosci. 9, 46-56.

Dhabhar, F.S., Burke, H.M., Epel, E.S., Mellon, S.H., Rosser, R., Reus, V.I., Wolkowitz, O.M., 2009. Low serum IL-10 concentrations and loss of regulatory association between IL-6 and IL-10 in adults with major depression. J. Psychiatr. Res. 43, 962-969.

Dickerson, S.S., Kemeny, M.E., Aziz, N., Kim, K.H., Fahey, J.L., 2004. Immunological effects of induced shame and guilt. Psychosom. Med. 66, 124-131.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctôt, K.L., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatry 67, 446-457.

Duivis, H.E., de Jonge, P., Penninx, B.W., Ya Na, B.C., B E, Whooley, M.A., 2011. Depressive symptoms, health behaviors, and subsequent inflammation in patients with coronary heart disease: Prospective findings from the Heart and Soul Study. Am. J. Psychiatry 168, 913-920.

Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. Br. Med. J. 315, 629-634.

Evans, D.L., Charney, D.S., Lewis, L., Golden, R.N., Gorman, J.M., Krishnan, K.R.R., Nemeroff, C.B., Bremner, J.D., Carney, R.M., Coyne, J.C., Delong, M.R., Frasure-Smith, N., Glassman, A.H., Gold, P.W., Grant, I., Gwyther, L., Ironson, G., Johnson, R.L., Kanner, A.M., Katon, W.J., Kaufmann, P.G., Keefe, F.J., Ketter, T., Laughren, T.P., Leserman, J., Lyketsos, C.G., McDonald, W.M., McEwen, B.S., Miller, A.H., Musselman, D., O'Connor, C., Petitto, J.M., Pollock, B.G., Robinson, R.G., Roose, S.P., Rowland, J., Sheline, Y., Sheps, D.S., Simon, G., Spiegel, D., Stunkard, A., Sunderland, T., Tibbits, J.P., Valvo, W.J., 2005. Mood disorders in the medically ill: Scientific review and recommendations. Biol. Psychiatry 58, 175-189.

Hamer, M., Molloy, G.J., de Oliveira, C., Demakakos, P., 2009. Persistent depressive symptomatology and inflammation: To what extent do health behaviours and weight control mediate this relationship? Brain. Behav. Immun. 23, 413-418.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56-62.

Henry, C.J., Huang, Y., Wynne, A.M., Godbout, J.P., 2009. Peripheral lipopolysaccharide (LPS) challenge promotes microglial hyperactivity in aged mice that is associated with exaggerated induction of both pro-inflammatory IL-1β and anti-inflammatory IL-10 cytokines. Brain. Behav. Immun. 23, 309-317.

Higgins, J.P.T., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. Br. Med. J. 327, 557-560.

Hiles, S.A., Baker, A.L., de Malmanche, T., Attia, J., in press. Interleukin-6, C-reactive protein and interleukin-10 after antidepressant treatment in people with depression: A meta-analysis. Psychol. Med.

Howren, M.B., Lamkin, D.M., Suls, J., 2009. Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. Psychosom. Med. 71, 171-186.

Irwin, M.R., Miller, A.H., 2007. Depressive disorders and immunity: 20 years of progress and discovery. Brain. Behav. Immun. 21, 374-383.

Janelidze, S., Mattei, D., Westrin, A., Träskman-Bendz, L., Brundin, L., 2011. Cytokine levels in the blood may distinguish suicide attempters from depressed patients. Brain. Behav. Immun. 25, 335-339.

Kapsimalis, F., Basta, M., Varouchakis, G., Gourgoulianis, K., Vgontzas, A., Kryger, M., 2008. Cytokines and pathological sleep. Sleep Medicine 9 (6), 603-614.

Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., Rush, A.J., Walters, E.E., Wang, P.S., 2003. The epidemiology of Major Depressive Disorder: Results from the National Comorbidity Survey Replication. JAMA, J. Am. Med. Assoc. 289, 3095-3105.

Kim, Y.-K., Lee, S.-W., Kim, S.-H., Shim, S.-H., Han, S.-W., Choi, S.-H., Lee, B.-H., 2008. Differences in cytokines between non-suicidal patients and suicidal patients in major depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 32, 356-361.

Kraus, M.R., Schäfer, A., Schöttker, K., Keicher, C., Weissbrich, B., Hofbauer, I., Scheurlen, M., 2008. Therapy of interferon-induced depression in chronic hepatitis C with citalopram: A randomised, double-blind, placebo-controlled study. Gut 57, 531-536.

Liu, Y., Ho, R.C.-M., Mak, A., in press. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: A meta-analysis and meta-regression. J. Affect. Disord.

Maes, M., Mihaylova, I., Kubera, M., Ringel, K., 2012. Activation of cell-mediated immunity in depression: Association with inflammation, melancholia, clinical staging and the fatigue and somatic symptom cluster of depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 36, 169-175.

Maes, M., Yirmyia, R., Noraberg, J., Brene, S., Hibbeln, J., Perini, G., Kubera, M., Bob, P., Lerer, B., Maj, M., 2009. The inflammatory and neurodegenerative hypothesis of depression: Leads for future research and new drug developments in depression. Metab. Brain Dis. 24, 27-53.

Marques-Deak, A.H., Neto, F.L., Dominguez, W.V., Solis, A.C., Kurcgant, D., Sato, F., Ross, J.M., Prado, E.B.A., 2007. Cytokine profiles in women with different subtypes of major depressive disorder. J. Psychiatr. Res. 41, 152-159.

Matthews, K.A., Schott, L.L., Bromberger, J.T., Cyranowski, J.M., Everson-Rose, S.A., Sowers, M., 2010. Are there bi-directional associations between depressive symptoms and C-reactive protein in mid-life women? Brain. Behav. Immun. 24, 96-101.

Mesquita, A.R., Correia-Neves, M., Roque, S., Castro, A.G., Vieira, P., Pedrosa, J., Palha, J.A., Sousa, N., 2008. IL-10 modulates depressive-like behavior. J. Psychiatr. Res. 43, 89-97.

Miller, A.H., Maletic, V., Raison, C.L., 2009. Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. Biol. Psychiatry 65, 732-741.

Motivala, S.J., Sarfatti, A., Olmos, L., Irwin, M.R., 2005. Inflammatory markers and sleep disturbance in major depression. Psychosom. Med. 67, 187-194.

Muller, N., Schwarz, M.J., Dehning, S., Douhe, A., Cerovecki, A., Goldstein-Muller, B., Spellmann, I., Hetzel, G., Maino, K., Kleindienst, N., Moller, H.J., Arolt, V., Riedel, M., 2006. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. Mol. Psychiatry 11, 680-684.

O'Connor, M.-F., Bower, J.E., Cho, H.J., Creswell, J.D., Dimitrov, S., Hamby, M.E., Hoyt, M.A., Martin, J.L., Robles, T.F., Sloan, E.K., Thomas, K.S., Irwin, M.R., 2009. To assess, to control, to exclude: Effects of biobehavioral factors on circulating inflammatory markers. Brain. Behav. Immun. 23, 887-897.

O'Donovan, A., Hughes, B.M., Slavich, G.M., Lynch, L., Cronin, M.-T., O'Farrelly, C., Malone, K.M., 2010. Clinical anxiety, cortisol and interleukin-6: Evidence for specificity in emotion-biology relationships. Brain. Behav. Immun. 24, 1074-1077.

Ouyang, W., Rutz, S., Crellin, N.K., Valdez, P.A., Hymowitz, S.G., 2011. Regulation and functions of the IL-10 family of cytokines in inflammation and disease. Annu. Rev. Immunol. 29, 71-109.

Pasco, J.A., Nicholson, G.C., Williams, L.J., Jacka, F.N., Henry, M.J., Kotowicz, M.A., Schneider, H.G., Leonard, B.E., Berk, M., 2010. Association of high-sensitivity C-reactive protein with de novo major depression. Br. J. Psychiatry 197, 372-377.

Pitsavos, C., Panagiotakos, D.B., Papageorgiou, C., Tsetsekou, E., Soldatos, C., Stefanadis, C., 2006. Anxiety in relation to inflammation and coagulation markers, among healthy adults: The ATTICA Study. Atherosclerosis 185, 320-326.

Pizzi, C., Mancini, S., Angeloni, L., Fontana, F., Manzoli, L., Costa, G.M., 2009. Effects of selective serotonin reuptake inhibitor therapy on endothelial function and inflammatory markers in patients with coronary heart disease. Clin. Pharmacol. Ther. 86, 527-532.

Pudar Hozo, S., Djulbegovic, B., Hozo, I., 2005. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med. Res. Methodol. 5.

Raison, C.L., Lin, J.-M.S., Reeves, W.C., 2009. Association of peripheral inflammatory markers with chronic fatigue in a population-based sample. Brain. Behav. Immun. 23, 327-337.

Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., Morag, A., Pollmacher, T., 2001. Cytokine-associated emotional and cognitive disturbances in humans. Arch. Gen. Psychiatry 58, 445-452.

Rocha, V.Z., Libby, P., 2009. Obesity, inflammation, and atherosclerosis. Nat. Rev. Cardiol. 6, 399-409.

Roque, S., Correia-Neves, M., Mesquita, A.R., Palha, J.A., Sousa, N., 2009. Interleukin-10: A key cytokine in depression? Cardiovascular Psychiatry and Neurology 2009, 1-5.

Rosenthal, R., 1979. The file drawer problem and tolerance for null results. Psychol. Bull. 86, 638-641.

Rothermundt, M., Arolt, V., Fenker, J., Gutbrodt, H., Peters, M., Kirchner, H., 2001. Different immune patterns in melancholic and non-melancholic major depression. Eur. Arch. Psychiatry Clin. Neurosci. 251, 90-97.

Rush, A.J., Zimmerman, M., Wisniewski, S.R., Fava, M., Hollon, S.D., Warden, D., Biggs, M.M., Shores-Wilson, K., Shelton, R.C., Luther, J.F., Thomas, B., Trivedi, M.H., 2005. Comorbid psychiatric disorders in depressed outpatients: Demographic and clinical features. J. Affect. Disord. 87, 43-55.

Saraiva, M., O'Garra, A., 2010. The regulation of IL-10 production by immune cells. Nat. Rev. Immunol. 10, 170-181.

Shelton, R.C., Miller, A.H., 2010. Eating ourselves to death (and despair): The contribution of adiposity and inflammation to depression. Prog. Neurobiol. 91, 275-299.

Steptoe, A., Hamer, M., Chida, Y., 2007. The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. Brain. Behav. Immun. 21, 901-912.

Toth, L.A., Opp, M.R., 2001. Cytokine- and microbially induced sleep responses of interleukin-10 deficient mice. Am. J. Physiol. Regul. Integr. Comp. Physiol. 280, R1806-R1814.

Tummers, B., van der Laan, J., Huyser, K., 2008. Data Thief III, http://datathief.org/.

Tynan, R.J., Weidenhofer, J., Hinwood, M., Cairns, M.J., Day, T.A., Walker, F.R., 2012. A comparative examination of the anti-inflammatory effects of SSRI and SNRI antidepressants on LPS stimulated microglia. Brain. Behav. Immun. 26, 469-479.

Tyring, S., Gottlieb, A., Papp, K., Gordon, K., Leonardi, C., Wang, A., Lalla, D., Woolley, M., Jahreis, A., Zitnik, R., Cella, D., Krishnan, R., 2006. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: Double-blind placebo-controlled randomized phase III trial. Lancet 367, 29-35.

Üstün, T.B., Ayuso-Mateos, J.L., Chatterji, S., Mathers, C., Murray, C.J.L., 2004. Global burden of depressive disorders in the year 2000. Br. J. Psychiatry 184, 386-392.

Van der Kooy, K., van Hout, H., Marwijk, H., Marten, H., Stehouwer, C., Beekman, A., 2007. Depression and the risk for cardiovascular diseases: Systematic review and meta analysis. Int. J. Geriatr. Psychiatry 22, 613-626.

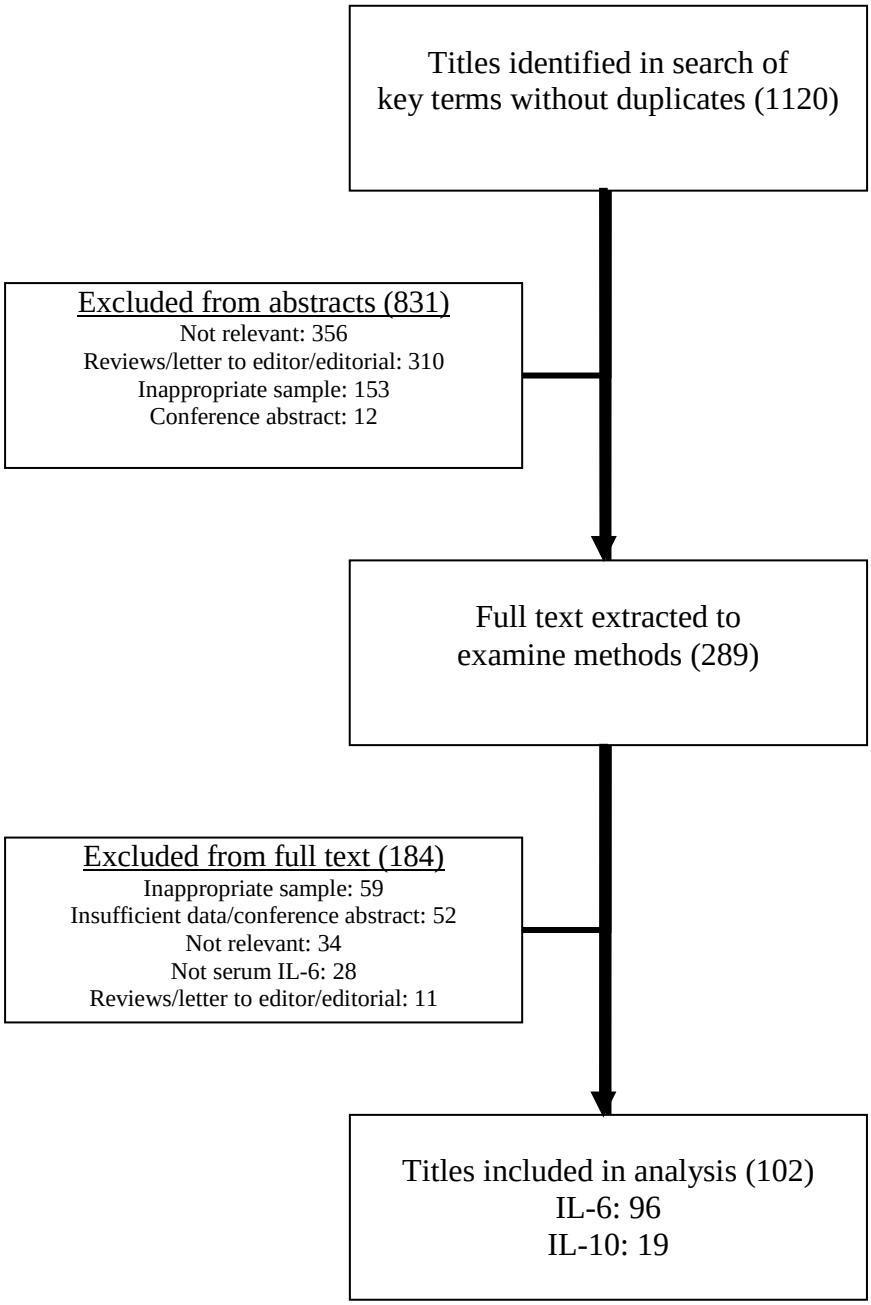

Figure 1. Summary of article extraction process and reasons for exclusion for the IL-6 and IL-10 meta-analyses. "Inappropriate samples" includes participants without depression or a control group, participants who are pregnant or undergoing cytokine treatment, and adolescents.

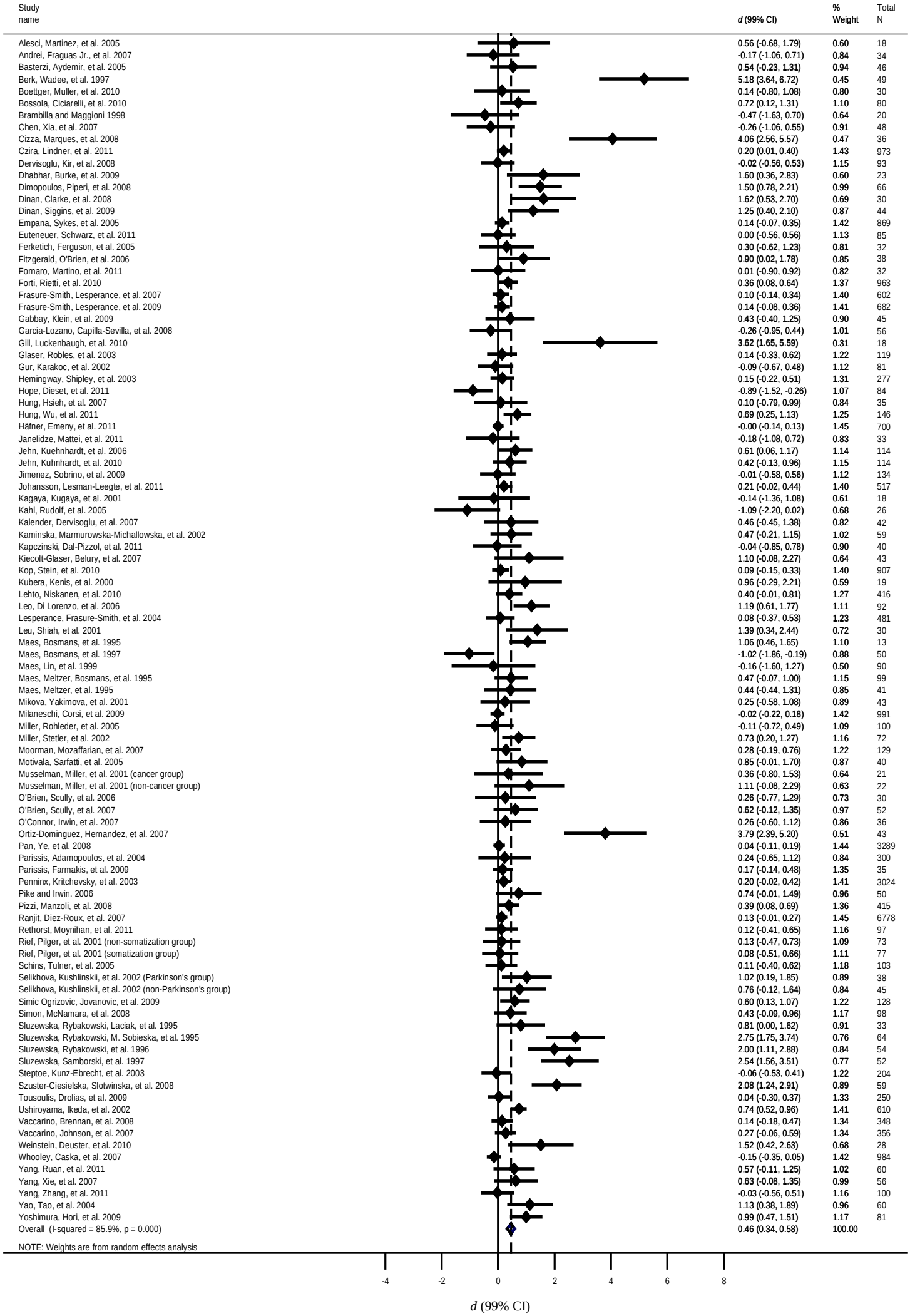
Study name
d (99% CI)
% Weight
Total N
Alesci, Martinez, et al. 2005 0.56 (-0.68, 1.79) 0.60 18
Andrei, Fraguas Jr., et al. 2007 -0.17 (-1.06, 0.71) 0.84 34
Basterzi, Aydemir, et al. 2005 0.54 (-0.23, 1.31) 0.94 46
Berk, Wadee, et al. 1997 5.18 (3.64, 6.72) 0.45 49
Boettger, Muller, et al. 2010 0.14 (-0.80, 1.08) 0.80 30
Bossola, Ciciarelli, et al. 2010 0.72 (0.12, 1.31) 1.10 80
Brambilla and Maggioni 1998 -0.47 (-1.63, 0.70) 0.64 20
Chen, Xia, et al. 2007 -0.26 (-1.06, 0.55) 0.91 48
Cizza, Marques, et al. 2008 4.06 (2.56, 5.57) 0.47 36
Czira, Lindner, et al. 2011 0.20 (0.01, 0.40) 1.43 973
Dervisoglu, Kir, et al. 2008 -0.02 (-0.56, 0.53) 1.15 93
Dhabhar, Burke, et al. 2009 1.60 (0.36, 2.83) 0.60 23
Dimopoulos, Piperi, et al. 2008 1.50 (0.78, 2.21) 0.99 66
Dinan, Clarke, et al. 2008 1.62 (0.53, 2.70) 0.69 30
Dinan, Siggins, et al. 2009 1.25 (0.40, 2.10) 0.87 44
Empana, Sykes, et al. 2005 0.14 (-0.07, 0.35) 1.42 869
Euteneuer, Schwarz, et al. 2011 0.00 (-0.56, 0.56) 1.13 85
Ferketich, Ferguson, et al. 2005 0.30 (-0.62, 1.23) 0.81 32
Fitzgerald, O'Brien, et al. 2006 0.90 (0.02, 1.78) 0.85 38
Fornaro, Martino, et al. 2011 0.01 (-0.90, 0.92) 0.82 32
Forti, Rietti, et al. 2010 0.36 (0.08, 0.64) 1.37 963
Frasure-Smith, Lesperance, et al. 2007 0.10 (-0.14, 0.34) 1.40 602
Frasure-Smith, Lesperance, et al. 2009 0.14 (-0.08, 0.36) 1.41 682
Gabbay, Klein, et al. 2009 0.43 (-0.40, 1.25) 0.90 45
Garcia-Lozano, Capilla-Sevilla, et al. 2008 -0.26 (-0.95, 0.44) 1.01 56
Gill, Luckenbaugh, et al. 2010 3.62 (1.65, 5.59) 0.31 18
Glaser, Robles, et al. 2003 0.14 (-0.33, 0.62) 1.22 119
Gur, Karakoc, et al. 2002 -0.09 (-0.67, 0.48) 1.12 81
Hemingway, Shipley, et al. 2003 0.15 (-0.22, 0.51) 1.31 277
Hope, Dieset, et al. 2011 -0.89 (-1.52, -0.26) 1.07 84
Hung, Hsieh, et al. 2007 0.10 (-0.79, 0.99) 0.84 35
Hung, Wu, et al. 2011 0.69 (0.25, 1.13) 1.25 146
Häfner, Emeny, et al. 2011 -0.00 (-0.14, 0.13) 1.45 700
Janelidze, Mattei, et al. 2011 -0.18 (-1.08, 0.72) 0.83 33
Jehn, Kuehnhardt, et al. 2006 0.61 (0.06, 1.17) 1.14 114
Jehn, Kuhnhardt, et al. 2010 0.42 (-0.13, 0.96) 1.15 114
Jimenez, Sobrino, et al. 2009 -0.01 (-0.58, 0.56) 1.12 134
Johansson, Lesman-Leegte, et al. 2011 0.21 (-0.02, 0.44) 1.40 517
Kagaya, Kugaya, et al. 2001 -0.14 (-1.36, 1.08) 0.61 18
Kahl, Rudolf, et al. 2005 -1.09 (-2.20, 0.02) 0.68 26
Kalender, Dervisoglu, et al. 2007 0.46 (-0.45, 1.38) 0.82 42
Kaminska, Marmurowska-Michallowska, et al. 2002 0.47 (-0.21, 1.15) 1.02 59
Kapczinski, Dal-Pizzol, et al. 2011 -0.04 (-0.85, 0.78) 0.90 40
Kiecolt-Glaser, Belury, et al. 2007 1.10 (-0.08, 2.27) 0.64 43
Kop, Stein, et al. 2010 0.09 (-0.15, 0.33) 1.40 907
Kubera, Kenis, et al. 2000 0.96 (-0.29, 2.21) 0.59 19
Lehto, Niskanen, et al. 2010 0.40 (-0.01, 0.81) 1.27 416
Leo, Di Lorenzo, et al. 2006 1.19 (0.61, 1.77) 1.11 92
Lesperance, Frasure-Smith, et al. 2004 0.08 (-0.37, 0.53) 1.23 481
Leu, Shiah, et al. 2001 1.39 (0.34, 2.44) 0.72 30
Maes, Bosmans, et al. 1995 1.06 (0.46, 1.65) 1.10 13
Maes, Bosmans, et al. 1997 -1.02 (-1.86, -0.19) 0.88 50
Maes, Lin, et al. 1999 -0.16 (-1.60, 1.27) 0.50 90
Maes, Meltzer, Bosmans, et al. 1995 0.47 (-0.07, 1.00) 1.15 99
Maes, Meltzer, et al. 1995 0.44 (-0.44, 1.31) 0.85 41
Mikova, Yakimova, et al. 2001 0.25 (-0.58, 1.08) 0.89 43
Milaneschi, Corsi, et al. 2009 -0.02 (-0.22, 0.18) 1.42 991
Miller, Rohleder, et al. 2005 -0.11 (-0.72, 0.49) 1.09 100
Miller, Stetler, et al. 2002 0.73 (0.20, 1.27) 1.16 72
Moorman, Mozaffarian, et al. 2007 0.28 (-0.19, 0.76) 1.22 129
Motivala, Sarfatti, et al. 2005 0.85 (-0.01, 1.70) 0.87 40
Musselman, Miller, et al. 2001 (cancer group) 0.36 (-0.80, 1.53) 0.64 21
Musselman, Miller, et al. 2001 (non-cancer group) 1.11 (-0.08, 2.29) 0.63 22
O'Brien, Scully, et al. 2006 0.26 (-0.77, 1.29) 0.73 30
O'Brien, Scully, et al. 2007 0.62 (-0.12, 1.35) 0.97 52
O'Connor, Irwin, et al. 2007 0.26 (-0.60, 1.12) 0.86 36
Ortiz-Dominguez, Hernandez, et al. 2007 3.79 (2.39, 5.20) 0.51 43
Pan, Ye, et al. 2008 0.04 (-0.11, 0.19) 1.44 3289
Parissis, Adamopoulos, et al. 2004 0.24 (-0.65, 1.12) 0.84 300
Parissis, Farmakis, et al. 2009 0.17 (-0.14, 0.48) 1.35 35
Penninx, Kritchevsky, et al. 2003 0.20 (-0.02, 0.42) 1.41 3024
Pike and Irwin. 2006 0.74 (-0.01, 1.49) 0.96 50
Pizzi, Manzoli, et al. 2008 0.39 (0.08, 0.69) 1.36 415
Ranjit, Diez-Roux, et al. 2007 0.13 (-0.01, 0.27) 1.45 6778
Rethorst, Moynihan, et al. 2011 0.12 (-0.41, 0.65) 1.16 97
Rief, Pilger, et al. 2001 (non-somatization group) 0.13 (-0.47, 0.73) 1.09 73
Rief, Pilger, et al. 2001 (somatization group) 0.08 (-0.51, 0.66) 1.11 77
Schins, Tulner, et al. 2005 0.11 (-0.40, 0.62) 1.18 103
Selikhova, Kushlinskii, et al. 2002 (Parkinson's group) 1.02 (0.19, 1.85) 0.89 38
Selikhova, Kushlinskii, et al. 2002 (non-Parkinson's group) 0.76 (-0.12, 1.64) 0.84 45
Simic Ogrizovic, Jovanovic, et al. 2009 0.60 (0.13, 1.07) 1.22 128
Simon, McNamara, et al. 2008 0.43 (-0.09, 0.96) 1.17 98
Sluzewska, Rybakowski, Laciak, et al. 1995 0.81 (0.00, 1.62) 0.91 33
Sluzewska, Rybakowski, M. Sobieska, et al. 1995 2.75 (1.75, 3.74) 0.76 64
Sluzewska, Rybakowski, et al. 1996 2.00 (1.11, 2.88) 0.84 54
Sluzewska, Samborski, et al. 1997 2.54 (1.56, 3.51) 0.77 52
Steptoe, Kunz-Ebrecht, et al. 2003 -0.06 (-0.53, 0.41) 1.22 204
Szuster-Ciesielska, Slotwinska, et al. 2008 2.08 (1.24, 2.91) 0.89 59
Tousoulis, Drolias, et al. 2009 0.04 (-0.30, 0.37) 1.33 250
Ushiroyama, Ikeda, et al. 2002 0.74 (0.52, 0.96) 1.41 610
Vaccarino, Brennan, et al. 2008 0.14 (-0.18, 0.47) 1.34 348
Vaccarino, Johnson, et al. 2007 0.27 (-0.06, 0.59) 1.34 356
Weinstein, Deuster, et al. 2010 1.52 (0.42, 2.63) 0.68 28
Whooley, Caska, et al. 2007 -0.15 (-0.35, 0.05) 1.42 984
Yang, Ruan, et al. 2011 0.57 (-0.11, 1.25) 1.02 60
Yang, Xie, et al. 2007 0.63 (-0.08, 1.35) 0.99 56
Yang, Zhang, et al. 2011 -0.03 (-0.56, 0.51) 1.16 100
Yao, Tao, et al. 2004 1.13 (0.38, 1.89) 0.96 60
Yoshimura, Hori, et al. 2009 0.99 (0.47, 1.51) 1.17 81
Overall (I-squared = 85.9%, p = 0.000) 0.46 (0.34, 0.58) 100.00
NOTE: Weights are from random effects analysis
-4
-2
0
2
4
6
8
d (99% CI)

Figure 2. Forest plot of standardized mean difference IL-6 between depressed and non-depressed groups for each study (Cohen's *d*, 99% CI). A positive effect size indicates that IL-6 is elevated in the depressed compared with the non-depressed group. The pooled effect size is provided as the black diamond at the bottom of the figure.

Table 1. Subgroup analyses for IL-6 related to depression, including the *N* number of studies included in each subgroup, subgroup effect sizes (ES; Cohen's *d*) and the difference in ES between subgroups relative to a reference category (denoted with "Ref").

Subgroups		**Subgroup effect sizes**				**Difference between subgroups**		
		N	**ES *(d)***	**99% CI**		**I^2 (%)**	**ES_{diff}**	**99% CI**	
Diagnostic interview	Yes	67	0.68***	0.46	0.91	87.9	Ref		
	No	32	0.20***	0.09	0.30	71.8	0.48***	0.23	0.73
Diagnosis	MDD	40	0.60***	0.36	0.84	80.1	Ref		
	No diagnosis	32	0.20***	0.09	0.30	71.8	0.40***	0.14	0.66
	MDD or lifetime MDD	5	0.38	-0.41	1.17	86.7	0.22	-0.61	1.05
	Other depression	12	0.49**	0.08	0.90	82.5	0.11	-0.37	0.59
	Includes people with bipolar depressive phase	10	1.53**	0.12	2.94	95.7	-0.93	-2.36	0.50
Patient source	Inpatient	28	0.65***	0.29	1.01	89.9	Ref		
	Outpatient	39	0.43***	0.24	0.63	78.3	0.22	-0.19	0.63
	Community	19	0.17***	0.05	0.28	67.1	0.48***	0.10	0.86
	Mixed in- & outpatients	4	0.13	-1.04	1.30	83.7	0.52	-0.70	1.74
Depressed group has antidepressant users	Yes	31	0.26***	0.09	0.43	81.8	Ref		
	No	41	0.80***	0.49	1.10	86.8	-0.54***	-0.89	-0.19
Control group has antidepressant users	Yes	16	0.08	-0.05	0.21	67.1	Ref		
	No	45	0.66***	0.40	0.93	84.0	-0.58***	-0.87	-0.29

***<.001, **<.01, *<.05; Note: Other depression includes minor depression, dysthymia, depression not otherwise specified.

Table 2. Subgroup analyses for IL-6 related to comorbidity.

Subgroups		**Subgroup effect sizes**				**Difference between subgroups**		
		N	**ES (*d*)**	**99% CI**		**I^2 (%)**	**ES_{diff}**	**99% CI**	
Comorbidity	None	64	0.66***	0.49	0.83	89.0	Ref		
	Cardiovascular	15	0.10*	-0.01	0.20	18.3	0.56***	0.36	0.76
	Renal	6	0.43***	0.01	0.75	67.1	0.23	-0.22	0.68
	Psychiatric	7	0.08	-0.83	0.99	85.0	0.58	-0.35	1.51
	Cancer	3	0.50***	0.13	0.87	0	0.16	-0.25	0.57
	Other	4	0.002	-0.54	0.54	54.7	0.66**	0.09	1.23
People with anxiety in depressed group	Excluded	19	0.51***	0.16	0.87	76.6	Ref		
	Included	9	0.65**	0.01	1.29	88.5	-0.14	-0.87	0.59
BMI	Normal weight	11	0.16	-0.14	0.44	65.3	Ref		
	Overweight/obese	30	0.26***	0.10	0.43	83.8	-0.10	-0.44	0.24
Smokers	Yes	38	0.29***	0.15	0.42	84.2	Ref		
	No	5	0.33	-0.31	0.98	78.6	-0.04	-0.70	0.62

***<.001, **<.01,*<.05

Table 3. Subgroup analyses for IL-6 related to measurement sensitivity.

Subgroup		**Subgroup effect sizes**				**Difference between subgroups**		
		N	**ES (*d*)**	**99% CI**		**I^2 (%)**	**ES_{diff}**	**99%CI**	
Definition sensitivity	Overall	99	0.46***	0.34	0.58	85.9	Ref		
	MDD diagnosis & no comorbidity	31	0.74***	0.44	1.04	80.3	-0.28*	-0.60	0.04
Matched	Age, gender	15	0.91***	0.35	1.46	91.3	Ref		
	Age, gender, BMI	7	1.10**	0.08	2.11	85.7	-0.19	-1.35	0.97
	Other matching	7	0.99**	0.13	1.85	87.9	-0.08	-1.11	0.95
	No matching	70	0.31***	0.19	0.43	81.8	0.60**	0.03	1.17
ES estimated from	Yes	27	0.23***	0.10	0.36	74.3	Ref		
median	No	72	0.58***	0.39	0.76	87.6	-0.35***	-0.58	-0.12
Mood assessed/blood	Yes	13	0.30	-0.12	0.73	83.4	Ref		
collected same day	No	9	0.41	-0.23	1.05	86.4	-0.11	-0.88	0.66
Samples frozen and	Yes	21	0.63	0.23	1.02	91.5	Ref		
thawed once	Unknown	78	0.43	0.30	0.55	83.1	0.20	-0.22	0.62
Morning sampling	Yes	58	0.59	0.38	0.80	87.4	Ref		
	No	3	0.38	-0.53	1.29	65.8	0.21	-0.72	1.14
Assay suppliers	R&D Quantikine ELISA, MN	36	0.29***	0.14	0.43	82.0	Ref		
	Sandwich ELISA, Eurogenetics	12	0.78	0.04	1.52	90.5	-0.49	-1.25	0.27

***<.001, **<.01,*<.05; Note: other matching includes age, gender, ethnicity, BMI, other demographics.

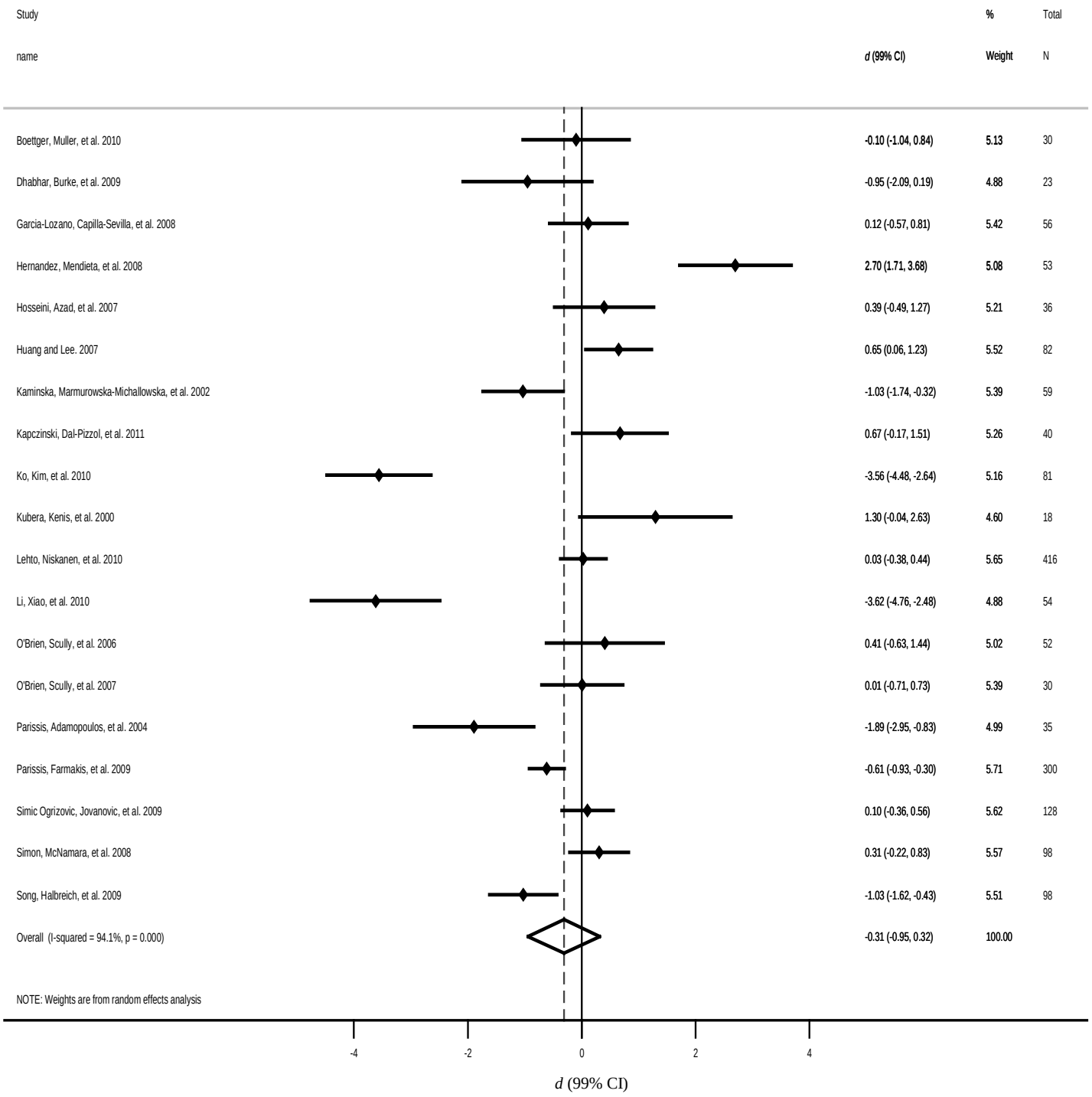

Figure 3. Forest plot of standardized mean difference IL-10 between depressed and non-depressed groups for each study (Cohen's *d*, 99% CI). A positive effect size indicates that IL-10 is elevated in the depressed compared with the non-depressed group.