Original article

Impact of data extraction errors in meta-analyses on the association between depression and peripheral inflammatory biomarkers: An umbrella review

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ABSTRACT

Background: Accumulating evidence suggests that alterations in inflammatory biomarkers are important in depression. However, previous meta-analyses disagree on these associations, and errors in data extraction may account for these discrepancies.

Methods: PubMed/MEDLINE, Embase, PsycINFO, and the Cochrane Library were searched from database inception to January 14, 2020. Meta-analyses of observational studies examining the association between depression and levels of tumor necrosis factor-alpha (TNF- α), interleukin 1-beta (IL-1β), interleukin-6 (IL-6), and C-reactive protein (CRP) were eligible. Errors were classified as follows: incorrect sample sizes, incorrectly used standard deviation, incorrect participant inclusion, calculation error, or analysis with insufficient data. We determined their impact on the results after correction thereof.

Results: Errors were noted in 14 of the 15 meta-analyses included. Across 521 primary studies, 118 (22.6%) showed the following errors: incorrect sample sizes (20 studies, 16.9%), incorrect use of standard deviation (35 studies, 29.7%), incorrect participant inclusion (7 studies, 5.9%), calculation errors (33 studies, 28.0%) and analysis with insufficient data (23 studies, 19.5%). After correcting these errors, 11 (29.7%) out of 37 pooled effect sizes changed by a magnitude of more than 0.1, ranging from 0.11 to 1.15. The updated meta-analyses showed that elevated levels of TNF- α, IL-6, CRP, but not IL-1β, are associated with depression.

Conclusions: These findings show that data extraction errors in meta-analyses can impact findings. Efforts to reduce such errors are important in studies of the association between depression and peripheral inflammatory biomarkers, for which high heterogeneity and conflicting results have been continuously reported.

Keywords: data extraction error; depression; inflammatory biomarker; meta-analysis; umbrella review

Introduction

A growing body of evidence indicates that alterations in immune-inflammatory pathways play important roles in the pathophysiology of depression (Maes, 1995, Miller and Raison, 2016). Compared with healthy controls, patients with depression show elevated blood levels of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin 1-beta (IL-1β), and IL-6 (Howren *et al.*, 2009, Liu *et al.*, 2012). In addition, C-reactive protein (CRP), an acute-phase reactant, has also been found to be elevated in depression (Wium-Andersen *et al.*, 2013).

However, given the number of primary studies reporting conflicting results on the associations between inflammatory biomarkers and depression, meta-analyses are typically employed as a state-of-the-art empirical summary, integrating data across multiple primary studies and providing a more reliable answer to a research question than a single study (Berlin and Golub, 2014). Nonetheless, whilst several meta-analyses have attempted to clarify the associations between depression and inflammatory biomarkers, they have still reported inconsistent findings (D'Acunto *et al.*, 2019, Dowlati *et al.*, 2010, Goldsmith *et al.*, 2016, Howren *et al.*, 2009, Kohler *et al.*, 2017, Liu *et al.*, 2012, Ng *et al.*, 2018, Osimo *et al.*, 2019, Perrin *et al.*, 2019). Although elevated peripheral levels of TNF-α were associated with depression in some meta-analyses (Dowlati *et al.*, 2010, Goldsmith *et al.*, 2016, Kohler *et al.*, 2017, Liu *et al.*, 2012, Perrin *et al.*, 2019), others reported no association between them (D'Acunto *et al.*, 2019, Ng *et al.*, 2018). Likewise, IL-1β was associated with depression in several meta-analyses (Howren *et al.*, 2009, Ng *et al.*, 2018), but not in others (D'Acunto *et al.*, 2019, Dowlati *et al.*, 2010, Goldsmith *et al.*, 2016, Kohler *et al.*, 2017, Liu *et al.*, 2012, Perrin *et al.*, 2019).

Errors in data extraction can be one potential explanation for why different meta-analyses

reach different conclusions for the same research question. Investigators who have attempted to replicate published meta-analyses found that 59%–100% contain errors (Ford *et al.*, 2010, Gotzsche *et al.*, 2007, Jones *et al.*, 2005). Such errors in data extraction can lead to overestimating or nullifying the significance of the results. For example, when performing a meta-analysis, it is sometimes necessary to standardize measurements on a uniform scale, such as standardized mean difference (SMD), before pooling across primary studies. During this process, sample sizes may be incorrectly exported (Park *et al.*, 2017), and standard errors (SEs) may be mistaken for standard deviations (SDs), which can substantially inflate point estimates and heterogeneity (Gotzsche *et al.*, 2007). Inaccuracy in calculation (Messori *et al.*, 1993) and data analysis with incomplete information (Buscemi *et al.*, 2006) can also occur during data extraction.

To address this, we selected four peripheral inflammatory biomarkers, TNF-α, IL-1β, IL-6, and CRP, which have been extensively investigated in relation to depression. Then, we examined errors in meta-analyses of the association between depression and the four peripheral inflammatory biomarkers. We employed an umbrella review of meta-analyses to evaluate the presence, frequency, and nature of errors in data extraction and their impact on the results. Furthermore, we corrected the errors and then re-estimated the meta-analytical associations between depression and these peripheral inflammatory biomarkers. Finally, we collected all primary studies included in the meta-analyses and calculated the updated total pooled effect sizes (ESs) of the association between depression and the inflammatory biomarkers. With the updated ESs, we aimed to evaluate the association of the immune-inflammatory pathway with depression.

Methods

The protocol for this study was registered in PROSPERO (CRD42019133888). We adhered to the Preferred Reported Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Moher *et al.*, 2009) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup *et al.*, 2000) (Supplementary Appendix 1 in the Supplement).

Search Strategy and Selection Criteria

Four investigators (SL, KMP, SJP, and WJK) searched PubMed/MEDLINE, Embase, PsycINFO, and the Cochrane Library for articles published between database inception and January 14, 2020 using the search terms (CRP OR IL-1beta OR IL-6 OR TNF-alpha) AND depress* AND meta using the [All Fields] search tag for all terms. The searching process was initially performed until February 11, 2019 and then repeated until January 14, 2020 to update the newly published meta-analyses. The full names and abbreviations of all four peripheral inflammatory biomarkers were employed in the search strategy. We chose eligible articles by consecutively screening their titles and abstracts, followed by their full texts (Figure 1). Disagreements were resolved via discussion among the authors SL, KHL, EL, and JIS.

We included meta-analyses of observational cross-sectional studies examining the association between unipolar or bipolar depression (Dargél *et al.*, 2015, Fernandes *et al.*, 2016, Goldsmith *et al.*, 2016, Rowland *et al.*, 2018) and levels of TNF-α, IL-1β, IL-6, or CRP in circulating blood (plasma/serum). ES metrics as outcome were limited to SMD [Cohen's d], Hedges' g, mean difference, or odds ratio, which are obtained from comparisons of the depressive and normal group. Some meta-analyses included primary studies for any

depressive disorder and others included only studies on major depressive disorders. Our definition of depression followed that of each original meta-analysis. The international prospective register of systematic reviews (PROSPERO) registration status was evaluated. We screened articles written in English or at least those with titles and abstracts in English and only included meta-analyses that reported ESs for individual primary studies or the data necessary for their calculation. Hereinafter, we have used the term "overlapping meta-analyses" to indicate meta-analyses of the same association between depression and an inflammatory biomarker, and "overlapping studies" to indicate primary studies that were included in more than one meta-analysis.

Data Extraction

From each meta-analysis, four investigators (SL, KMP, SJP, and WJK) extracted the first author, publication date, literature search date, inflammatory biomarker of interest, model of analysis (e.g., fixed effect or random effects), sample sizes, maximally adjusted individual study estimates and corresponding 95% confidence intervals (CIs), and ES metrics presented for results (e.g., SMD [Cohen's *d*], Hedges' *g*, mean difference, or odds ratio). From the primary studies included in the meta-analyses, we extracted sample sizes and means ± SDs, means ± SEs, or medians and interquartile ranges (IQRs) for each inflammatory biomarker. If data were presented in terms of a median and IQR, the calculation method for their conversion to mean ± SD was investigated. If a study compared two or more subgroups of depression to the same control, we combined the subgroups to create a single pair-wise comparison. A few primary studies that reported stimulated levels of inflammatory biomarkers from *in vitro* assays were found in one meta-analysis (Perrin *et al.*, 2019). In this case, extracted data were used for evaluation of the detection of errors and recalculation of

ESs in the meta-analysis, but not in the calculation of total pooled results from all primary studies. If data were presented only in graphs, they were extracted with GetData Graph Digitizer (version 2.26) (GetData Graph Digitizer, 2013). If there were any discrepancies in extracted data among individual raters, the most appropriate data were selected through consensus-building discussion.

Data Analysis

We recalculated ESs and 95% CIs of primary studies included in the meta-analyses and reanalyzed each meta-analysis accordingly. Pooled ESs, 95% CIs, and p-values were recalculated using Comprehensive Meta-Analysis (version 3.3.070, Biostat, Englewood, NJ, USA). The level of statistical significance was set at $p < 0.05$.

To evaluate discrepancies between initial and re-estimated results, we applied 0.1 as a cut-off point in accordance with previous studies that also evaluated data extraction errors and disagreements of results in meta-analyses (Gotzsche *et al.*, 2007, Tendal *et al.*, 2009). Meanwhile, we followed the ES metrics of the original meta-analyses (i.e., SMD, Hedges' *g*, mean difference, or odds ratio) in recalculation. If our recalculated results for an ES or its CI differed from those of a primary study reported in the meta-analysis by 0.1 or more, this was regarded as a change in results. Then, we thoroughly investigated the reason of the difference. If an error was identified during the investigation, this was classified as either "incorrect sample sizes," "incorrectly used SD," "incorrect participant inclusion," "calculation error," or "analysis with insufficient data," as indicated below. We defined a case in which sample sizes in a primary study were wrongly extracted as incorrect sample sizes. If an extracted SD from a primary study was incorrect, the case was regarded as an incorrectly used SD. When a primary study that did not meet the inclusion criteria of each meta-analysis was included, the

case was defined as incorrect participant inclusion. Calculation error was defined as a case in which the reported effect size was inaccurate despite no errors in reported primary study data for calculating effect size. If not enough information with which to calculate SMD was provided in a primary study, the case was classified as an analysis with insufficient data.

We conducted data analysis as follows. At first, we evaluated the presence and type of errors in all primary studies in each meta-analysis. Next, we re-evaluated errors in only overlapping studies included in more than one meta-analysis. If data were extracted directly from previous meta-analyses, not from primary studies, and an error in the previous meta-analyses was noted, there was a chance of error duplication from the previous meta-analyses. Thus, we recalculated pooled ESs of the meta-analyses after correcting all errors. If there was a case in which an initial pooled ES was different by more than 0.1 from our recalculated value, this was presented as a "change in result." Lastly, we gathered all primary studies included in the meta-analyses and calculated total pooled ESs and the 95% CIs of associations between depression and the four peripheral inflammatory biomarkers using a random effects model and SMD as an ES metric. To assess heterogeneity among primary study ESs, the I^2 index was calculated. We assessed the presence of publication bias using funnel plots and Egger's tests. Data in primary studies presented with SEs were converted to SDs, and calculation methods for converting medians and IQRs to means and SDs were applied in recalculation, if necessary (Luo *et al.*, 2018, Wan *et al.*, 2014). If ESs were presented with metrics other than SMD, we recalculated SMD with the information provided in the primary studies.

Results

Database

A total of 517 potentially eligible articles were retrieved by the literature search (Figure 1). During the screening process, 502 articles were excluded, with 15 articles included for analyses (Table 1) (Bizik, 2010, D'Acunto *et al.*, 2019, Dargél *et al.*, 2015, Dowlati *et al.*, 2010, Ellul *et al.*, 2016, Fernandes *et al.*, 2016, Goldsmith *et al.*, 2016, Howren *et al.*, 2009, Kohler *et al.*, 2017, Liu *et al.*, 2012, Munkholm *et al.*, 2013, Ng *et al.*, 2018, Osimo *et al.*, 2019, Perrin *et al.*, 2019, Rowland *et al.*, 2018). The publication years of the meta-analyses ranged from 2010 to 2019. All meta-analyses exhibited significant heterogeneity among primary studies. Only two (13.3%) recently published meta-analyses were registered in PROSPERO (D'Acunto *et al.*, 2019, Perrin *et al.*, 2019).

Errors detected across meta-analyses

Errors detected in meta-analyses of the association between depression and the four peripheral inflammatory biomarkers are detailed in Table 2. The number of primary studies included in the meta-analyses ranged from 3 to 61. Except for the meta-analysis performed by Rowland et al. (2018), which investigated the association of bipolar depression with TNF-α, IL-6, and CRP (Rowland *et al.*, 2018), all meta-analyses (93.3%) had at least one type of an error. Overall, among the 521 primary studies included in the meta-analyses, errors were identified for 118 (22.6%) studies. The types of errors included incorrect sample sizes (16.9%), incorrectly used SD (29.7%), incorrect participant inclusion (5.9%), calculation error (28.0%), or analysis with insufficient data (19.5%). Among the different types of errors, incorrectly used SD was considered to be the most frequent.

Errors detected across overlapping primary studies

A total of 305 overlapping primary studies were included in the meta-analyses (Table 3). Overall, 61 of the 305 primary studies (20.0%) were associated with incorrect data extraction. "Twelve from 79 overlapping studies of TNF- α (15.2%) were found with data extraction errors. In the overlapping studies of IL-1β, IL-6, and CRP, 20.5%, 17.5%, and 44.4% of each studies showed errors, respectively." The types of errors consisted of incorrect sample sizes (24.6%), incorrectly used SD (44.2%), incorrect participant inclusion (8.2%), calculation error (19.7%), or analysis with insufficient data (3.3%). Again, incorrectly used SD was the most frequent error among overlapping studies.

Re-estimation of meta-analytical findings

Table 4 shows a comparison of originally calculated pooled ESs and their CIs with our recalculated values. Eleven (29.7%) of the 37 pooled ESs from overlapping meta-analyses changed by more than 0.1 after recalculation, ranging from 0.11 to 1.15, and those changes were categorized as a "change in results." In 11 pooled ESs for TNF-α, two (18.2%) recalculated pooled ESs were classified as a change in results. In studies of IL-1β, the error rates were higher compared to studies of TNF- α. Five (62.5%) out of eight recalculated pooled ESs for IL-1β showed a change in results. During recalculation and comparison of pooled ESs of studies of IL-1β, two pooled ESs by Ellul and colleagues (Ellul *et al.*, 2016) were not included because their meta-analysis did not specify a method to classify high- and low-quality studies. Thus, it was not possible to separate and recalculate the pooled ESs of the high- and low-quality studies in the same way. Therefore, we had to recalculate a pooled ES by integrating all studies in the meta-analysis. Although the recalculated pooled ES

differed from a non-significant result of low-quality studies, we were unable to determine a change in results because those ESs were derived from non-comparable data. In 12 and 6 pooled ESs for IL-6 and CRP, three (25.0%) and one (16.7%) recalculated pooled ESs were changes in results, respectively.

We also included all primary studies for each inflammatory biomarker and calculated total pooled SMDs of the associations with depression. The number of primary studies for the four peripheral inflammatory biomarkers ranged from 39 to 112. We found that elevated peripheral levels of three inflammatory biomarkers (TNF-α, IL-6, and CRP) were significantly associated with depression. Total pooled ESs with 95% CIs for TNF-α, IL-6, and CRP were 0.49 (95% CI 0.34 to 0.65), 0.46 (95% CI 0.38 to 0.54), and 0.27 (95% CI 0.21 to 0.33), respectively. IL-1β was not associated with depression. Significant heterogeneity was found for all four biomarkers, with I^2 values ranging from 85.1% to 88.2% (Supplementary Figures 1–4 in the Supplement). Funnel plots and Egger's tests showed publication bias among studies of TNF-α, IL-6, and CRP (all $p < 0.001$), but not among studies of IL-1β ($p = 0.257$) (Supplementary Figures 5–8 in the Supplement).

Discussion

We found a considerable number of errors in 14 (93.3%) of the 15 overlapping meta-analyses of the association between depression and four peripheral inflammatory biomarkers. Of the 521 primary studies included in the overlapping meta-analyses, errors were identified for 118 (22.6%) studies. The most common errors were incorrect use of SDs (29.7%), followed by calculation errors (28.0%), analysis with insufficient data (19.5%), incorrect sample sizes (16.9%), and incorrect participant inclusion (5.9%). From the 305 overlapping studies that were included in more than one meta-analysis, errors were found in 61 (20.0%) of them. Again the most common errors were incorrectly used SDs (44.2%), followed by incorrect sample sizes (24.6%), calculation errors (19.7%), incorrect participant inclusion (8.2%), and analysis with insufficient data (3.1%). After correcting these errors and repeating the analyses, 11 (29.7%) of 37 pooled ESs from the meta-analyses changed the magnitude of the effect size by more than 0.1, ranging from 0.11 to 1.15. The updated meta-analyses showed that elevated levels of peripheral TNF-α, IL-6, and CRP, but not IL-1β, were associated with depression.

Incorrectly identifying sample sizes is a potential meta-analytical problem. Although this type of error was more prominent among overlapping studies of CRP, it was also noted in studies of the other three inflammatory biomarkers. As the data extraction process is usually performed manually, it may increase the risk of errors. In future, machine learning may be applied to search for and screen studies to include in a meta-analysis and further improve the meta-analytic research (Xiong *et al.*, 2018).

An incorrectly used SD was the most common data extraction error in our umbrella review, consistent with previous reports of SEs mistaken for SDs (Gotzsche *et al.*, 2007, Tendal *et al.*, 2009). This type of error can inflate point estimates and artificially reduce CIs substantially

(Gotzsche *et al.*, 2007), impacting pooled ESs and estimated heterogeneity. Therefore, it can change the clinical meaningfulness of meta-analytical results. Some primary studies did not even indicate precisely whether their results were presented with SEs or SDs. In the review of Jones et al. (2005), 34 systematic reviews conducted by the Cochrane Cystic Fibrosis and Genetic Disorders Group were evaluated for data-handling and reporting errors (Jones *et al.*, 2005). In result, errors were found in 20 reviews, which four (20.0%) out of the 20 reviews were related with incorrectly used SDs. Thirty-five primary studies in 11 meta-analyses included in our study were found to have incorrectly used SDs. Accordingly, this type of error may be more frequent in meta-analytical studies in psychiatry research than in other medical disciplines.

Inaccuracies in participant inclusion and calculation were also noticed. Some studies that were not related to depression and inflammatory biomarkers or that did not meet the inclusion criteria of a meta-analysis were found to be erroneously included in the meta-analytic results (Koenig *et al.*, 1997, Komulainen *et al.*, 2007). Ford et al. (2010) reported in their review that five (62.5%) out of eight meta-analyses of pharmacological interventions for irritable bowel syndrome had included studies that were ineligible according to the predefined eligibility criteria (Ford *et al.*, 2010). In our study of 15 meta-analyses, only seven primary studies included in three meta-analyses were related to this type of error, and the error was relatively less frequent than that of the study conducted by Ford et al..

In some cases, even though no error was found in the reported primary study data, inaccurate effect sizes were identified. This can lead us to presume that there were calculation errors and a possible discrepancy in data used for actual calculation and reported data (Soneji, 2018). In the review of Gøtzsche et al. (2007), 27 meta-analyses published in 2004 that had used SMD were included for the evaluation of errors. The authors randomly selected two trials from

each meta-analysis and found that 10 (37%) of the 27 meta-analyses had at least one error. In the 10 meta-analyses with errors, one (8.3%) out of 12 trials was related to calculation errors. Although it would be difficult to compare the calculation error rate of our results to that of the review directly, we can presume that considerable calculation errors may also influence results in psychiatry.

In some cases, primary studies did not report sufficient information about their analyses. Therefore, with the absence of essential data for meta-analysis, it was not possible to extract data from some primary studies (Steptoe *et al.*, 2003, Suarez, 2004). In line with this, non-statistically significant effects (NSUEs), which are frequently unreported, should be addressed. Some studies with non-significant group differences sometimes did not present any statistics that are necessary to be converted into ES. Recent statistical approaches (e.g., MetaNSUE) have been developed to overcome this problem (Albajes-Eizagirre *et al.*, 2019, Radua *et al.*, 2015).

Like many previous meta-analyses (Dowlati *et al.*, 2010, Fernandes *et al.*, 2016, Goldsmith *et al.*, 2016, Kohler *et al.*, 2017, Liu *et al.*, 2012, Osimo *et al.*, 2019), total pooled ESs of the four peripheral inflammatory biomarkers in our study showed that elevated peripheral levels of TNF-α, IL-6, and CRP, but not IL-1β, are associated with depression. We also found significant heterogeneity among primary studies of all four biomarkers, presumably reflecting diversity in the characteristics of individual studies and the important roles of biological, clinical, and technical confounders.

Some limitations of our umbrella review and meta-analysis should be acknowledged. The severity and duration of depression, medication status, and other confounding factors, such as body mass index can affect the association between depression and inflammatory biomarkers (Beurel *et al.*, 2020, Köhler-Forsberg *et al.*, 2017). However, such factors were not identically

adjusted in primary studies included in the overlapping meta-analyses. The significant heterogeneity among primary studies also reveals that the total pooled ESs of the four biomarkers should be interpreted and applied carefully to individual levels. We included unipolar and bipolar depression and summarized those data together. However, as differences between unipolar and bipolar depression have been reported (Brunoni *et al.*, 2020, Goya-Maldonado *et al.*, 2016), this should be taken into consideration before generalizing our results. In addition, data were extracted from graphs in 51 primary studies. Data extracted from graphs may be less accurate than data extracted from numbers, and incorrectly used SD and calculation errors can be related to inaccuracies in data extraction from graphs. However, only three cases of incorrectly used SD and nine cases of calculation error were noticed in all extracted data from graphs, and our results were not primarily affected by it. Although any discrepancies during study selection and data extraction were resolved via discussion among the raters, the methods of reporting interrater reliability were not used in our study (Belur *et al.*, 2018). Lastly, although we spent much time and effort checking for the presence of errors in previous meta-analyses, the possibility of errors in our umbrella review itself cannot be excluded.

Although the statistical calculations in meta-analyses are ostensibly simple, data extraction and analysis are particularly prone to errors. Our study findings show that data extraction in meta-analyses can lead to significant errors. We noted that the errors could change the statistical significances of the association between depression and inflammatory biomarkers. Because errors in data extraction may influence ES and inflate heterogeneity among studies, efforts to reduce data extraction errors are important in studies of the association between depression and peripheral inflammatory biomarkers, for which high heterogeneity and conflicting results have continuously been reported.

Contributors

SL, KHL, EL, and JIS designed the study. SL, KMP, SJP, and WJK performed the literature search and screening; extracted, analyzed, and interpreted the data; and made the figures and tables. Any discrepancies were resolved via discussion among SL, KHL, EL, and JIS. SL, EL, and JIS drafted the manuscript. JL, AK, LS, MS, BS, AK (Koyanagi), LJ, AS, TT, ED, HO, ARB, AFC, JR, SKA, KN, and PFP were involved in critically revising the manuscript for important intellectual content. All authors approved the final version of the manuscript for publication. EL and JIS contributed as joint corresponding authors.

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Conflict of interests

We declare no competing interests.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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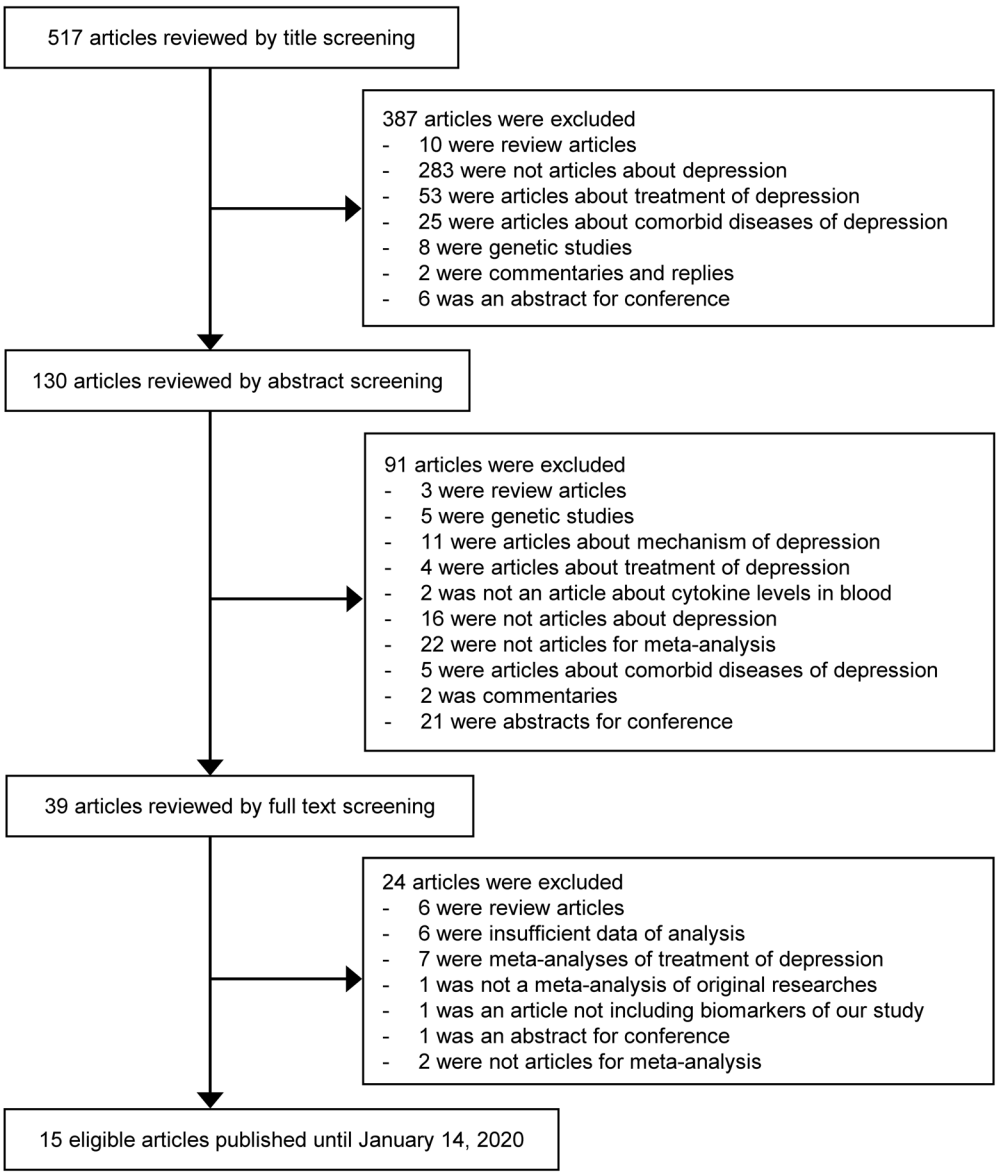
Figure Legends

Figure 1. Flow chart of literature search and screening.



Tables

Table 1. Literature search, analysis, and reporting of overlapping meta-analyses of the association between depression and peripheral inflammatory biomarkers

First author, Year	Publication date	Search date	Included analyses				PROSPERO Registration
			Effect size metrics	Heterogeneity	Publication bias	Meta-regression	
TNF-α							
D'Acunto, 2019	June 2019	July 2018	Hedges' *g*	+	Egger's test	-	+
Perrin, 2019	June 2019	October 2018	SMD	+	Funnel plot	+	-
Ng, 2018	August 2018	March 2017	SMD	+	Egger's test	+	-
Köhler, 2017	January 2017	May 2016	Hedges' *g*	+	Funnel plot, Egger's test, trim and fill, fail-safe N	+	-
Goldsmith, 2016	February 2016	March 2015	Hedges' *g*	+	Funnel plot, Egger's test	+	-
Liu, 2012	August 2012	February 2011	SMD	+	Egger's test	+	-
Dowlati, 2010	March 2010	August 2009	MD	+	Funnel plots, rank correlation tests	-	N/A
Rowland, 2018	September 2018	February 2017	SMD	+	Funnel plot	-	-
Munkholm, 2013	January 2013	January 2012	SMD	+	No	-	-
IL-1β							
D'Acunto, 2019	June 2019	July 2018	Hedges' *g*	+	Egger's test	-	+
Ng, 2018	August 2018	March 2017	SMD	+	Egger's test	+	-
Köhler, 2017	January 2017	May 2016	Hedges' *g*	+	Funnel plot, Egger's test, trim and fill, fail-safe N	+	-
Goldsmith, 2016	February 2016	March 2015	Hedges' *g*	+	Funnel plot, Egger's test	+	-
Liu, 2012	August 2012	February 2011	SMD	+	Egger's test	+	-
Dowlati, 2010	March 2010	August 2009	MD	+	Funnel plots, rank correlation tests	-	N/A
Howren, 2009	February 2009	January 2008	SMD	+	Funnel plot, fail-safe N	+	N/A
Ellul, 2016	December 2016	January 2016	SMD	+	Funnel plot, Egger's test	-	-
IL-6							
Perrin, 2019	June 2019	October 2018	SMD	+	Funnel plot	+	-
Ng, 2018	August 2018	March 2017	SMD	+	Egger's test	+	-
Köhler, 2017	January 2017	May 2016	Hedges' *g*	+	Funnel plot, Egger's test, trim and fill, fail-safe N	+	-
Goldsmith, 2016	February 2016	March 2015	Hedges' *g*	+	Funnel plot, Egger's test	+	-
Liu, 2012	August 2012	February 2011	SMD	+	Egger's test	+	-
Bizik, 2010	June 2010	October 2009	SMD	+	Fail-safe N	-	N/A
Dowlati, 2010	March 2010	August 2009	MD	+	Funnel plots, rank correlation tests	-	N/A
Howren, 2009	February 2009	January 2008	SMD	+	Funnel plot, fail-safe N	+	N/A
Rowland, 2018	September 2018	February 2017	SMD	+	Funnel plot	-	-
Munkholm, 2013	January 2013	January 2012	SMD	+	No	-	-
CRP							
Osimo, 2019	September 2019	July 2018	OR	+	Funnel plot, Egger's test	+	+
Ng, 2018	August 2018	March 2017	SMD	+	Egger's test	+	-
Howren, 2009	February 2009	January 2008	SMD	+	Funnel plot, fail-safe N	+	N/A
Rowland, 2018	September 2018	February 2017	SMD	+	Funnel plot	-	-
Fernandes, 2016	December 2016	August 2016	Hedges' *g*	+	Funnel plot, trim and fill, fail-safe N test	+	-
Dargel, 2015	February 2015	June 2013	SMD	+	Funnel plot, Egger's test	-	-

PROSPERO, international prospective register for systematic review protocols; SMD, standardized mean difference; MD, mean difference; OR, odds ratio TNF-α, tumor necrosis factor-α; IL-1β, interleukin 1-β; IL-6, interleukin 6; CRP, C-reactive protein; N/A, not applicable.

Table 2. Results from overlapping meta-analyses of the association between depression and peripheral inflammatory biomarkers

First author, Year	Included diagnosis of patients	No. of studies/papers used	No. of cases/controls	Statistical significance	Heterogeneity	Publication bias	Errors				
							Incorrect sample sizes	Incorrectly used SD	Incorrect participant inclusion	Calculation error	Analysis with insufficient data[a]
TNF-α											
D'Acunto, 2019	DD	4	72/61	No	No	Yes	0	0	0	0	0
Perrin, 2019	DD	15	604/864	Yes	Yes	N/A	0	2	0	0	0
Ng, 2018	DD	5	478/4611	No	Yes	N/A	0	0	0	0	0
Köhler, 2017	MDD	42	1742/1478	Yes	Yes	Yes	2	1	1	2	0
Goldsmith, 2016	MDD, BD	BD: 2 Acute MDD: 8 Chronic MDD: 8	BD: 44/105 Acute: 296/281 Chronic: 362/439	BD: No Acute MDD: Yes Chronic MDD: No	BD: No Acute MDD: Yes Chronic MDD: Yes	BD: N/A Acute MDD: No Chronic MDD: N/A	0	Chronic MDD: 1	0	0	0
Liu, 2012	MDD	15	541/444	Yes	Yes	No	0	1	0	1	0
Dowlati, 2010	MDD	13	438/350	Yes	Yes	No	0	4	0	0	0
Rowland, 2018	BD	6	81/253	Yes	Yes	N/A	0	0	0	0	0
Munkholm, 2013	BD	3	39/155	No	Yes	N/A	0	2	0	0	0
IL-1β											
D'Acunto, 2019	DD	4	72/61	No	Yes	No	0	1	0	0	0
Ng, 2018	DD	5	314/895	Yes	Yes	N/A	0	0	0	0	0
Köhler, 2017	MDD	22	784/722	No	No	No	1	0	0	0	0
Goldsmith, 2016	MDD, BD	Acute MDD: 4 Chronic MDD: 4	Acute MDD: 116/112 Chronic MDD: 138/190	Acute MDD: Yes Chronic MDD: No	Acute MDD: Yes Chronic MDD: Yes	N/A	0	Chronic MDD: 1	0	0	0
Ellul, 2016	MDD	21	824/1085	High-quality studies: Yes Low-quality studies: No	High-quality studies: Yes Low-quality studies: Yes	N/A	3	2	0	0	2
Liu, 2012	MDD	10	290/290	No	Yes	No	1	1	0	0	0
Dowlati, 2010	MDD	9	267/246	No	Yes	No	1	2	0	0	0
Howren, 2009	DD	14	323/346[b]	Yes	Yes	Yes	0	1	1	4	1
IL-6											
Perrin, 2019	DD	23	1607/1042	Yes	Yes	N/A	0	3	0	0	0
Ng, 2018	DD	9	2016/7211	Yes	Yes	No	0	0	0	1	0
Köhler, 2017	MDD	42	1587/1183	Yes	No	No	0	1	1	0	0
Goldsmith, 2016	MDD, BD	BD: 3 Acute MDD: 10 Chronic MDD: 7	BD:102/344 Acute MDD: 306/216 Chronic MDD: 189/211	BD: No Acute MDD: Yes Chronic MDD: Yes	BD: Yes Acute MDD: Yes Chronic MDD: Yes	BD: N/A Acute MDD: No Chronic MDD: No	0	Chronic MDD: 2	0	0	0
Liu, 2012	MDD	18	508/415	Yes	Yes	No	1	2	0	0	0
Bizik, 2010	DD	16	433/581	Yes	Yes	Yes	1	3	0	0	0
Dowlati, 2010	MDD	16	492/400	Yes	Yes	No	2	4	0	0	0
Howren, 2009	DD	61	3020/10598[b]	Yes	Yes	Yes	1	0	2	12	12
Rowland, 2018	BD	6	130/471	No	Yes	N/A	0	0	0	0	0
Munkholm, 2013	BD	3	88/352	No	Yes	N/A	0	0	0	0	0

CRP											
Osimo, 2019	DD	17	7761/155728	Yes	Yes	No	2	0	1	0	0
Ng, 2018	DD	9	2513/11991	No	Yes	No	0	1	0	1	0
Howren, 2009	DD	49	4050/23179[b]	Yes	Yes	Yes	1	0	1	8	8
Rowland, 2018	BD	3	91/329	No	No	N/A	0	0	0	0	0
Fernandes, 2016	BD	11	441/922	Yes	Yes	No	2	0	0	4	0
Dargel, 2015	BD	4	107/297	No	Yes	N/A	2	0	0	0	0
Total											
Primary studies		521					20	35	7	33	23
(Meta-analyses)		(15)					(9)	(11)	(3)	(5)	(2)

SMD, standardized mean difference; DD, depressive disorder, BD, bipolar depression; MDD, major depressive disorder; TNF-α, tumor necrosis factor-α; IL-1β, interleukin 1-β; IL-6, interleukin 6; CRP, C-reactive protein; N/A, not applicable.

[a]Analysis with insufficient data indicates that sufficient information with which to calculate SMD was not provided in a primary study.

[b]Effect sizes in some single population studies were calculated using correlation coefficients. In such cases, the number of all participants in the study was not included in this column.

Table 3. Summary of characteristics of overlapping primary studies of peripheral inflammatory biomarkers with errors

Characteristic of error	Number of studies (%)	
TNF-α		
Total no. of overlapping studies of TNF-α	79 (100%)	
Total no. of overlapping studies of TNF-α with errors	**12 (15.2%)**	
Incorrect sample sizes		1 (8.3%)
Incorrectly used SD		8 (66.7%)
Incorrect participant inclusion		1 (8.3%)
Calculation error		2 (16.7%)
Analysis with insufficient data		0 (0%)
IL-1β		
Total no. of overlapping studies of IL-1β	73 (100%)	
Total no. of overlapping studies of IL-1β with errors	**15 (20.5%)**	
Incorrect sample sizes		4 (26.7%)
Incorrectly used SD		6 (40.0%)
Incorrect participant inclusion		1 (6.7%)
Calculation error		2 (13.3%)
Analysis with insufficient data		2 (13.3%)
IL-6		
Total no. of overlapping studies of IL-6	126 (100%)	
Total no. of overlapping studies of IL-6 with errors	**22 (17.5%)**	
Incorrect sample sizes		5 (22.7%)
Incorrectly used SD		12 (54.5%)
Incorrect participant inclusion		1 (4.6%)
Calculation error		4 (18.2%)
Analysis with insufficient data		0 (0%)
CRP		
Total no. of overlapping studies of CRP	27 (100%)	
Total no. of overlapping studies of CRP with errors	**12 (44.4%)**	
Incorrect sample sizes		5 (41.7%)
Incorrectly used SD		1 (8.3%)
Incorrect participant inclusion		2 (16.7%)
Calculation error		4 (33.3%)
Analysis with insufficient data		0 (0%)
Total for all four peripheral inflammatory biomarkers		
Total no. of overlapping studies of all peripheral inflammatory biomarkers	305 (100%)	
Total no. of overlapping studies of all peripheral inflammatory biomarkers with errors	**61 (20.0%)**	
Incorrect sample sizes		15 (24.6%)
Incorrectly used SD		27 (44.2%)
Incorrect participant inclusion		5 (8.2%)
Calculation error		12 (19.7%)
Analysis with insufficient data		2 (3.3%)

SD, standard deviation; TNF-α, tumor necrosis factor-α; IL-1β, interleukin 1-β; IL-6, interleukin 6; CRP, C-reactive protein. "Analysis with insufficient data" indicates that sufficient information with which to calculate SMD was not provided in a primary study.

Table 4. Comparison of results from overlapping meta-analyses with recalculated effect sizes and confidence intervals

First author, year	Model	Outcome metrics	Reported		Recalculated		Change in results[a]	Type of data extraction error
			ES (95% CI)	p-value	ES (95% CI)	p-value		
TNF-α								
D'Acunto, 2019	Random effects	Hedges' *g*	0.35 (-0.01 to 0.70)	0.053	**0.35 (0.01 to 0.70)**	**0.045**	None	No errors.
Perrin, 2019	Random effects	SMD	0.40 (0.12 to 0.68)	0.006	0.49 (0.16 to 0.82)	0.004	None	SD (Carvalho, 2013; Lamers, 2013).
Ng, 2018	Random effects	SMD	0.11 (-0.12 to 0.35)	0.351	0.12 (-0.12 to 0.35)	0.334	None	No errors.
Köhler, 2017	Random effects	Hedges' *g*	0.68 (0.43 to 0.92)	<0.001	0.65 (0.41 to 0.88)	<0.001	None	Sample (Eller, 2009; Farid Hosseini, 2007), SD (O'Donovan, 2013), PI (O'Brien, 2007), and calculation (Baek, 2013; Grassi-Oliveira, 2009),
Goldsmith, 2016	Fixed effect	Hedges' *g*	-0.16 (-0.53 to 0.21)	0.4	-0.16 (-0.53 to 0.21)	0.386	None	No errors in the BD subgroup.
			0.35 (0.17 to 0.53)	<0.01	0.39 (0.20 to 0.57)	<0.001	None	No errors in the acute MDD subgroup.
			0.05 (-0.10 to 0.19)	0.52	0.07 (-0.08 to 0.22)	0.332	None	SD (Einvik, 2012) in the chronic MDD subgroup.
Liu, 2012	Random effects	SMD	0.56 (0.13 to 0.99)	0.01	0.49 (0.10 to 0.89)	0.014	None	SD (Pavon, 2006) and calculation (Tuglu, 2003).
Dowlati, 2010	Random effects	MD	3.97 (2.24 to 5.71)	<0.001	**3.14 (1.61 to 4.66)**	**<0.001**	**Changed[b]**	SD (O'Brien, 2007; Pavon, 2006; Tuglu, 2003; Yang, 2007).
Rowland, 2018	Random effects	SMD	2.09 (0.82 to 3.36)	<0.001	2.17 (0.85 to 3.49)	0.001	None	No errors.
Munkholm, 2013	Random effects	SMD	4.31 (-0.57 to 9.19)	0.08	**3.16 (0.02 to 6.29)**	**0.048**	**Changed**	SD (Kapczinski, 2011; O'Brien, 2006).
Total pooled results of all primary studies	Random effects	SMD	-	-	**0.49 (0.34 to 0.65)**	**<0.001**	**-**	71 primary studies included.
IL-1β								
D'Acunto, 2019	Random effects	Hedges' *g*	0.47 (-0.20 to 1.15)	0.169	**0.26 (-0.27 to 0.78)**	**0.335**	**Changed**	SD (Miklowitz, 2016).
Ng, 2018	Random effects	SMD	0.64 (0.06 to 1.21)	0.026	0.65 (0.08 to 1.22)	0.026	None	No errors.
Köhler, 2017	Random effects	Hedges' *g*	0.03 (-0.29 to 0.35)	0.847	**0.16 (-0.21 to 0.53)**	**0.402**	**Changed**	Sample (Alcocer-Gomez, 2014).
Goldsmith, 2016	Fixed effect	Hedges' *g*	-0.22 (-0.49 to 0.06)	0.13	-0.19 (-0.46 to 0.08)	0.164	None	No errors in the acute MDD subgroup.
			0.21 (-0.04 to 0.47)	0.1	0.22 (-0.04 to 0.47)	0.096	None	SD (Einvik, 2012) in the chronic MDD subgroup.
Ellul, 2016	Random effects	SMD	-0.54 (-1.03 to -0.83)[c]	0.021	**0.36 (0.03 to 0.70)**	**0.035**	**-**	Sample (Alcocer-Gomez, 2013; Marques-Deak, 2007; van den Biggelaar, 2006), SD (Pavon, 2006; Piletz, 2006), and ID (Hughes, 2012; Yang, 2007).
			0.10 (-0.45 to 0.66)	0.715				
Liu, 2012	Random effects	SMD	-0.53 (-1.36 to 0.32)	0.221	**-0.13 (-0.79 to 0.53)**	**0.697**	**Changed**	Sample (Kagaya, 2001) and SD (Pavon, 2006).
Dowlati, 2010	Random effects	MD	-1.58 (-3.59 to 0.43)	0.39	**-1.35 (-3.69 to 1.00)**	**0.26**	**Changed[b]**	Sample (Kagaya, 2001) and SD (Pavon, 2006; Yang, 2007).
Howren, 2009	Random effects	SMD	0.35 (0.03 to 0.67)	0.03	**0.24 (-0.15 to 0.63)**	**0.229**	**Changed**	SD (Kagaya, 2001), PI (Levine, 1999), calculation (Ferketich, 2005; Huang, 2007; Miller, 2002; Owen, 2001), and ID (Hekler, 2007).
Total pooled results of all primary studies	Random effects	SMD	-	-	0.17 (-0.06 to 0.39)	0.143	**-**	39 primary studies included.
IL-6								

Perrin, 2019	Random effects	SMD	0.61 (0.36 to 0.85)	<0.001	**0.50 (0.27 to 0.74)**	**<0.001**	**Changed**	SD(Carvalho, 2013; Lamers, 2013, Maes, 1995c).
Ng, 2018	Random effects	SMD	0.38 (0.16 to 0.60)	<0.001	0.38 (0.16 to 0.60)	<0.001	None	Calculation (Nadroski, 2016).
Köhler, 2017	Random effects	Hedges' *g*	0.62 (0.49 to 0.76)	<0.001	0.64 (0.50 to 0.78)	<0.001	None	SD (O'Donovan, 2013) and PI (O'Brien, 2007).
Goldsmith, 2016	Fixed effect	Hedges' *g*	0 (-0.23 to 0.23)	0.98	0 (-0.23 to 0.23)	0.99	None	No errors in the BD subgroup.
			0.76 (0.56 to 0.95)	<0.01	0.74 (0.55 to 0.92)	<0.001	None	No errors in the acute MDD subgroup.
			0.39 (0.2 to 0.59)	<0.01	0.40 (0.20 to 0.60)	<0.001	None	SD (Dhabhar, 2009; Einvik, 2012) in the chronic MDD subgroup.
Liu, 2012	Random effects	SMD	0.68 (0.44 to 0.92)	<0.001	0.61 (0.38 to 0.84)	<0.001	None	Sample (Kagaya, 2001) and SD (Dhabhar, 2009; Pavon, 2006).
Bizik, 2010	Random effects	SMD	1.06 (0.59 to 1.52)	<0.001	**0.71 (0.43 to 0.99)**	**<0.001**	**Changed**	Sample (Kagaya, 2001) and SD (Alesci, 2005; Dhabhar, 2009; Maes, 1995a).
Dowlati, 2010	Random effects	MD	1.78 (1.23 to 2.33)	<0.001	**1.87 (0.92 to 2.81)**	**<0.001**	**Changed**[b]	Sample (Kagaya, 2001; O'Brien, 2007) and SD (Dhabhar, 2009; Maes, 1995a; Pavon, 2006; Yang, 2007).
Howren, 2009	Random effects	SMD	0.25 (0.18 to 0.31)	<0.001	0.27 (0.19 to 0.34)	<0.001	None	Sample (Kagaya, 2001), PI (Cyranowski, 2007; Lutgendorf, 1999), calculation (Ferketich, 2005; Jacobson, 2008; Jehn, 2006; Kiecolt-Glaser, 2007; Kudoh, 2001; Maes, 1995a; Maes, 1997; Miller, 2002; Motivala, 2005; Sluzewska, 1995; Soygur, 2007 (cancer and normal)), and ID (Allen-Mersh, 1998; Costanzo, 2005; Ferruci, 2002; Glaser, 2003; Haack, 1999; Hekler, 2007; Koening, 1997; Ranjit, 2007; Steptoe, 2003; Suarez, 2003; Whooley, 2007 (males and females)).
Rowland, 2018	Random effects	SMD	0.67 (-0.08 to 1.42)	0.08	0.63 (-0.13 to 1.39)	0.106	None	No errors.
Munkholm et al., 2013	Random effects	SMD	1.04 (-0.54 to 2.62)	0.2	1.05 (-0.45 to 2.55)	0.17	None	No errors.
Total pooled results of all primary studies	Random effects	SMD	-	-	**0.46 (0.38 to 0.54)**	**<0.001**	-	112 primary studies included.
CRP								
Osimo, 2019	Random effects	OR	1.46 (1.22 to 1.75)	<0.001	1.40 (1.31 to 1.50)	<0.001	None	Sample (Cepeda, 2016; Ekinci, 2017) and PI (Kling, 2007).
Ng, 2018	Random effects	SMD	0.5 (0 to 1)	0.05	**0.19 (-0.01 to 0.39)**	**0.062**	**Changed**	SD (Kop, 2002) and calculation (Bremmer, 2008).
Howren, 2009	Random effects	SMD	0.22 (0.15 to 0.28)	<0.001	0.14 (0.09 to 0.19)	<0.001	None	Sample (Almeida, 2007), PI (Kling, 2006), calculation (Arai, 2006; Hornig, 1998; Hung, 2007; Liukkonen, 2006 (males and females); Miller, 2002; Shimbo, 2006; Vaccarino, 2007), and ID (Danner, 2003 (males and females); Douglas, 2004 (males and females); Komulainen, 2007; Ranjit, 2007; Steptoe, 2003; Suares, 2004).
Rowland, 2018	Random effects	SMD	-0.02 (-0.25 to 0.21)	0.86	-0.02 (-0.25 to 0.21)	0.86	None	No errors.

Fernandes, 2016	Random effects	SMD	0.67 (0.23 to 1.11)	0.003	0.74 (0.32 to 1.16)	0.001	None	Sample (Cunha, 2008; Jacoby, 2016) and calculation (Bai, 2013; Dickerson, 2015; Hung, 2007; Su, 2011).
Dargel, 2015	Random effects	SMD	0.28 (-0.17 to 0.73)	0.227	0.31 (-0.17 to 0.78)	0.206	None	Sample (Cunha, 2008; Fontoura, 2012).
Total pooled results of all primary studies	Random effects	SMD	-	-	**0.27 (0.21 to 0.33)**	**<0.001**	-	80 primary studies included.

BD, bipolar depression; MDD, major depressive disorder; SMD, standardized mean difference; MD, mean difference; ES, effect size; SD, standard deviation; CI, confidence interval; PI, participant nclusion; ID, insufficient data; TNF-α, tumor necrosis factor-α; IL-1β, interleukin 1-β; IL-6, interleukin 6; CRP, C-reactive protein.

If our recalculation of the pooled ES for each meta-analysis differed from that of the original meta-analysis by 0.1 or more, this is denoted as "changed."

When the MD was converted to SMD, the difference in pooled SMD between the original meta-analysis and our recalculation was 0.1 or more.

The first row of reported ESs presents the results of high-quality studies, and the second row presents the result of low-quality studies. The recalculated ES results from all primary studies.

Online Supplementary Material

Impact of data extraction errors in meta-analyses on the association between depression and peripheral inflammatory biomarkers: An umbrella review

Number of eAppendix: 1

Number of eFigure: 8

Supplementary Appendix 1. PRISMA checklist and MOOSE Checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4-5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8-9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8-9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10-11

Section/topic	#	Checklist item	Reported on page #
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10-11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10-11
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10-11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10-11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-13, Table 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-14 Table 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13-14, Supplements
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	6-7
2	Hypothesis statement	6-7
3	Description of study outcome(s)	6-7
4	Type of exposure or intervention used	6-7
5	Type of study designs used	6-7
6	Study population	6-7
Reporting of search strategy should include		
7	Qualifications of searchers (e.g., librarians and investigators)	NA
8	Search strategy, including time period included in the synthesis and key words	8
9	Effort to include all available studies, including contact with authors	8-9
10	Databases and registries searched	8
11	Search software used, name and version, including special features used (e.g., explosion)	9-10
12	Use of hand searching (e.g., reference lists of obtained articles)	8-9
13	List of citations located and those excluded, including justification	Figure 1
14	Method of addressing articles published in languages other than English	9
15	Method of handling abstracts and unpublished studies	NA
16	Description of any contact with authors	NA
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	8-9
18	Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)	8-9
19	Documentation of how data were classified and coded (e.g., multiple raters, blinding and interrater reliability)	9-10, 18
20	Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate)	8-9
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	NA
22	Assessment of heterogeneity	11
23	Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	10-11
24	Provision of appropriate tables and graphics	Tables 1-4, Figure 1, Supplement file

Item No	Recommendation	Reported on Page No
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Tables 3, Supplement file
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (e.g., subgroup analysis)	NA
28	Indication of statistical uncertainty of findings	12-14
Reporting of discussion should include		
29	Quantitative assessment of bias (e.g., publication bias)	NA
30	Justification for exclusion (e.g., exclusion of non-English language citations)	NA
31	Assessment of quality of included studies	NA
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	15-17
33	Generalization of the conclusions (i.e., appropriate for the data presented and within the domain of the literature review)	15-17
34	Guidelines for future research	NA
35	Disclosure of funding source	19

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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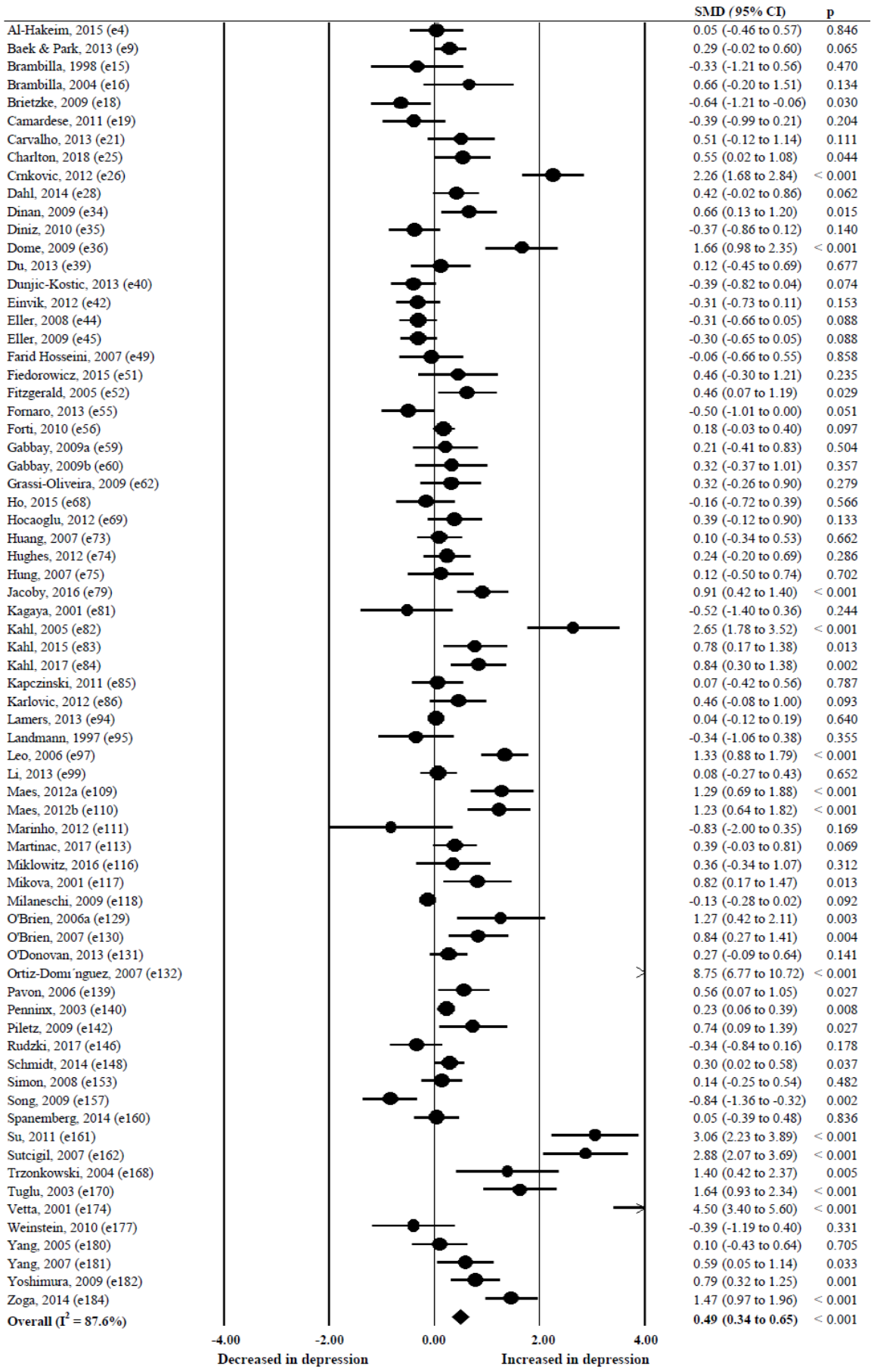
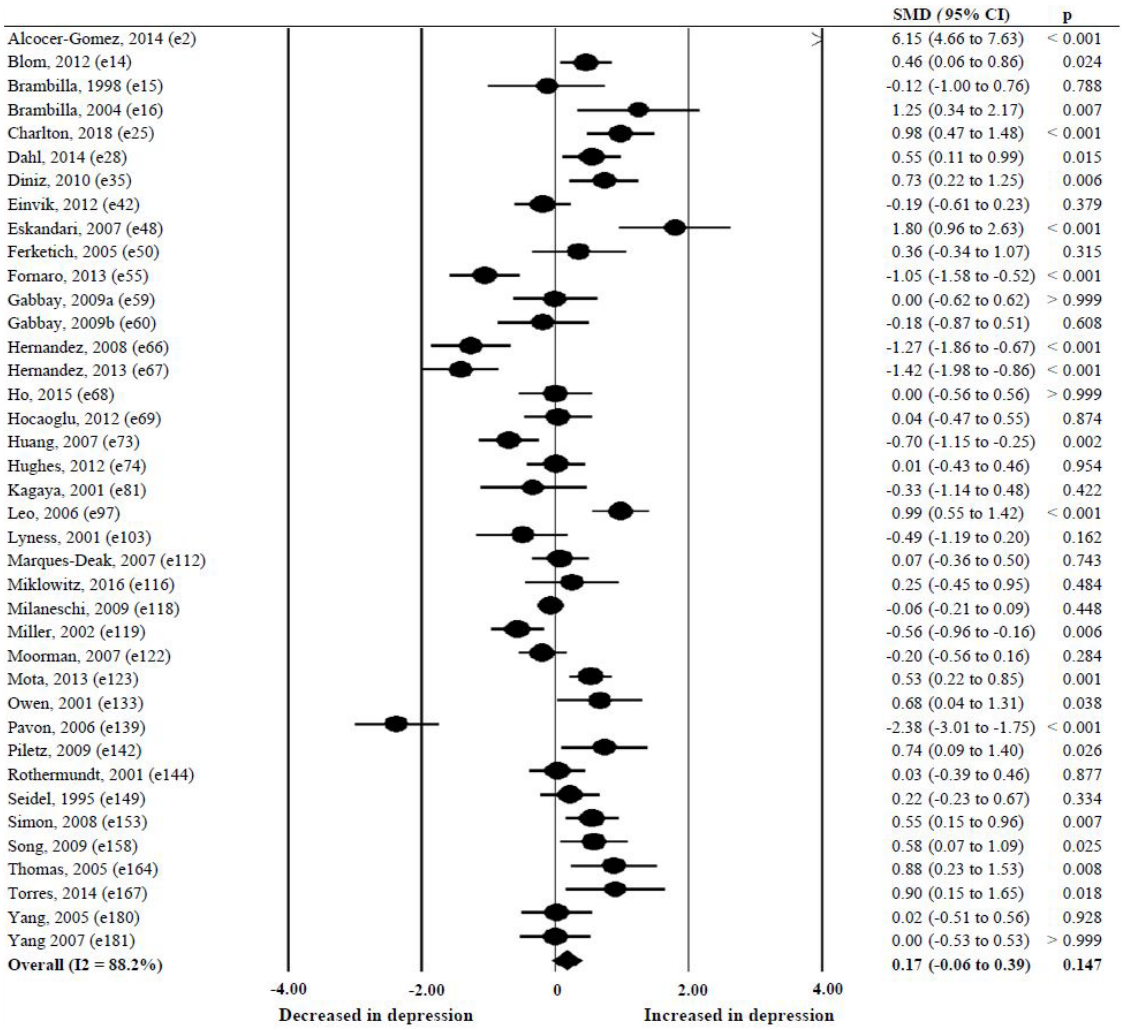
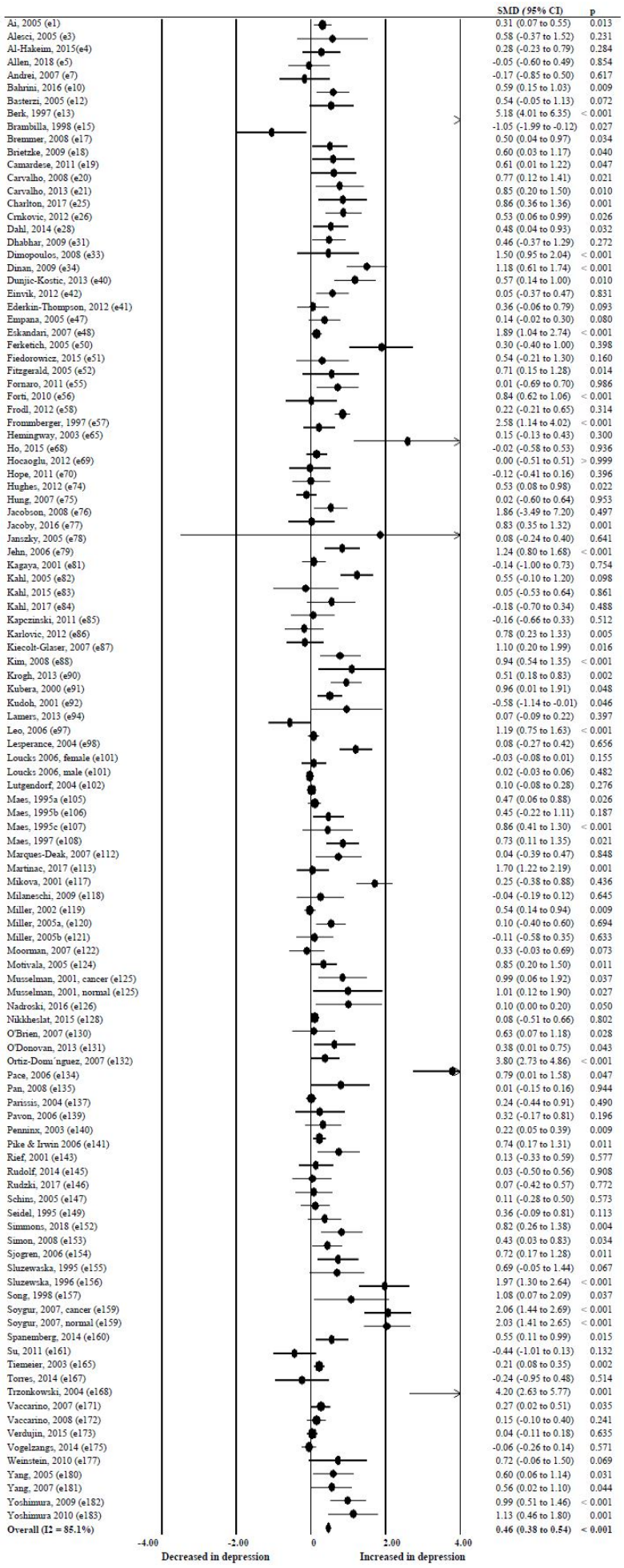


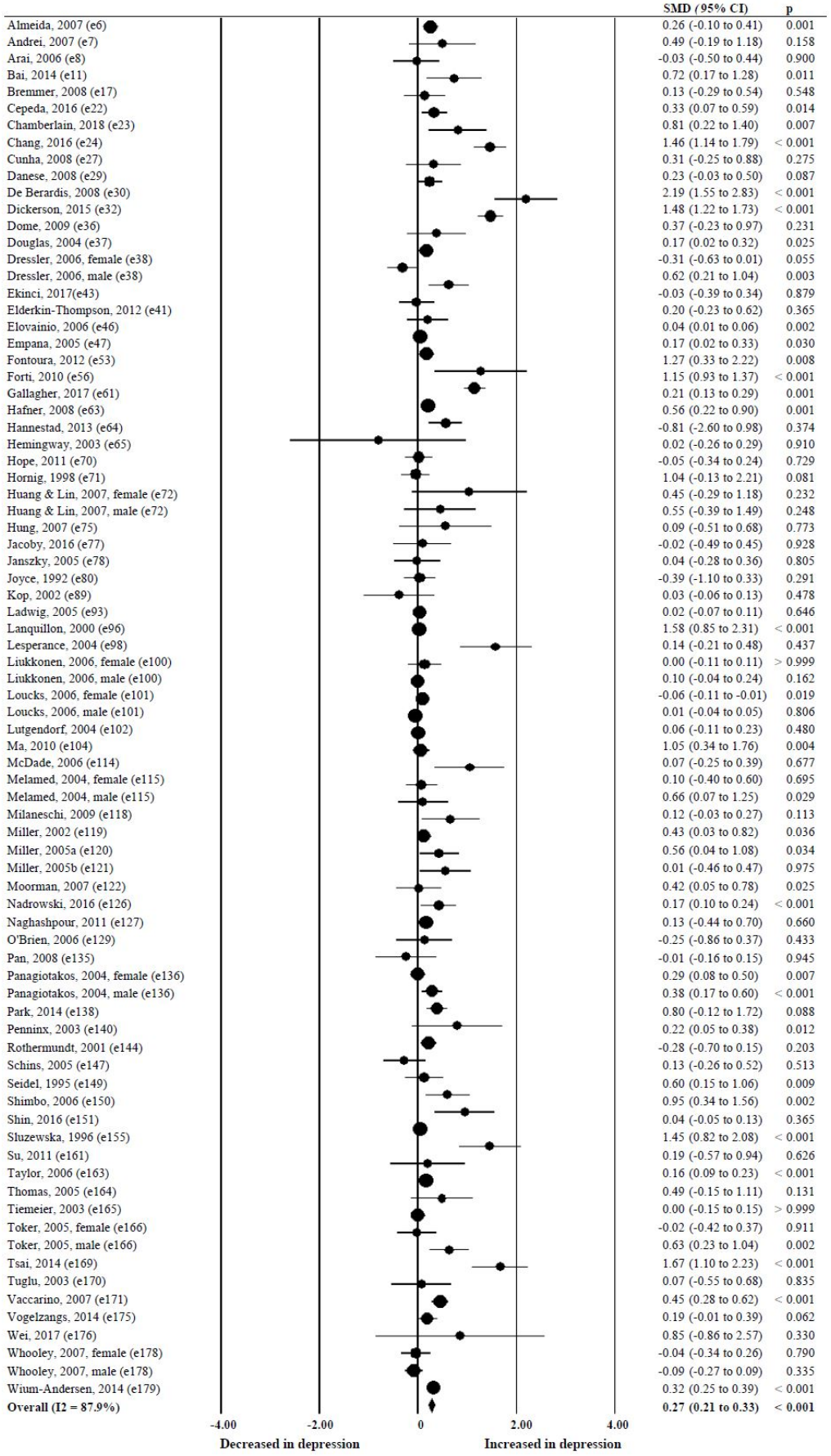
Supplementary Figure 1. Forest plot of primary studies that investigated TNF-α. TNF-α, tumor necrosis factor-alpha; SMD, standardized mean difference; CI, confidence interval.



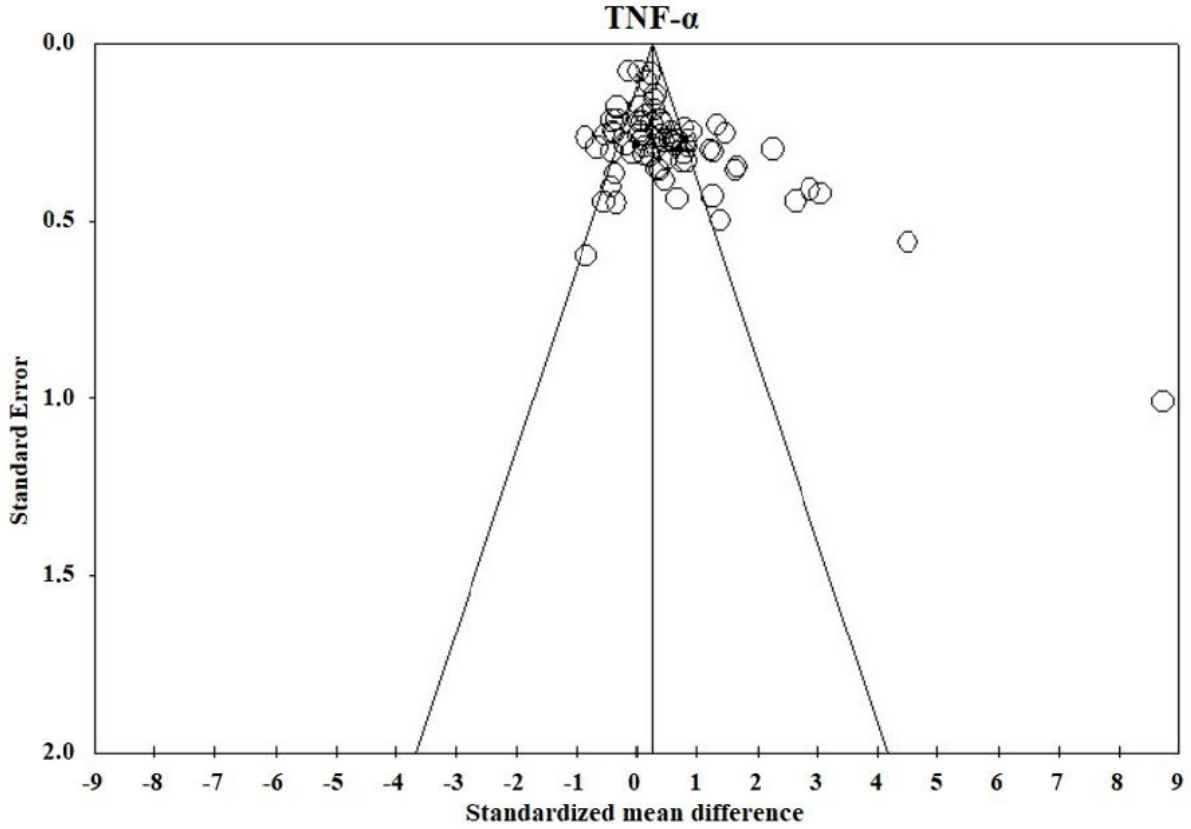
Supplementary Figure 2. Forest plot of primary studies that investigated IL-1β. IL-1β, interleukin 1-beta; SMD, standardized mean difference; CI, confidence interval.



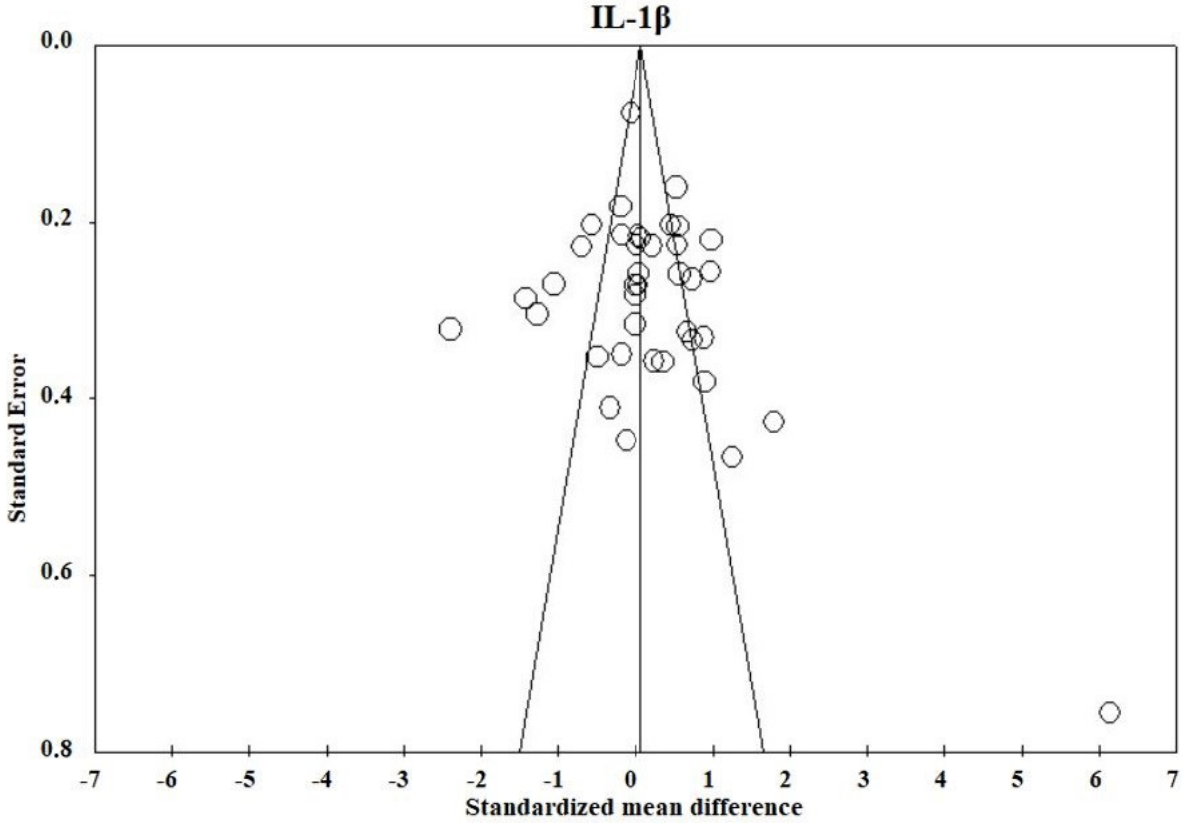
Supplementary Figure 3. Forest plot of primary studies that investigated IL-6. IL-6, interleukin 6; SMD, standardized mean difference; CI, confidence interval.


SMD (95% CI)
p
Almeida, 2007 (e6) 0.26 (-0.10 to 0.41) 0.001
Andrei, 2007 (e7) 0.49 (-0.19 to 1.18) 0.158
Arai, 2006 (e8) -0.03 (-0.50 to 0.44) 0.900
Bai, 2014 (e11) 0.72 (0.17 to 1.28) 0.011
Bremmer, 2008 (e17) 0.13 (-0.29 to 0.54) 0.548
Cepeda, 2016 (e22) 0.33 (0.07 to 0.59) 0.014
Chamberlain, 2018 (e23) 0.81 (0.22 to 1.40) 0.007
Chang, 2016 (e24) 1.46 (1.14 to 1.79) < 0.001
Cunha, 2008 (e27) 0.31 (-0.25 to 0.88) 0.275
Danese, 2008 (e29) 0.23 (-0.03 to 0.50) 0.087
De Berardis, 2008 (e30) 2.19 (1.55 to 2.83) < 0.001
Dickerson, 2015 (e32) 1.48 (1.22 to 1.73) < 0.001
Dome, 2009 (e36) 0.37 (-0.23 to 0.97) 0.231
Douglas, 2004 (e37) 0.17 (0.02 to 0.32) 0.025
Dressler, 2006, female (e38) -0.31 (-0.63 to 0.01) 0.055
Dressler, 2006, male (e38) 0.62 (0.21 to 1.04) 0.003
Ekinci, 2017(e43) -0.03 (-0.39 to 0.34) 0.879
Elderkin-Thompson, 2012 (e41) 0.20 (-0.23 to 0.62) 0.365
Elovainio, 2006 (e46) 0.04 (0.01 to 0.06) 0.002
Empana, 2005 (e47) 0.17 (0.02 to 0.33) 0.030
Fontoura, 2012 (e53) 1.27 (0.33 to 2.22) 0.008
Forti, 2010 (e56) 1.15 (0.93 to 1.37) < 0.001
Gallagher, 2017 (e61) 0.21 (0.13 to 0.29) 0.001
Hafner, 2008 (e63) 0.56 (0.22 to 0.90) 0.001
Hannestad, 2013 (e64) -0.81 (-2.60 to 0.98) 0.374
Hemingway, 2003 (e65) 0.02 (-0.26 to 0.29) 0.910
Hope, 2011 (e70) -0.05 (-0.34 to 0.24) 0.729
Hornig, 1998 (e71) 1.04 (-0.13 to 2.21) 0.081
Huang & Lin, 2007, female (e72) 0.45 (-0.29 to 1.18) 0.232
Huang & Lin, 2007, male (e72) 0.55 (-0.39 to 1.49) 0.248
Hung, 2007 (e75) 0.09 (-0.51 to 0.68) 0.773
Jacoby, 2016 (e77) -0.02 (-0.49 to 0.45) 0.928
Janszky, 2005 (e78) 0.04 (-0.28 to 0.36) 0.805
Joyce, 1992 (e80) -0.39 (-1.10 to 0.33) 0.291
Kop, 2002 (e89) 0.03 (-0.06 to 0.13) 0.478
Ladwig, 2005 (e93) 0.02 (-0.07 to 0.11) 0.646
Lanquillon, 2000 (e96) 1.58 (0.85 to 2.31) < 0.001
Lesperance, 2004 (e98) 0.14 (-0.21 to 0.48) 0.437
Liukkonen, 2006, female (e100) 0.00 (-0.11 to 0.11) > 0.999
Liukkonen, 2006, male (e100) 0.10 (-0.04 to 0.24) 0.162
Loucks, 2006, female (e101) -0.06 (-0.11 to -0.01) 0.019
Loucks, 2006, male (e101) 0.01 (-0.04 to 0.05) 0.806
Lutgendorf, 2004 (e102) 0.06 (-0.11 to 0.23) 0.480
Ma, 2010 (e104) 1.05 (0.34 to 1.76) 0.004
McDade, 2006 (e114) 0.07 (-0.25 to 0.39) 0.677
Melamed, 2004, female (e115) 0.10 (-0.40 to 0.60) 0.695
Melamed, 2004, male (e115) 0.66 (0.07 to 1.25) 0.029
Milaneschi, 2009 (e118) 0.12 (-0.03 to 0.27) 0.113
Miller, 2002 (e119) 0.43 (0.03 to 0.82) 0.036
Miller, 2005a (e120) 0.56 (0.04 to 1.08) 0.034
Miller, 2005b (e121) 0.01 (-0.46 to 0.47) 0.975
Moorman, 2007 (e122) 0.42 (0.05 to 0.78) 0.025
Nadrowski, 2016 (e126) 0.17 (0.10 to 0.24) < 0.001
Naghashpour, 2011 (e127) 0.13 (-0.44 to 0.70) 0.660
O'Brien, 2006 (e129) -0.25 (-0.86 to 0.37) 0.433
Pan, 2008 (e135) -0.01 (-0.16 to 0.15) 0.945
Panagiotakos, 2004, female (e136) 0.29 (0.08 to 0.50) 0.007
Panagiotakos, 2004, male (e136) 0.38 (0.17 to 0.60) < 0.001
Park, 2014 (e138) 0.80 (-0.12 to 1.72) 0.088
Penninx, 2003 (e140) 0.22 (0.05 to 0.38) 0.012
Rothermundt, 2001 (e144) -0.28 (-0.70 to 0.15) 0.203
Schins, 2005 (e147) 0.13 (-0.26 to 0.52) 0.513
Seidel, 1995 (e149) 0.60 (0.15 to 1.06) 0.009
Shimbo, 2006 (e150) 0.95 (0.34 to 1.56) 0.002
Shin, 2016 (e151) 0.04 (-0.05 to 0.13) 0.365
Sluzewska, 1996 (e155) 1.45 (0.82 to 2.08) < 0.001
Su, 2011 (e161) 0.19 (-0.57 to 0.94) 0.626
Taylor, 2006 (e163) 0.16 (0.09 to 0.23) < 0.001
Thomas, 2005 (e164) 0.49 (-0.15 to 1.11) 0.131
Tiemeier, 2003 (e165) 0.00 (-0.15 to 0.15) > 0.999
Toker, 2005, female (e166) -0.02 (-0.42 to 0.37) 0.911
Toker, 2005, male (e166) 0.63 (0.23 to 1.04) 0.002
Tsai, 2014 (e169) 1.67 (1.10 to 2.23) < 0.001
Tuglu, 2003 (e170) 0.07 (-0.55 to 0.68) 0.835
Vaccarino, 2007 (e171) 0.45 (0.28 to 0.62) < 0.001
Vogelzangs, 2014 (e175) 0.19 (-0.01 to 0.39) 0.062
Wei, 2017 (e176) 0.85 (-0.86 to 2.57) 0.330
Whooley, 2007, female (e178) -0.04 (-0.34 to 0.26) 0.790
Whooley, 2007, male (e178) -0.09 (-0.27 to 0.09) 0.335
Wium-Andersen, 2014 (e179) 0.32 (0.25 to 0.39) < 0.001
Overall (I2 = 87.9%) 0.27 (0.21 to 0.33) < 0.001
-4.00
-2.00
0
2.00
4.00
Decreased in depression
Increased in depression

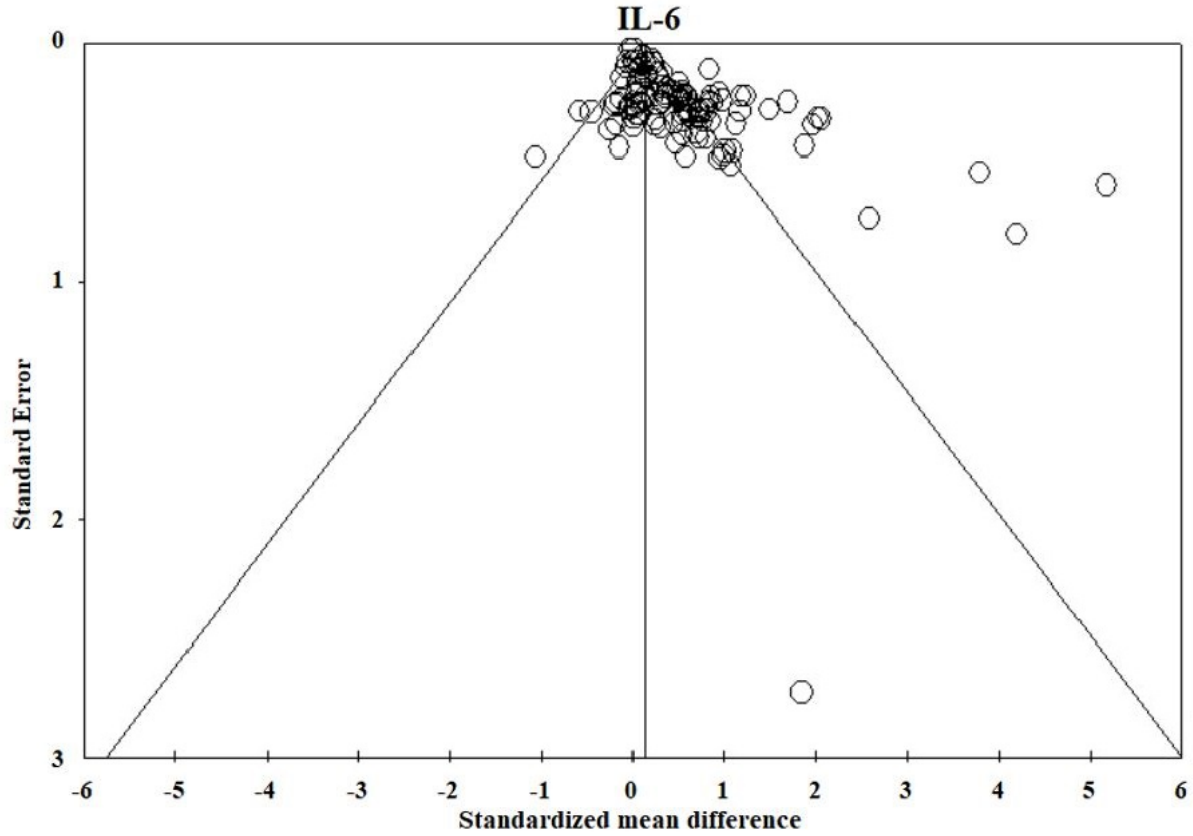
Supplementary Figure 4. Forest plot of primary studies that investigated CRP. CRP, C-reactive protein; SMD, standardized mean difference; CI, confidence interval.



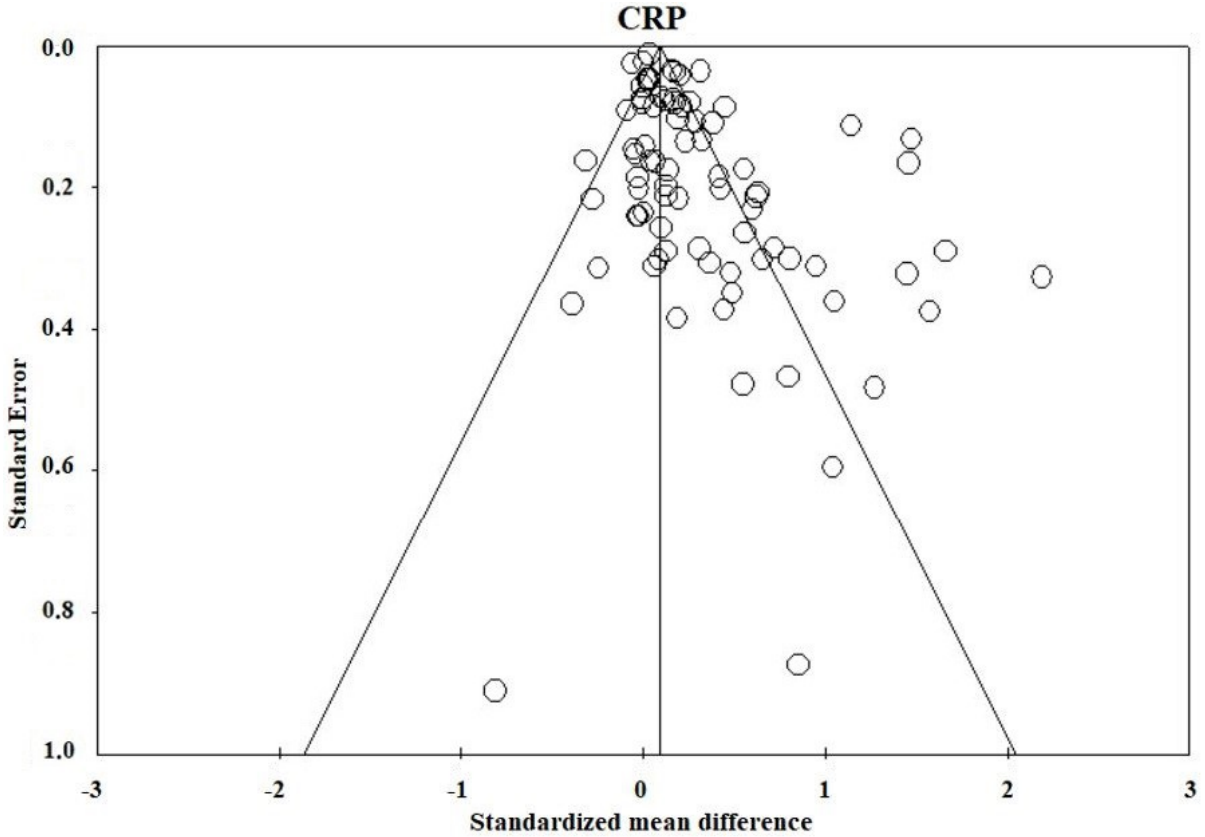
Supplementary Figure 5. Funnel plot of primary studies that investigated TNF-α. TNF-α, tumor necrosis factor-alpha.



Supplementary Figure 6. Funnel plot of primary studies that investigated IL-1β. IL-1β, interleukin 1-beta.



Supplementary Figure 7. Funnel plot of primary studies that investigated IL-6. IL-6, interleukin 6.



Supplementary Figure 8. Funnel plot of primary studies that investigated CRP. CRP, C-reactive protein.

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