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Meta-analysis

Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies

Köhler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, Stubbs B, Solmi M, Veronese N, Herrmann N, Raison CL, Miller BJ, Lanctôt KL, Carvalho AF. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies.

Objective: To conduct a systematic review and meta-analysis of studies that measured cytokine and chemokine levels in individuals with major depressive disorder (MDD) compared to healthy controls (HCs).
Method: The PubMed/MEDLINE, EMBASE, and PsycINFO databases were searched up until May 30, 2016. Effect sizes were estimated with random-effects models.
Result: Eighty-two studies comprising 3212 participants with MDD and 2798 HCs met inclusion criteria. Peripheral levels of interleukin-6 (IL-6), tumor necrosis factor (TNF)-alpha, IL-10, the soluble IL-2 receptor, C-C chemokine ligand 2, IL-13, IL-18, IL-12, the IL-1 receptor antagonist, and the soluble TNF receptor 2 were elevated in patients with MDD compared to HCs, whereas interferon-gamma levels were lower in MDD (Hedge's $g = -0.477$, $P = 0.043$). Levels of IL-1β, IL-2, IL-4, IL-8, the soluble IL-6 receptor (sIL-6R), IL-5, CCL-3, IL-17, and transforming growth factor-beta 1 were not significantly altered in individuals with MDD compared to HCs. Heterogeneity was large (I^2: 51.6–97.7%), and sources of heterogeneity were explored (e.g., age, smoking status, and body mass index).
Conclusion: Our results further characterize a cytokine/chemokine profile associated with MDD. Future studies are warranted to further elucidate sources of heterogeneity, as well as biosignature cytokines secreted by other immune cells.

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Summations

- Evidence indicates that peripheral immune activation may be involved in the pathophysiology of major depressive disorder.
- Herein, we conducted an updated meta-analytic review of 82 studies that measured cytokines and/or chemokines in individuals with major depressive disorder and healthy controls.
- Levels of IL-6, TNF-α, 10, the soluble IL-2 receptor, C-C chemokine ligand 2, IL-13, IL-18, IL-12, the IL-1 receptor antagonist, and the soluble TNF receptor 2 were elevated, whereas interferon-γ levels were reduced in individuals with major depressive disorder compared to controls. These results add in the characterization of a putative cytokine/chemokine profile for major depressive disorder.

Considerations

- A large degree of heterogeneity was evident in this literature. Potential sources of heterogeneity were not consistently reported across included studies.
- Methodological quality has varied across included studies.

Introduction

In the past two decades, an increasing body of evidence indicates that aberrations in immune-inflammatory pathways and activation of cell-mediated immunity represent important pathophysiological pathways for the development of major depressive disorder (MDD) (1, 2). In addition, converging experimental and clinical research points that reciprocal neuroimmune interactions may contribute to the neurobiology of MDD (3, 4). A low-grade inflammatory response characterized by increased numbers of granulocytes and monocytes (1), as well as the elevated levels of acute phase reactants (e.g., C-reactive protein and haptoglobin) (5, 6), inflammatory cytokines (7), and possibly chemokines (8), has been demonstrated in groups of individuals with MDD compared to healthy controls (HCs). These peripheral immune abnormalities may influence brain function through several mechanisms. For example, evidence indicates that cytokines may cross the blood-brain barrier, while certain cytokines (e.g., IL-1β) may convey signals to the brain via afferent nerves like the vagus (2, 4). The pathophysiological role of proinflammatory cytokines in MDD is further supported by preclinical research indicating that proinflammatory cytokines may promote depressive-like behaviours, whereas TNF-α and IL-6 receptor knockout mice exhibit resilience to stress-induced depressive-like behaviours (9–11). In addition, a recent meta-analysis estimates that ~25% of patients with chronic hepatitis C develop depression after treatment with the proinflammatory cytokine interferon-α (IFN-α) (12). The common denominator among these findings is that peripheral immune dysregulation may represent an important pathway for inducing functional and structural brain changes that underpin the pathophysiology of MDD. Perhaps as a consequence of this, peripheral inflammatory mediators have emerged as promising candidate biomarkers for MDD (13), although evidence of bias may limit inferences derived from the literature on peripheral biomarkers for MDD (14).

A meta-analysis that included 24 studies provided evidence that peripheral levels of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are significantly elevated in individuals with MDD compared to healthy controls (HCs) (7). However,

between-study heterogeneity for these estimates was high (7). A more recent cumulative meta-analysis confirmed that peripheral levels of IL-6 are elevated in individuals with MDD and HCs, whereas no consistent evidence of changes in TNF-α and IL-1β in patients with MDD compared to controls was found (5). This significant degree of heterogeneity could be explained by a number of factors including but not limited to the following: differences in assay methods across laboratories, medication status, and potential confounders (e.g., body mass index and smoking). Furthermore, it has been increasingly recognized that the phenotypic heterogeneity of MDD may contribute to discrepant findings. For example, melancholic depression is associated with elevated HPA axis activity (15, 16), whereas individuals with atypical depression appear to have higher levels of proinflammatory markers (16). In addition, each individual cytokine/chemokine may have different functions relevant to the pathophysiology of MDD. For example, some cytokines/chemokines are predominantly proinflammatory, whereas others are mainly anti-inflammatory, and some of these immune mediators have been increasingly implicated in neuroplasticity mechanisms (17, 18). Therefore, the characterization of peripheral levels of a wider array of cytokines and chemokines may be of particular relevance to this field.

Aims of the study

Since the publication of these previous meta-analyses (5, 7, 19, 20), additional studies have been conducted examining a wider range of immune biomarkers. Therefore, the aims of this large, collaborative meta-analysis were to investigate differences in peripheral levels of a wider range of cytokines and chemokines among individuals with major depressive disorder compared to healthy controls and to explore potential sources of heterogeneity across studies. We anticipated that the large number of new studies would allow for a more precise characterization of the role of cytokines and chemokines as peripheral biomarkers for major depressive disorder.

Methods

This study comprised a between-group meta-analysis of studies that compared cytokine or chemokine levels between adults with MDD and healthy controls. We complied with the Preferred Reported Items for Systematic Reviews and Meta-analysis (PRISMA) statement (21). The literature search, title/abstract screening, final decision on eligibility after full-text review, and data extraction were independently performed by two investigators. An *a priori* defined yet unpublished protocol was followed.

Search strategy

A systematic search was conducted in the PubMed/MEDLINE, EMBASE, and PsycINFO databases from inception up until May 30, 2016. The detailed search strings used in this review are presented in the supporting information that accompanies the online version of this article. This search strategy was augmented through tracking the citation of included articles in Google Scholar (22).

Study selection

We included original references published in any language. Eligible studies had to measure peripheral cytokine or chemokine levels in adult subjects (age ≥ 18 years old) that met either DSM (23) or ICD (24) criteria for MDD, and a comparison group of healthy controls (HCs). The following exclusion criteria were adopted: (i) studies that reported that participants had medical and/or psychiatric comorbidities were excluded (except current smoking); (ii) studies that included pregnant women or women in the postpartum period; (iii) case reports or case series ($N < 10$); (iv) studies that assayed the mediators in specimens/tissues other than blood; and (v) studies in animals. The authors of meeting abstracts that met inclusion criteria were contacted by e-mail to provide data for analysis (no additional data were provided).

Data extraction

For each cytokine/chemokine, we extracted the means, variance estimates [standard deviation (SD), standard error of the mean (SEM), or 95% confidence interval (CI)], and sample sizes for both MDD and HC groups. From studies that presented only results of the comparison of the MDD and HC groups, we extracted the appropriate measure (z-score or t-score). In studies that provided median ± IQR or median ± range, we estimated the mean ± SD following a standard method (25). We also extracted the following data whenever available: (i) first author, (ii) publication year, (iii) gender distribution of study sample (% females), (iv) mean age and BMI, (v) mean illness duration (years), (vi) treatment status (drug-free during assessment and/or treatment-naïve), (vii) percentage of the sample with atypical and/or melancholic depression, (viii) measurement of depressive symptoms, and (ix) % of current smokers.

Methodological quality of included studies

We devised a score to estimate the methodological quality of each study based on the following

parameters: (i) study sample ≥ 50 participants (1 = Yes; 0 = No); (ii) Did the study control results for potential confounders (e.g., age, BMI, gender, race)? (1 = Y; 0 = No); (iii) Were participants with MDD and HCs age- and gender-matched? (1 = Y; 0 = No); (iv) Was the time of sample collection specified? (e.g., morning vs. evening) (1 = Y; 0 = No); (v) Were participants with MDD free of antidepressant drugs during sample collection? (1 = Y; 0 = No); and (vi) Reporting of either the manufacturer of the test or its parameters (detection limit and coefficient of variation) (1 = Y; 0 = No). Thus, the score may vary from 0 to 6, with higher scores indicating better methodological quality.

Statistical analysis

Because studies used different measurement methods, we estimated a standardized mean difference and 95% CI (Hedges's g) for each immune mediator, which provides an unbiased effect size (ES) adjusted for small sample sizes (26). We assessed the heterogeneity across studies using the Cochran Q test, which provides a weighted sum of the squares of the deviations of individual study ES estimates from the overall estimate. In addition, heterogeneity across studies was quantified with the I^2 statistic, which indicates the percentage of total variation across several studies due to heterogeneity and which is considered high when ≥50% (27). We anticipated a high degree of heterogeneity. Therefore, we pooled ES using a random-effects model according to the DerSimonian and Laird method (28). Meta-analyses were conducted only for immune mediators with at least three individual datasets.

Studies with statistically non-significant (i.e., negative) results are less likely to be published than studies with significant results (14, 29). To assess publication bias, we inspected a funnel plot graph for asymmetry and calculated the Egger's regression test for funnel plot asymmetry (30). Evidence of small-study effects (indicative of publication bias) was considered when the P-value of the Egger's test was <0.1, and the ES of the largest study was more conservative or changed direction when compared with the overall ES estimate (funnel plots of ES estimates in which evidence of publication bias was observed are illustrated in Figs S10–S14) (14). The trim-and-fill procedure was used to estimate the ES adjusting for publication bias (31), while the fail-safe N (i.e., the file drawer statistic) was used to determine how many additional studies would be necessary to turn a significant ES non-significant (32).

We explored potential sources of heterogeneity across studies for each ES estimate, using either subgroup (if there were at least three studies in each subgroup) or random-effects meta-regression analyses. Meta-regression analyses were conducted only when at least 10 studies provided moderator; this decision was made *a priori* because with fewer datasets, this analytic tool may provide spurious results (33). The following variables were considered in meta-regression analyses: sample size, mean age of MDD group, mean age of the HC group, differences in mean age (MDD group *minus* HC group), mean body mass index (BMI) of MDD group, mean BMI of the HC group, differences in mean BMI (MDD group *minus* HC group), % of females in the MDD group, % of females in the HC group, difference in % of females (MDD group *minus* HC group), % of current smokers, latitude of the country where the study was executed, depression severity (expressed as a percentage of the cutoff for severe depression in the rating scale), methodological quality of each included study, and mean illness duration in years. Studies were weighted in such a way that investigations with more precise parameters (indicated by sample size and 95% CI) had more influence in meta-regression analyses (34). For statistically significant ES estimates, we performed sensitivity analyses in which we excluded each study from analyses to verify whether a single study turned results non-significant or otherwise changed the direction of the ES. In addition, cumulative meta-analysis was performed for significant ES with at least 10 datasets.

All analyses were conducted in Stata MP software version 14.0 (Stata Corp, College Station, TX, USA) using the metan package. Statistical significance was considered at an alpha level of 0.05.

Results

Study selection

Following removal of duplicates, the title/abstracts of 4911 unique references were screened for eligibility. A total of 4432 references were excluded, while 479 full texts were retrieved and screened for eligibility. Of those articles, 397 were excluded (see Table S1 for reasons for exclusion). Finally, 82 original studies met inclusion criteria, which provided data from 6010 participants (3212 participants with MDD and 2798 HCs). Figure 1 provides the PRISMA flowchart for study selection.

Characteristics and methodological quality of included studies

Of the 82 studies included in our meta-analysis, in 43 studies (52.4%), participants with MDD and HCs were age- and gender-matched, while 35
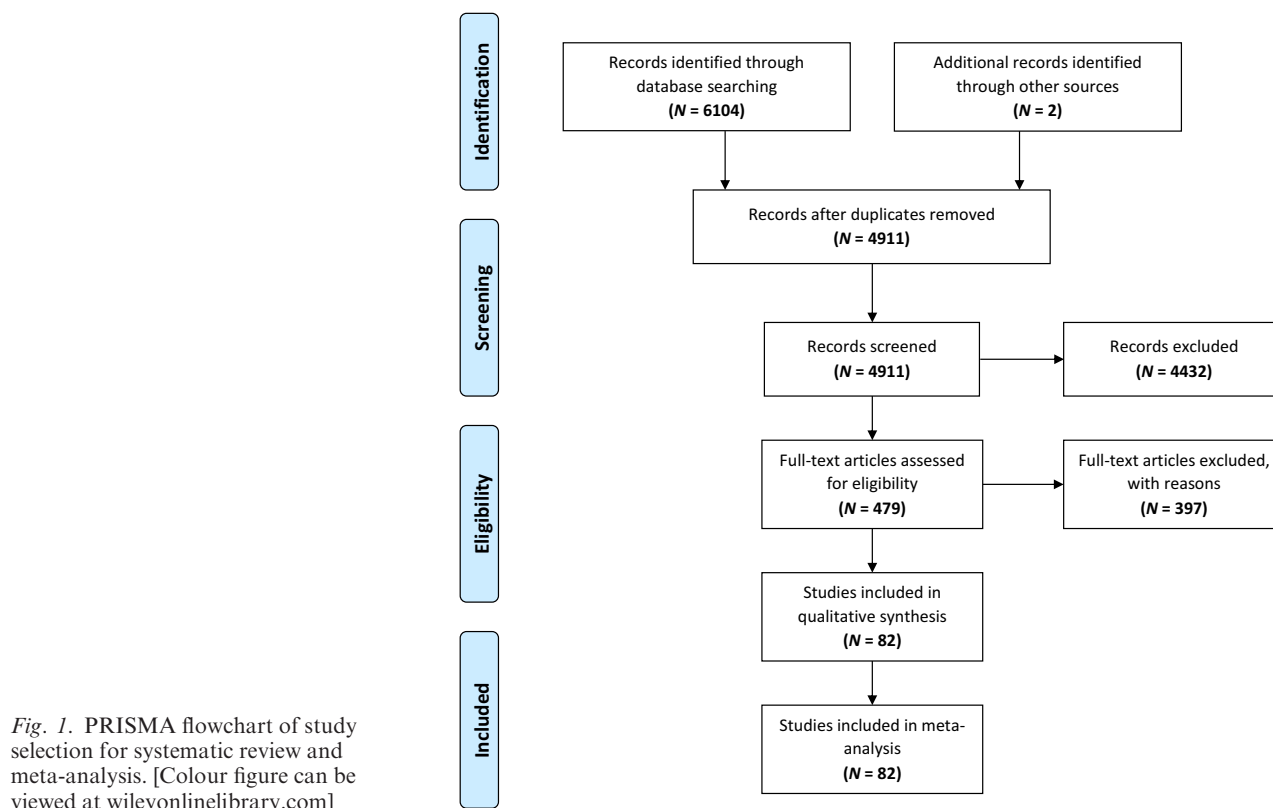
Fig. 1. PRISMA flowchart of study selection for systematic review and meta-analysis. [Colour figure can be viewed at wileyonlinelibrary.com]

studies (42.7%) adjusted results for potential confounders (e.g., age, gender distribution, depressive symptom scores, or BMI). In addition, most studies ($k = 81$; 98.8%) either reported the manufacturer of the assay or provided values of the coefficient of variation (CV) of the test. In addition, most studies ($k = 65$; 79.3%) provided data regarding medication status, whereas three (3.7%) included only treatment-naïve (i.e., never treated with antidepressants) participants with MDD. Finally, most studies did not provide information on illness duration ($k = 56$; 68.3%); the remaining studies included MDD participants with illness duration of 2.97 ± 6.15 (mean $\pm$ SD) years. The methodological quality scores of each study varied from 1 to 6 (median: 4) (Table S2).

Studies of IL-6

Il-6 measurements were extracted from 42 studies (1587 cases and 1183 controls). Participants with MDD had higher concentrations compared to HCs ($g = 0.621$; $P < 0.001$; Table 1 and Fig. 2a). No evidence of small-study effects (which provides an indication of publication bias) was observed. Possible sources for the large heterogeneity ($I^2 = 64.9\%$) were explored using meta-regression and subgroup analyses (Tables S3 and S4). In meta-regression analyses, differences in gender distribution (% females) in the MDD and HC groups emerged as a significant moderator ($P = 0.046$). Subgroup analyses showed that heterogeneity was smaller in studies that measured IL-6 in serum and whole blood samples compared to plasma, while results suggest that the measurement of IL-6 with ELISA is associated with higher heterogeneity compared to other types of assay.

Of 42 studies that measured IL-6, 10 provided adjusted differences in peripheral levels of this cytokine to confounders (e.g., age, gender, BMI, smoking, among other variables specific to the study) (35–44). We re-calculated this ES considering those adjusted values. Then, the overall ES of IL-6 was 0.543 (95% CI = 0.435 0.651; $P < 0.001$). The I^2 value was 49.8% ($P < 0.001$). In addition, we performed a subgroup analysis considering studies which did vs. did not adjust comparisons to confounders. The overall ES for the unadjusted studies was 0.574 (95% CI = 0.437–0.711; $P < 0.001$; $k = 32$), with an I^2 of 52.3% ($P < 0.001$). The overall ES for the adjusted studies was 0.467 (95% CI = 0.303–0.631; $P < 0.001$; $k = 10$), with a I^2 of 38.6% ($P = 0.101$). Therefore, studies that adjusted to potential confounders had a lower degree of heterogeneity.

In sensitivity analysis, the exclusion of any individual study from the analysis did not alter the direction or statistical significance of the ES

Table 1. Primary meta-analyses of studies measuring peripheral cytokines and chemokines in individuals with MDD vs. healthy controls

Mediator	N Studies	N MDD	N Controls	ES (95% CI)	P-value (overall)*	I^2	P-value (Egger)†	Small-study effects‡	Fail-safe N	Adjusted ES (95% CI)§
IL-6	42	1587	1183	0.621 (0.486–0.755)	**<0.001**	64.9	0.950	N	2497	0.621 (0.486–0.755)
TNF-α	42	1620	1457	0.675 (0.431–0.919)	**<0.001**	90.0	**0.009**	Y	2431	0.675 (0.431–0.919)
IL-1β	22	779	727	0.032 (−0.291–0.354)	0.847	89.3	0.180	N	0	−0.152 (−0.477–0.173)
IFN-γ	17	700	770	−0.477 (−0.939 to −0.015)	**0.043**	94.0	**<0.001**	Y	95	−0.477 (−0.939 to −0.015)
IL-10	17	608	675	0.375 (0.008–0.742)	**0.045**	89.2	0.277	N	107	0.375 (0.008–0.742)
IL-2	10	357	476	−0.108 (−0.900–0.683)	0.789	95.8	0.918	N	1	−0.108 (−0.900–0.683)
IL-4	10	350	450	−0.533 (−1.073–0.007)	0.053	91.0	**0.085**	Y	41	−0.533 (−1.073–0.007)
sIL-2 receptor	10	489	391	0.735 (0.418–1.052)	**<0.001**	77.5	0.741	N	224	0.735 (0.418–1.052)
CCL-2	8	285	287	1.718 (0.641–2.794)	**0.002**	96.3	**0.044**	Y	144	1.718 (0.641–2.794)
IL-8	7	306	217	0.032 (−0.346–0.410)	0.869	76.9	0.229	N	0	0.032 (−0.346–0.410)
sIL-6 receptor	7	344	256	0.330 (−0.008–0.667)	0.055	71.3	0.115	N	12	0.330 (−0.008–0.667)
IL-13	6	243	373	1.836 (0.812–2.861)	**<0.001**	96.0	**0.009**	Y	255	1.432 (0.445–2.418)
IL-18	5	135	143	1.720 (0.379–3.062)	**0.012**	95.3	0.105	N	114	1.720 (0.379–3.062)
IL-12	4	135	301	1.229 (0.275–2.182)	**0.012**	92.9	0.609	N	71	1.229 (0.275–2.182)
IL-1Ra	4	148	110	0.449 (0.082–0.815)	**0.016**	51.6	0.986	N	9	0.449 (0.082–0.815)
IL-5	4	198	322	0.396 (−0.072–0.865)	0.097	82.1	0.105	N	18	0.396 (−0.072–0.865)
CCL-3	3	110	98	1.974 (−0.231–4.179)	0.079	97.5	0.180	N	52	1.974 (−0.231–4.179)
IL-17	3	85	106	−0.121 (−0.537–0.295)	0.569	51.6	0.212	N	0	−0.121 (−0.537–0.295)
TGF-β1	3	110	68	−1.480 (−4.756–1.797)	0.376	97.7	0.367	N	5	−1.480 (−4.756–1.797)
sTNFR2	3	94	101	1.173 (0.409–1.938)	**0.003**	83.2	0.368	N	36	1.173 (0.409–1.938)

CI, confidence interval; ES, effect size; MDD, major depressive disorder; Y, Yes; N, No; NA, Not applicable; statistically significant results are in bold.

*In Z-test of overall effect.

†In Egger's test of publication bias.

‡$P < 0.1$ in Egger's test of publication bias and effect size of the largest study more conservative than the overall effect size or in the opposite direction.

§Adjusted using Duval and Tweedie's trim-and-fill procedure.

estimate (Fig. S15). Cumulative meta-analysis indicated that ES estimates are consistent across studies since 1996 (Fig. S26).

Studies of TNF-α

TNF-α was investigated across 42 studies, and levels were significantly higher in the MDD group compared to HCs, while there was evidence of small-study effects ($g = 0.638$; $P < 0.001$; Table 1 and Fig. 2b); the ES was unaltered after adjustment for publication bias (Table 1). Heterogeneity was large ($I^2 = 90.0\%$). The percentage of current smokers in both the MDD and HC groups moderated the ES; in both groups, a higher prevalence of smokers was associated with a higher ES estimate (Table S3). The methodological quality of included studies also emerged as a significant moderator (Table S3). The ES estimate was smaller in studies with better methodological quality. In addition, levels of TNF-α were not significantly altered in individuals with melancholic depression compared to controls ($g = 0.141$; $k = 4$; $P = 0.418$). Sensitivity analysis indicated that the exclusion of any single study (one at a time) did not alter the direction or statistical significance of the ES estimate (Fig. S16). In the cumulative meta-analysis, this ES estimate remained consistent (moderate) after

the addition of the most recent eight studies, which had similar ES estimates (Fig. S27).

Studies of IL-1β

Levels of IL-1β did not significantly differ between MDD and HC groups across 22 included studies (Hedge's $g = 0.032$, $P = 0.847$; Table 1; Fig. S1). No evidence of small-study effects was observed (Table 1). The heterogeneity was large ($I^2 = 89.3\%$). The mean BMI of participants with MDD emerged as a potential source of heterogeneity in meta-regression analysis; a larger BMI was associated with a higher ES estimate (Table S3). In addition, subgroup analyses suggest that heterogeneity is lower in studies that measured this immune mediator in whole blood (compared to studies that assayed IL-1β in serum or plasma) and in studies that used stimulated leukocytes (Table S4).

Studies of IFN-γ

Data for IFN-γ were extracted from 17 studies, and levels were reduced in subjects with MDD compared to the HCs (Table 1; Fig. 3a). There was evidence of small-study effects, but adjustment for publication bias did not change the ES
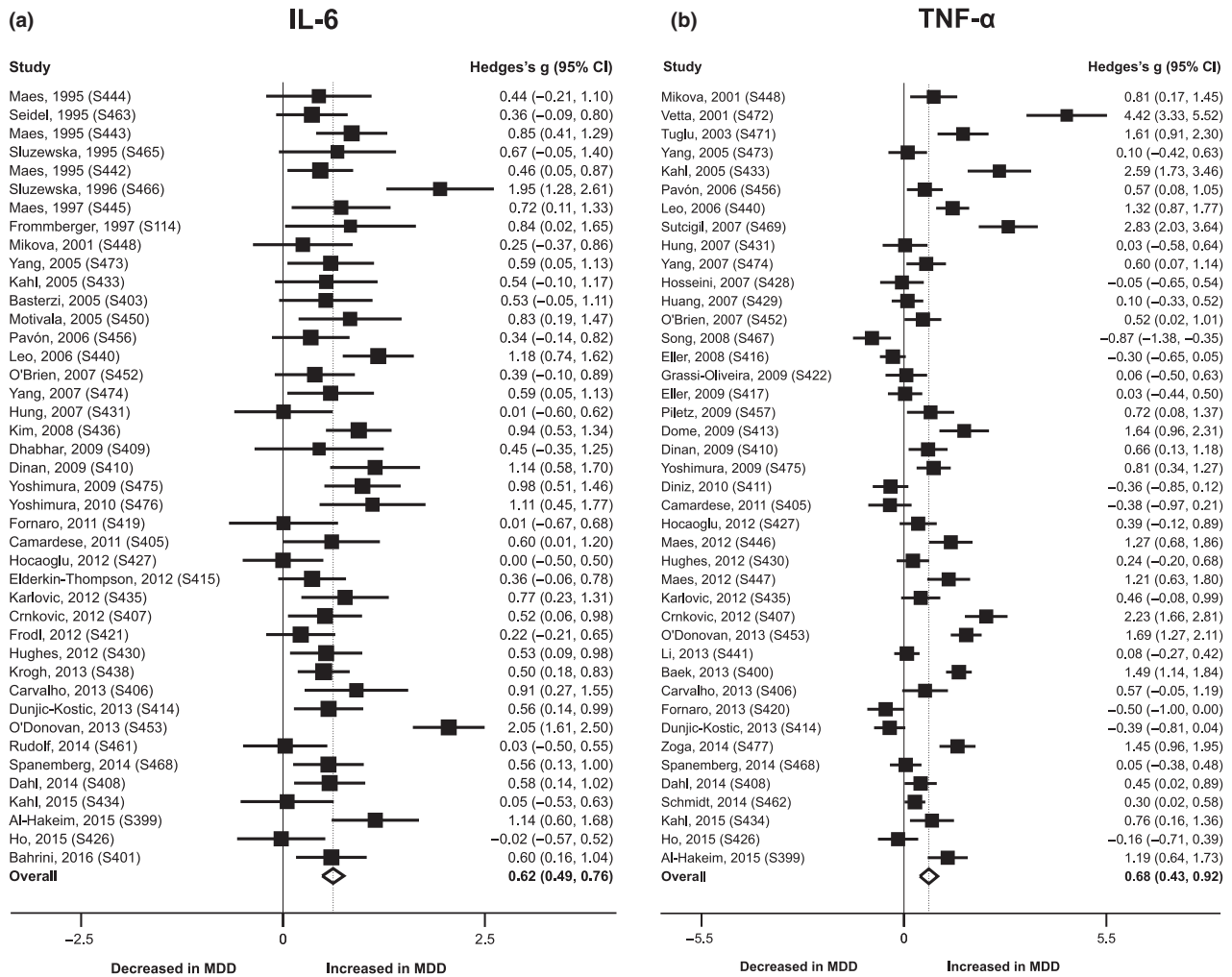
Fig. 2. Forest plots of studies which measured (a) IL-6 or (b) TNF-α or in participants with MDD compared to HCs. Effect size estimates are presented as Hedge's *g* with 95% confidence intervals (CIs). Square sizes are proportional to the ES of each study. References are presented in the supporting information.

($g = -0.452$; Table 1 and Fig. 3a). Heterogeneity was large ($I^2 = 94.0\%$). Mean BMI of the HC group, publication year, sample size, and mean age of the MDD and HC groups emerged as potential sources of heterogeneity in meta-regression analyses (Table S3). Sensitivity analysis revealed that the exclusion of 10 studies from analysis one by one rendered the ES estimate non-significant (Fig. S17). In addition, the cumulative meta-analysis indicates that the ES estimates for IFN-γ have not been consistent over time (Fig. S28).

Studies of IL-10

IL-10 levels were investigated in 17 studies, and levels were significantly higher in the MDD group compared to HCs, with a small ES ($g = 0.375$, $P = 0.045$) (Table 1 and Fig. 3b). No evidence of small-study effects was verified (Table 1). Heterogeneity was large ($I^2 = 89.2\%$), and subgroup

analyses suggest that heterogeneity is lower in studies that assayed IL-10 in plasma compared to serum. In addition, the ES was significant only in studies that followed a non-matched design (Table S4). Furthermore, IL-10 levels were not significantly altered in participants with MDD who were antidepressant-free when this cytokine was assayed, whereas these levels remained significantly elevated in participants with MDD who were using antidepressants (Table S4). Sensitivity analyses showed that the exclusion of 11 of 17 studies one at a time rendered the ES estimate non-significant (Fig. S18). In addition, the cumulative meta-analysis indicates that the ES has not been consistent over time (Fig. S29).

Studies of soluble IL-2 (sIL-2) receptor

We found evidence that sIL-2 receptor levels were significantly higher in the MDD group
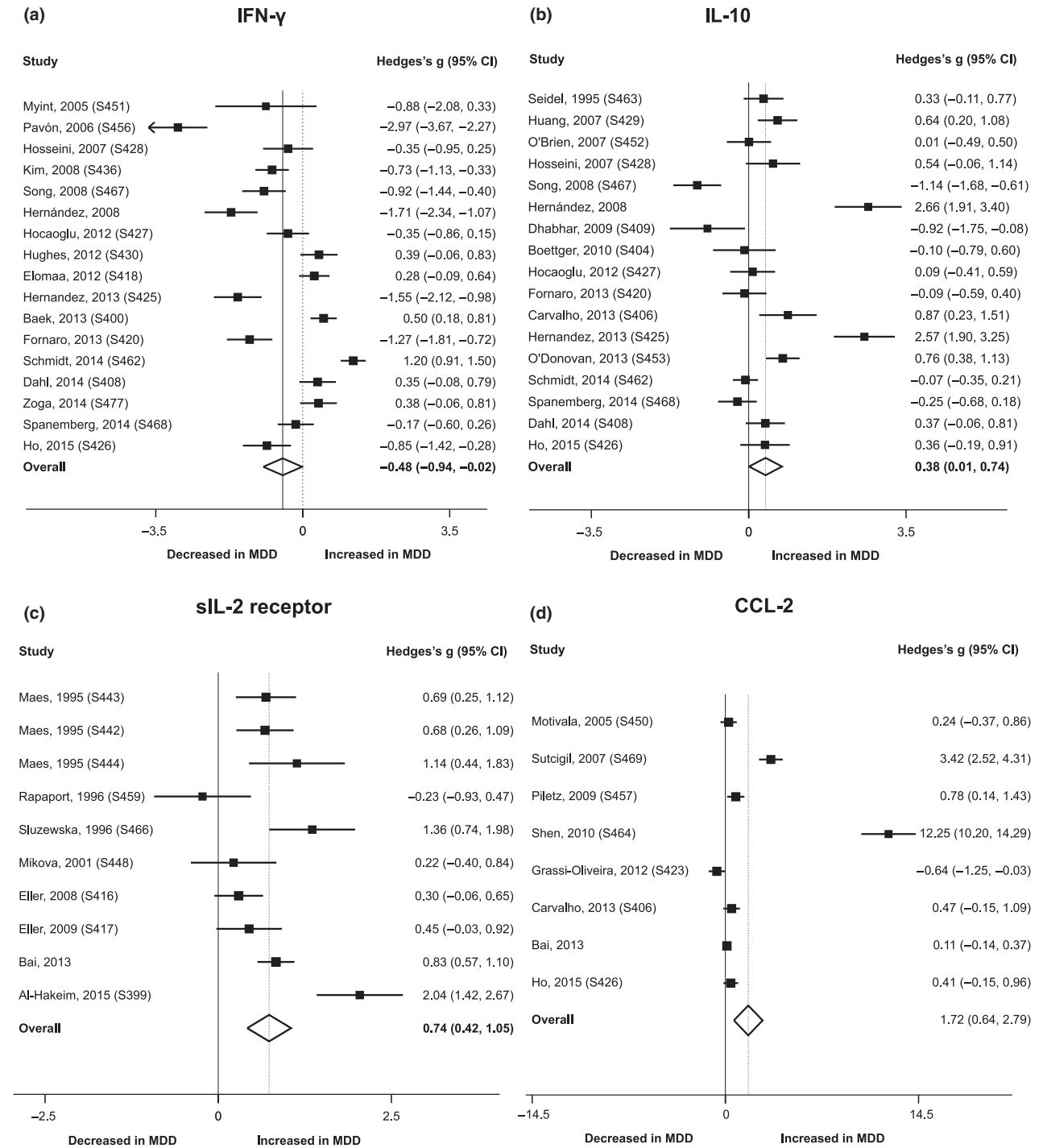
Fig. 3. Forest plots of studies which measured (a) IFN-γ or (b) IL-10 or (c) sIL-2R or (d) CCL-2 in participants with MDD compared to HCs. Effect size estimates are presented as Hedge's g with 95% confidence intervals (CIs). Square sizes are proportional to the ES of each study. References are presented in the supporting information.

compared to HCs with a moderate ES estimate (Hedge's $g = 0.735$, $P < 0.001$) (Table 1; Fig. 3c). No evidence of small-study effects was observed, and between-study heterogeneity was large ($I^2 = 77.5\%$). Subgroup analyses suggested that heterogeneity was lower in studies that measured sIL2 in plasma (compared to serum) as well as in studies in which MDD and HC groups were not age- and gender-matched (Table S4). In sensitivity analysis, the exclusion of included studies one at a time did not alter the direction or significant of the ES estimate.

Moreover, the cumulative meta-analysis indicated that this ES estimate has been consistent over time (Fig. S30).

Studies of C-C chemokine ligand 2 (CCL-2)

Levels of CCL-2 were significantly higher in participants with MDD compared to HCs with a large ES ($g = 1.718$; $P = 0.045$) (Table 1; Fig. 3d). There was evidence of small-study effects (Table 1). However, the ES was not altered after adjustment for publication bias. Heterogeneity was large ($I^2 = 96.3\%$). The ES was not significant in studies which utilized a matched design (Table S4). In sensitivity analysis, we found that the exclusion of the study by Shen et al. (45) from the analysis turned this ES non-significant (Fig. S20).

Studies of IL-13

Levels of IL-13 were significantly higher in participants with MDD compared to HCs ($g = 1.836$; $P < 0.001$) (Table 1; Fig. 4a). The ES estimate remained large even after adjustment for publication bias ($g = 1.432$). The heterogeneity was large ($I^2 = 96.0\%$), but could not be reliably explored due to the limited number of included studies ($k = 6$).

Studies of IL-18

Levels of IL-18 were significantly higher in the MDD group compared to the HC group (Table 1; Fig. 4b). The ES estimate was high ($g = 1.720$; $P = 0.012$), although a limited number of studies were included in this meta-analysis ($k = 5$). Heterogeneity was large ($I^2 = 95.3\%$), and no evidence of small-study effects was observed (Table 1).

Studies of IL-12

Peripheral levels of IL-12 were significantly more elevated in individuals with MDD compared to HCs, with a large ES estimate ($g = 1.229$; $P = 0.012$) (Table 1; Fig. 4c). The heterogeneity was large ($I^2 = 92.9\%$), and no evidence of small-study effects was observed (Table 1). In addition, sensitivity analysis revealed that this ES could be biased by a possible outlier (46) (Fig. S22).

Studies of IL-1 receptor antagonist (IL-1Ra)

Peripheral levels of IL-1Ra were higher in the MDD group compared to HCs ($g = 0.449$; $P = 0.016$) (Table 1; Fig. 4d). Heterogeneity was

large ($I^2 = 51.6\%$), while no evidence of small-study effects was observed (Table 1). However, sensitivity analyses revealed that this ES could be biased by at least three possible outliers (42, 47, 48) (Fig. S24).

Studies of soluble TNF receptor 2 (sTNFR2)

Three studies indicate that sTNFR2 levels are higher in individuals with MDD compared to HCs with a large ES ($g = 1.173$; $P = 0.003$), but high heterogeneity ($I^2 = 83.2\%$) (Table 1; Fig. 4e). No evidence of small-study effects was observed. However, sensitivity analysis shows that removal of the study by Papakostas et al. (49) turned this ES estimate non-significant (Fig. S25).

Other mediators

Levels of IL-2, IL-4, the soluble IL-6 receptor (sIL-6R), IL-8, IL-5, CCL-3, IL-17, and transforming growth factor-β (TGF-β) were measured in at least three studies and were thus meta-analyzed. Levels of these immune mediators did not significantly differ between individuals with MDD and HCs (Table 1). Forest plots for these meta-analyses are provided in the supporting information (Figs S2–S9).

Discussion

This meta-analysis provides the largest evidence synthesis conducted to date of studies that have investigated peripheral levels of cytokines and chemokine peripheral levels in individuals with MDD compared to HCs. Our results suggest that levels of IL-6, TNF-α, IL-10, the sIL-2R, CCL-2, IL-13, IL-18, IL-12, and the sTNFR2 can be significantly elevated in individuals with MDD compared to HCs, while IFN-γ levels may be slightly reduced in the MDD group compared to HCs.

The results of our meta-analysis add significant evidence to a previous meta-analysis (7), while a recent meta-analysis was limited to studies which investigated IL-1β, TNF-α, and IL-6 (5). The previous meta-analysis found elevated levels of TNF-α and IL-6 in depressive patients compared to HCs (7). A recent meta-analysis aimed to compare peripheral levels of cytokines among patients with schizophrenia, bipolar disorder, and also MDD (50). This recent meta-analysis also investigated the effects of antidepressant treatment on blood cytokine levels in patients with MDD (50). However, this meta-analysis included only 30 studies. In addition, a fixed-effects models were used to estimate ESs, which may be inaccurate when
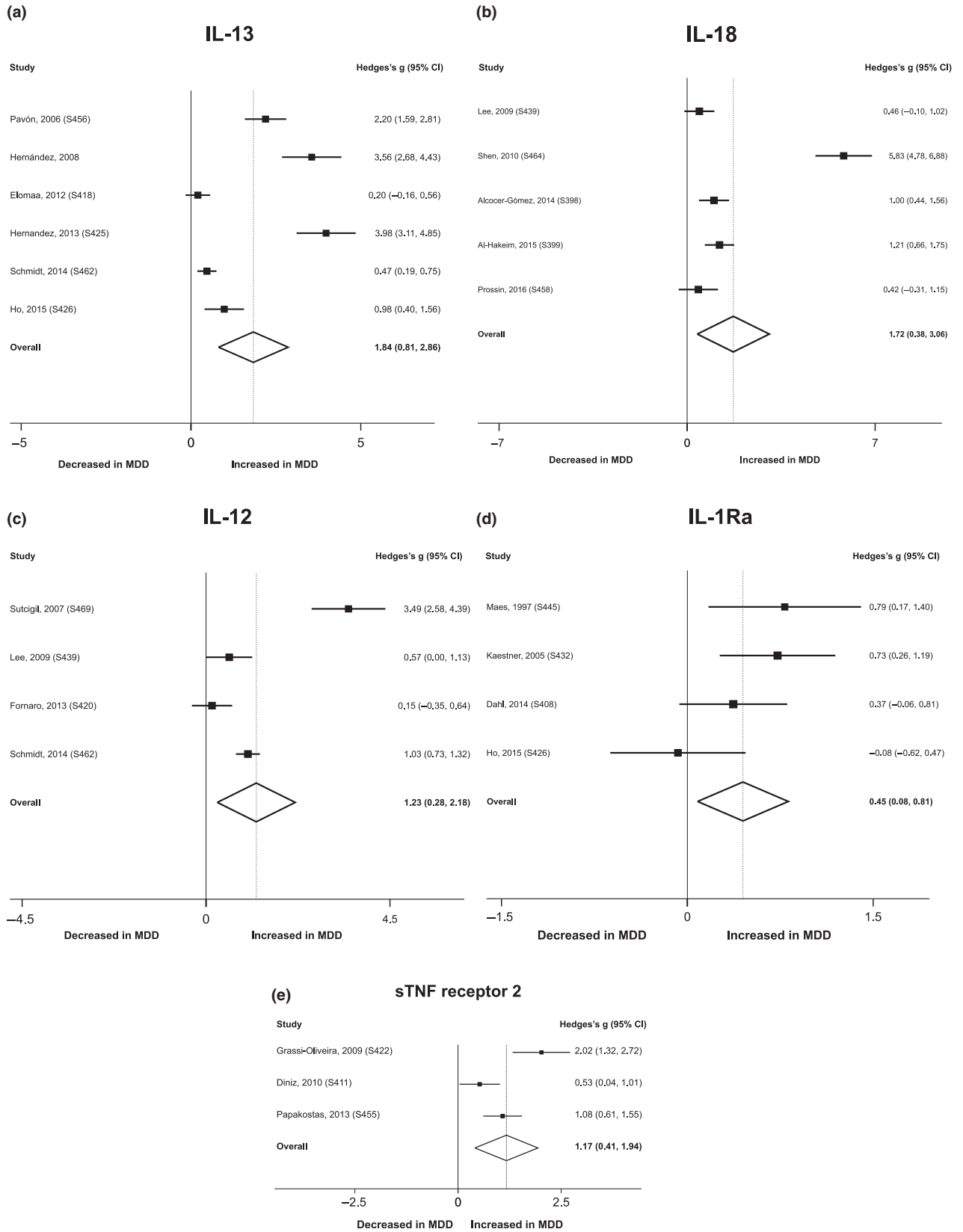
Fig. 4. Forest plots of studies which measured (a) IL-13 or (b) IL-18 or (c) IL-12 or (d) IL-1Ra or (e) sTNFR2 in participants with MDD compared to HCs. Effect size estimates are presented as Hedge's *g* with 95% confidence intervals (CIs). Square sizes are proportional to the ES of each study. References are presented in the supporting information.

heterogeneity is large (27). We confirmed that a high level of heterogeneity across studies characterizes this evolving field (5, 7). In addition, due to the larger number of included studies, we could more accurately explore potential sources of heterogeneity than has previously been possible.

A significant proportion of individuals with MDD exhibits a high prevalence of comorbid medical (e.g., metabolic) and psychiatric conditions (51, 52), which may contribute to immune activation in MDD. For example, it has been postulated that comorbid obesity may lead to a more pernicious outcome in MDD in part due to shared immune-inflammatory pathways (53, 54). Therefore, we *a priori* excluded studies in which participants with MDD had clearly identified comorbidities and examined the influence of other relevant confounders. This approach identified the fact that mean BMI values of the MDD group (IL-1β and IFN-γ), mean BMI of the HC control group (IFN-γ), and current smoking (TNF-α) significantly moderated these estimates. These findings are consistent with the hypothesis that adiposity-driven inflammation may contribute to MDD-related morbidity (55, 56). In addition, it has been postulated that smoking and an unhealthy lifestyle (e.g., poor diet) could be relevant sources of immune activation in MDD (57).

Cytokines and chemokines have been classically subdivided as anti-inflammatory and proinflammatory. However, emerging evidence indicates that this subdivision may be overly simplistic. For example, IL-6 may activate a classical pathway and a trans-signaling pathway, which may have predominantly anti- and proinflammatory activities respectively (58). We found elevated IL-6 levels in participants with MDD compared to HCs. The sIL-6R was examined in relatively few studies, and its peripheral levels were more elevated in the MDD group compared to HCs at the trend level. It is worthy to note that IL-6 was cytokine more extensively investigated in this meta-analysis, with a consistent moderate ES observed in cumulative meta-analysis. In addition, IL-6 and IL-1β may contribute to the pathophysiology of a subset of patients with MDD via excessive release of corticotrophin-releasing hormone (CRH) and by the promotion glucocorticoid receptor resistance, which may ultimately impair the negative feedback regulation of the HPA axis (59, 60).

We found evidence that IFN-γ may be reduced in participants with MDD compared to HCs. However, the ES was small and sensitivity analyses pointed to significant outliers. Furthermore, levels of IFN-γ were most often close to the limit of detection of previously available assay kits, which

may lead to analytical variability. In addition, previous studies found elevated levels of IFN-γ in stimulated peripheral blood mononuclear cells (PBMCs) of individuals with MDD compared to healthy controls, which may provide a more accurate measure of this cytokine (61, 62).

Ronald Smith was the first to propose a macrophage theory for depression in the early 1990's (63). Macrophages and their counterparts in the CNS are crucial cells of the innate immune system, which can alter and adapt their phenotypes depending on their prime activity (a M1-activated phenotype has a primary role in acute defense against pathogens, whereas a M2 phenotype is primarily involved in clearing damaged tissues and repairing activities) (64). Evidence pointing to a role of M1 cells (including microglial cells and CNS macrophages) in MDD has accumulated (2, 65). A clear limitation of this meta-analysis rests on fact that the periphery may not reflect pathophysiological events in the CNS. However, preclinical studies indicate that the blockade of the trafficking of peripheral monocytes to the brain reduced proinflammatory cytokine production and decreased depressive-like behaviours in rodent stress models (66). Thus, peripheral M1 cells could be a main source of elevated cytokines in MDD (4). This meta-analysis evidenced elevated levels of CCL-2, IL-6, IL-12, TNF-α, and IL-1β, which are immune mediators secreted by M1 macrophages albeit not selectively (67).

The inflammatory response is tightly controlled at critical set points, and the maintenance of a healthy immune state is not a passive state, but may require an active expression of immunoregulatory genes (68). Regulatory T-cells (TRegs) are master immune regulators and play a significant role in immune tolerance (69). We found an elevation of IL-10 levels in individuals with MDD compared to HCs. This cytokine is predominantly secreted by TRegs (70). However, subgroup analyses found that this cytokine was not elevated in antidepressant-free participants with MDD, which may underscore an indirect effect of antidepressant drugs. In addition, TGF-β that is another biosignature cytokine of TRegs was not significantly altered in participants with MDD compared to HCs. Thus, a relative lack of counter-regulatory immune mechanisms may contribute to peripheral inflammation in MDD.

The main limitation of this meta-analysis is the high degree of heterogeneity of some estimates. Although we have identified some significant moderators, some possible sources of heterogeneity could not be investigated due to the lack of data across studies, while data on other potential

moderators (e.g., physical activity and diet quality) (57) were not provided by included studies and thus could not be controlled for. Notwithstanding, we could not investigate whether length of disease and number of affective episodes as possible moderators of ESs estimates due to the lack of data across studies, a previous meta-analysis, which used a different definition had found suggestive that some differences in peripheral levels of cytokines may occur in acute compared to chronic MDD relative to HCs (50). Furthermore, the current use of antidepressant drugs did not emerge as a significant moderator in our analyses. However, our exploratory meta-regressions could have limited power to detect this effect, and previous evidence indicates that antidepressant drugs may impact peripheral cytokine levels at follow-up (50). It has been postulated that melancholic depression is associated with an overactive HPA axis and possibly lower inflammation due to the modulatory effects of cortisol (15, 71). We found that few studies have categorized patients in melancholic vs. atypical depression, although we found that TNF-α levels did not differ when individuals with melancholic depression were compared to HCs. In addition, cytokines/chemokines appear to be involved in the pathophysiology of suicidal behaviour (72). Furthermore, technical challenges in the assessment of certain mediators (e.g., IL-2 and IFN-γ) (73) as well as differences in the standardization of assays across different laboratories could have contributed to the heterogeneity of some estimates. It is worthy to note that although a predefined protocol was followed, we did not publish or otherwise registered it in a public database. Finally, the methodological quality of included studies has varied, and in our exploratory meta-regression analyses, this factor emerged as a significant moderator of differences in TNF-α levels between participants with MDD and HCs.

In conclusion, this meta-analysis indicates that several cytokines and CCL-2 are elevated in MDD. Our results confirm that cell-mediated immune activation may be an important pathophysiological aspect of MDD. In addition, our results provide directions for further research. For example, emerging preclinical evidence and a recent theoretical framework indicate that TH17 cells could play a significant role in the biology of depression (74, 75). However, few studies have investigated peripheral levels of IL-17, IL-17F, and IL-22, which are biosignature cytokines of TH17 cells (76). Thus, the characterization of the precise peripheral immune profile associated with MDD remains a work in progress.

Declaration of interests

In the past 3 years, CLR has served on the scientific advisory board for Usona Institute. In addition, he has served on the speaker's bureau of Merck and Sunovion and on the advisory board of Otsuka and Pamlab. All other authors report no conflict of interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Forest plot of studies that investigated IL-1β.

Fig. S2. Forest plot of studies that investigated IL-2.

Fig. S3. Forest plot of studies that investigated IL-4.

Fig. S4. Forest plot of studies that investigated soluble IL-6 receptor (sIL-6 receptor).

Fig. S5. Forest plot of studies that investigated IL-8.

Fig. S6. Forest plot of studies that investigated IL-5.

Fig. S7. Forest plot of studies that investigated CCL-3.

Fig. S8. Forest plot of studies that investigated IL-17.

Fig. S9. Forest plot of studies that investigated TGF-β1.

Fig. S10. Funnel plot of studies that investigated TNF-α.

Fig. S11. Funnel plot of studies that investigated IFN-γ.

Fig. S12. Funnel plot of studies that investigated IL-4.

Fig. S13. Funnel plot of studies that investigated CCL-2.

Fig. S14. Funnel plot of studies that investigated IL-13.

Fig. S15. Sensitivity analysis for the meta-analysis of studies that investigated IL-6.

Fig. S16. Sensitivity analysis for the meta-analysis of studies that investigated TNF-α.

Fig. S17. Sensitivity analysis for the meta-analysis of studies that investigated IFN-γ.

Fig. S18. Sensitivity analysis for the meta-analysis of studies that investigated IL-10.

Fig. S19. Sensitivity analysis for the meta-analysis of studies that investigated soluble IL-2 receptor (sIL-2 receptor).

Fig. S20. Sensitivity analysis for the meta-analysis of studies that investigated CCL-2.

Fig. S21. Sensitivity analysis for the meta-analysis of studies that investigated IL-13.

Fig. S22. Sensitivity analysis for the meta-analysis of studies that investigated IL-18.

Fig. S23. Sensitivity analysis for the meta-analysis of studies that investigated IL-12.

Fig. S24. Sensitivity analysis for the meta-analysis of studies that investigated IL-1 receptor antagonist (IL-1Ra).

Fig. S25. Sensitivity analysis for the meta-analysis of studies that investigated sTNF receptor 2.

Fig. S26. Cummulative meta-analysis of studies that investigated IL-6.

Fig. S27. Cummulative meta-analysis of studies that investigated TNF-α.

Fig. S28. Cummulative meta-analysis of studies that investigated IFN-γ.

Fig. S29. Cummulative meta-analysis of studies that investigated IL-10.