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The longitudinal associations of inflammatory biomarkers and depression revisited: systematic review, meta-analysis, and meta-regression

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Abstract

The innate immune system is dysregulated in depression; however, less is known about the longitudinal associations of depression and inflammatory biomarkers. We investigated the prospective associations of depression and inflammatory biomarkers [interleukin-6 (IL-6), Tumor Necrosis Factor–Alpha (TNF-α), and C-reactive protein (CRP)] in community samples, both unadjusted and adjusted for covariates. The review, registered with PROSPERO, searched for published and unpublished studies via MEDLINE/PsycINFO/PsycARTICLES/EMBASE/Proquest Dissertation. Standardized Fisher transformations of the correlation/beta coefficients, both unadjusted and adjusted for covariates, were extracted from studies examining the prospective associations of depression and inflammatory biomarkers. Systematic review conducted in January, 2019 included 38 studies representing 58,256 participants, with up to 27 studies included in random-effects meta-analysis. Higher CRP/IL-6 were associated with future depressive symptoms, and higher depressive symptoms were associated with higher future CRP/IL-6 in both unadjusted and adjusted analyses – this is the first meta-analysis reporting an adjusted association of IL-6 with future depression. The adjusted prospective associations of depression with CRP/CRP with depression were substantially attenuated and small in magnitude. No significant associations were observed for TNF-α. No conclusive results were observed in studies of clinical depression. Meta-regression indicated that the association of depression and future CRP was larger in older samples and in studies not controlling for possible infection. Small, prospective associations of depression and inflammatory biomarkers are observed in both directions, particularly for IL-6; however, the strength and importance of this relationship is likely obscured by the heterogeneity in depression and profound study/methodological differences. Implications for future studies are discussed.

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Introduction

Depression is a highly prevalent psychiatric disorder that typically occurs early in life, follows a relapsing, remitting course and is associated with a severe disease burden (1–3). Although the cardinal symptoms of depression are low mood and anhedonia (4), depression is accompanied by a wide range of symptoms, including disrupted appetite, sleep, and cognitive dysfunction. In fact, 227 unique symptom profiles exist by which an individual can meet criteria for a depression diagnosis (5), and in a study of 2,154 depressed individuals, 137 unique symptom profiles were observed (6). Rather than capturing a discrete disease process, it is likely that multiple subtypes of depression exist, each characterized by partially distinct etiologies, risk factors, and disruptions to neurobiological systems (7), which may explain why one in three depressed patients do not respond to conventional treatments (8). Since the early 1990s, accumulating evidence suggests that dysregulated immune functioning may characterize one subtype of depression (9, 10).

There is considerable evidence that both ‘arms’ of the immune system – the innate immune system’s rapid and non-specific response to antigens and the adaptive immune system’s slower, antibody-generating, specific response - are dysregulated in depression [see Irwin and Miller (11)]. There also is a better understanding of the humoral, neural, and cellular pathways by which peripheral immune activation can lead to the type of disruptions in neurotransmitter metabolism, neural plasticity, neuroendocrine function, and neural circuitry that are commonly observed in depression (12–14). In particular, there is strong evidence that activation of the innate immune system leads to “sickness behaviors” (e.g., anhedonia, fatigue) that are characteristic of depression (15). Inflammatory biomarkers that index the innate immune response [interleukin-6 (IL-6), Tumor Necrosis Factor – Alpha (TNF-α), and C-reactive protein (CRP)] are consistently elevated in clinical (16) and community (17) samples of depressed individuals. Moreover, when the innate immune system is activated via administration of an endogenous cytokine, interferon-α, 30-50% of medical patients develop clinical depression (18), unless prophylactically treated with an antidepressant (13, 19). Less powerful activation of the innate immune response through administration of a purified endotoxin or vaccination also reliably induces depressive symptoms (15, 20).

It has not been completely established, however, whether inflammation is a cause (15, 21), consequence (22), or correlate of depression (13). Moreover, the observed associations of inflammation and depression may be some combination of the above relationships (e.g., bidirectional) or caused by a common underlying risk factor (e.g., genotype, stress, adiposity, diet) (23, 24). Despite being well-positioned to identify the temporal relationship between inflammation and depression, longitudinal studies thus far report an inconsistent pattern of results with inflammation predicting depression (25, 26), depression predicting inflammation (27, 28), bidirectional associations (29, 30), and null results (31, 32). To date, no comprehensive meta-analysis has examined the temporal relationships between inflammatory biomarkers and depression across the lifespan, although prior work has been conducted either (i) using a very small number of studies (33) or (ii) in elderly samples (34). Equally importantly, despite widespread knowledge of the many covariates that can influence circulating levels of inflammatory biomarkers (33) and the profound differences observed across studies in (i) sample characteristics (size, age, gender, socioeconomic

status), (ii) how inflammation and depression are measured (fasting versus non-fasting/finger prick versus venipuncture blood draws; depression diagnosis versus depressive symptoms), (iii) study design (time to follow-up, inclusion/exclusion criteria), and (iv) analytic approach (e.g., handling of outliers, exclusion of acute illness, statistical approach), no study has systematically investigated how these characteristics may modulate the associations of inflammation and depression.

This systematic review and meta-analysis qualitatively and quantitatively synthesize the ever increasing number of longitudinal studies investigating inflammation and depression *and* investigate sources of heterogeneity in effect sizes via meta-regression. We focus on three inflammatory biomarkers (IL-6/TNF-α/CRP) that closely index activation of the innate immune system because the innate immune system is hypothesized to play a causal role in depression and these biomarkers are the most commonly reported inflammatory biomarkers used in observational studies. Examining the longitudinal associations of inflammatory biomarkers and depression can contribute substantially to a theoretical understanding of the role played by the innate immune system in depression. Given the general pattern of small, bidirectional associations between depression and inflammatory biomarkers observed in prior studies, we hypothesize that inflammatory biomarkers will be associated with elevated future depression and that depression will be associated with elevated future inflammatory biomarkers.

Methods

Data Sources

The systematic review and meta-analysis followed PRISMA/MOOSE guidelines and was registered in PROSPERO (CRD42018112132) in November, 2018 prior to data collection. We searched databases (MEDLINE/PsycINFO/PsycARTICLES/EMBASE/Proquest Dissertation) in January, 2019 for theses/articles written in English since January, 1970 that indicated prospective data for depression and/or inflammatory biomarkers using the following search terms: (depress* OR mood OR affect) and (inflamm* OR interleukin OR IL-1 OR IL-6 OR Tumor Necrosis Factor OR TNF OR C-Reactive OR CRP OR cytokine) and (longitudinal OR prospective OR follow-up OR followup).

Study Selection

Two authors (NMG/TN) iteratively reviewed titles, then abstracts, before conducting a full text review of potentially eligible studies. At each stage, decisions between raters were compared and discrepancies resolved by consensus. Articles were included if: depression was measured via standardized self-report questionnaires/diagnostic assessment; inflammation was assessed via saliva, blood, or lumbar puncture to deliver estimates of CRP, IL-6, or TNF-α; and samples were community-based, population-representative and longitudinal in design. We excluded manuscripts if: participants were recruited on the basis of a medical/psychiatric diagnosis; data were based on non-human studies; outcome data were unavailable and could not be supplied by the authors; and results were reported in conferences, abstracts, editorials and/or letters only. When multiple manuscripts were based on a single cohort, the manuscript with the largest sample was included. Bibliographies were

searched for relevant manuscripts/conference proceedings and included when appropriate. Community samples not recruited randomly were included when broadly representative of the community (e.g., convenience sample included if using a diverse sample of employees, population-based sample over-sampled minority group(s), broadly representative but risk-enriched sample). Study quality was appraised using a modification of the Newcastle Ottawa scale for cross sectional studies (35) and based on a prior meta-analysis (34) – see Supplementary Table 1 for quality assessment scores and Supplementary Table 2 for quality assessment protocol.

Data Extraction

Two authors independently extracted data. Outcomes of interest were: adjusted and unadjusted prospective linear associations (correlation/standardized beta coefficients) between depressive symptoms (A) and inflammatory biomarkers (B). Where possible, we extracted both the unadjusted/least adjusted measure of association between A and B and the most adjusted measure of association for A and B. If the appropriate statistics were not reported in the manuscript, but could be extrapolated from data presented in the manuscript (e.g., standardizing coefficients), this was undertaken. When data were not reported, manuscript authors were contacted twice via email requesting data. The following information also was extracted: author; year of publication; country; analytic sample size; baseline age; sex; race; follow-up duration; depression assessment method; inflammatory biomarker assessment method; CRP values ≥10 removed from analyses; fasting status; time of blood draw; covariates included in statistical models; exclusion criteria, and kit used to assay inflammatory biomarkers.

Statistical Analysis

Meta-analyses were conducted in R (36) using ‘metafor’ (37). Random effects models, selected to address known methodological/analytical heterogeneity, examined the unadjusted and adjusted associations of inflammatory biomarkers (CRP/IL-6/TNF-α) with subsequent depression and the unadjusted and adjusted associations of depression with subsequent inflammatory biomarkers (CRP/IL-6/TNF-α). The DerSimonian-Laird estimator was used to estimate the variance of the distribution of true effect sizes and Fisher’s z-transformation was applied to correlation coefficients and reverse transformed for forest plots. Statistical heterogeneity was assessed using Cochrane Q and the inconsistency index (I^2), which tests whether there is significant variability in the magnitude of effect sizes across studies. Subgroup analyses used a fixed effects model to examine whether effect sizes differed in studies controlling or not controlling for possible acute infection (effect sizes were estimated separately in subgroups utilizing a random-effects-model). Meta-regression was performed when the number of studies was greater than 10. Publication bias was examined visually using a funnel plot and statistically with Egger’s regression intercept test. Sensitivity analyses replicated meta-analyses in: strictly defined community samples, in studies measuring inflammatory biomarkers in venous blood, when examining *change* in depression/inflammation, and in high quality studies.

Results

Study Selection

From 11,176 identified articles, 73 were selected for full-text review and 38 were included for systematic review (24, 25, 27–32, 38–65) and 27 for meta-analysis (see Figure 1 for complete information). Details on the excluded 45 studies can be found in Supplementary Table 3. Study characteristics (summarized in Table 1) indicate substantial variability in sample characteristics and study methodologies – see supplementary information ('Study Characteristics') for a complete discussion.

Inflammatory Biomarkers and Subsequent Depression

There were 32 studies that examined the association between at least one inflammatory biomarker (CRP: 25; IL-6: 17; TNF-α: 9) and subsequent depression. Baseline CRP was associated with future depressive symptoms in 52% (k=12) of all studies, which reduced to 20% (k=5) following adjustment for covariates. Baseline IL-6 was associated with future depressive symptoms in 25% of studies (k=4), which reduced to 13% (k=2) when adjusting for covariates. Baseline TNF-α was associated significantly with future depressive symptoms in 0% of studies, which increased to 11% (k=1) when adjusting for covariates.

Meta-analysis: Random effects meta-analysis reported a significant association of baseline unadjusted CRP [f(r)=.058, p < .0001, k=18] and adjusted CRP [(f(r)=.022, p=.002, k=19)] with future depression – see Figure 2. Baseline unadjusted IL-6 [f(r)=.053, p=.002, k=11] and adjusted IL-6 [f(r)=.043, p < .0001, k=10] were associated significantly with future depression – see Figure 3. Neither unadjusted baseline TNF-α [f(r)=-.008, p=.83, k=5] nor adjusted TNF-α, [f(r)=.013, p=.64, k=5] were associated with future depression.

Meta-regression: The association between baseline CRP and future depression was greater in older samples (SD=25.48 years; b=.026, p=.016, k=18), but not for IL-6 (p=.99). Likewise, the association of baseline CRP (but not IL-6) and future depression was significantly greater in studies that did not remove participants with extreme CRP values (CRP: b=.032, p=.049, k=18). The size of the association of baseline CRP with future depression was smaller when baseline inflammation was controlled for (difference = 0.038, p = 0.007, k = 18), but not for IL-6 (p = 0.36). Neither sex, race, nor time to follow-up predicted the association of CRP/IL-6 with future depression.

Heterogeneity/Publication bias: There was substantial heterogeneity in the association of inflammatory biomarkers and future depression, which typically decreased in adjusted associations. There was no indication of publication bias for CRP, IL-6 or TNF-α – complete details provided as supplementary information ('Heterogeneity and Publication Bias') and in Supplementary Figure 1.

Sensitivity analyses: Results did not differ when analyses were replicated in: community samples alone, in studies using venous blood draws, when controlling for baseline depression, and in high quality studies. An exception to this was that higher TNF-α

predicted higher depressive symptoms in studies controlling for baseline depression, [f(r)=0.061, p=.049, k=3]. See Supplementary Table 4 for complete information.

Depression and Subsequent Inflammatory Biomarkers

Twenty-two studies examined the association between depression and at least one future inflammatory biomarker (CRP: 17; IL-6: 8; TNF-α: 5). Baseline depression was associated with future CRP in 65% (k=11) of studies, which reduced to 6% (k=1) after adjusting for confounding factors. Depression was associated with future IL-6 in 38% (k=3) of studies, which increased to 60% (k=3) when adjusting for confounding factors. Baseline depression was not associated with TNF-α in unadjusted (k=5) or adjusted analyses (k=3).

Meta-analysis: Baseline depression was associated with future CRP in unadjusted [f(r)=.051, p < .0001, k=14] and adjusted analyses [f(r)=.011, p=.038, k=14] and for IL-6 in unadjusted [f(r)=.090, p < .0001, k=6] and adjusted [f(r)=.094, p=.016, k=5] analyses – see Figure 4. Baseline depression was not associated significantly with future TNF-α in either unadjusted [f(r)=.015, p=0.49, k=5] or adjusted [f(r)=0.022, p=.48, k=5] analyses.

Meta-regression: The unadjusted association of baseline depressive symptoms and future CRP was not dependent on age (p=.733), sex (p=.716), the percentage of the sample who identified as Caucasian (p=.935), time to follow-up (p=.746) or whether extreme CRP values were removed (p=.639). Insufficient studies existed to perform meta-regression for IL-6/TNF-α.

Heterogeneity/Publication bias: There was substantial heterogeneity in the association of depression and future inflammatory biomarkers. There was no indication of publication bias for CRP, IL-6 or TNF-α. Complete details provided as supplementary information ('Heterogeneity and Publication Bias') and in Supplementary Figure 2.

Sensitivity analyses: Replication of analyses in community samples alone, in studies using venous blood draws, when controlling for baseline inflammation, and in high quality studies did not yield substantially differing results, except that depression did not predict higher CRP assayed in venous blood, [f(r)=0.015, p=.076, k=9]. See Supplementary Table 5 for complete information.

Inflammatory Biomarkers and Clinical Depression

Six studies examined the prospective associations of inflammatory biomarkers and a future depression diagnosis (assessed via clinical interview). Considerable heterogeneity in sample characteristics and methodologies were evident. Although CRP was reported to be associated with first onset of depression in a sample of middle-aged women (56), no association was observed in other studies (27, 49). Similarly, inflammatory cytokines (IL-6/TNF-α) did not predict onset of future clinical depression in other studies (44, 51, 63). Three studies examining whether a depression diagnosis predicted subsequent inflammation found that clinical depression predicted higher future CRP. In a prospective study of 1,420 children followed through adolescence, only the cumulative number of episodes predicted future CRP following adjustment for covariates (27). Incident depression, independent of

relevant covariates, was significantly associated with increased IL-1β, IL-6, and IL-8 levels in 732 Koreans aged 65+ assessed at two-year follow-up (51). Finally, current, but not remitted depression, was associated with higher levels of future CRP (but not IL-6 or TNF-α) in a representative sample of 3,118 individuals at 5 year follow-up (63).

Discussion

This is the largest, most comprehensive meta-analysis examining the prospective associations of depressive symptoms and inflammatory biomarkers. Based on systematic review of 38 studies containing 58,256 participants and meta-analysis of 27 studies of 47,999 individuals, both CRP and IL-6 were associated with future depressive symptoms – importantly, this is the first meta-analysis to demonstrate a prospective association of IL-6 with depression when controlling for covariates. Depression also was associated with future CRP and IL-6 in both systematic review and meta-analysis. However, the associations of CRP and depression as well as depression and CRP were substantially attenuated following adjustment for covariates and the size of adjusted associations were small ($r \leq .02$). Importantly, the association between depressive symptoms and future CRP was larger in older samples and in studies that did not control for possible acute infection. For studies measuring clinical depression, conclusive associations between depression and inflammatory biomarkers were not observed. There was no evidence for prospective relationships between TNF-α and depression.

Longitudinal studies are crucial in understanding whether inflammatory biomarkers prospectively predict future depression (supporting a causal role), are a correlate of depression, whether they are risk markers of other risk factors (e.g., BMI), or whether inflammation is a consequence of depression (or some combination of the above relationships). Both CRP and IL-6 were associated significantly with future depression in unadjusted and adjusted analyses; these results differ from previous meta-analyses insofar as this is the first study reporting that adjusted IL-6 is associated with future depression (33, 34). This result is unsurprising because IL-6 is arguably the inflammatory biomarker most consistently associated with depression in humans (66) and, instead, likely reflects the greater number of studies examining IL-6 that were included in this review. Moreover, this finding is consistent with a recent Mendelian randomization study which found that the genetic variants responsible for heightened circulating CRP/IL-6 are causally involved in the etiology of depression in a large, population-based sample (67).

There was a small, but consistent, association linking depression with future IL-6. This may reflect the pro-inflammatory effect of multiple behaviors that often accompany depression (e.g., substance use/sedentary behavior/poor diet) (22). However, although statistically significant, depression was not substantially associated with future CRP ($r = .01$) once relevant covariates were included, a finding observed previously (34). It is particularly notable that the number of studies reporting significant associations for CRP in systematic review dropped from 65% to 6% of studies once covariates were included. In particular, multiple studies identified BMI, a known risk factor for depression reliably associated with CRP ($r \approx .4$), as a confounding (26, 27, 39) or mediating (24, 42) variable. Although the association of CRP and depression may be spurious, inflammatory biomarkers also may play

a mechanistic role linking the known association of BMI and depression (24). Thus, care is needed when interpreting the association of depression and inflammatory biomarkers in adjusted analyses.

The longitudinal associations of inflammatory biomarkers and depression observed in this review, particularly in the case of IL-6, suggest that the immune system may be implicated in the etiology of depression; however, caution is needed when interpreting results. First, whereas inflammatory biomarkers are reliably elevated in depression (16), it is less clear whether they remain elevated when depression enters remission. There is some evidence that treatments (pharmacological/cognitive-behavioral) decrease concentrations of inflammatory biomarkers, that decreased concentrations of biomarkers are correlated with reductions in depressive symptoms, and that, following treatment, inflammatory biomarkers do not differ between controls and depressed individuals (68, 69). Thus, it may be that elevated inflammatory biomarkers are not elevated outside of a depressive episode, thereby reducing their detectability in longitudinal studies. Instead, the innate immune system may be 'primed' towards an exaggerated inflammatory response, which may only lead to depression in the context of an immune challenge (15). Second, elevated inflammatory biomarkers typically are observed in a subset (25-30%) of depressed individuals, reducing the ability to detect mean level associations (10, 70). It is noteworthy that the association of CRP and future depression was significantly higher in older samples – it may be that dysregulated inflammatory processes indexed by CRP are more important in older populations, in line with existing theories of geriatric depression (71). Finally, there is growing appreciation that elevated levels of IL-6 may not necessarily reflect a state of chronic, low-grade inflammation (72), and thus, may index other pathological processes implicated in depression. More work is needed to understand for whom inflammatory processes play a role in the etiology of depression as well as a more nuanced understanding of the role played by inflammatory biomarkers in immune functioning.

This review highlights the profound methodological differences observed across studies, which may contribute to weak/inconsistent findings. Inflammatory biomarkers fluctuate according to both (largely) fixed (sex/SES/race) and (largely) varying factors [kit used(details on kit used to measure inflammatory biomarkers provided in Supplementary Table 6)/exercise/substance-use/medication-use/medical status] (73). Although some variability may be difficult to avoid, such as worse health status in elderly samples or the known effect of kit selection on concentrations of inflammatory biomarkers (74), greater effort is needed to produce comparable results. For example, there was remarkable variability in how researchers handled CRP values ≥10. CRP values ≥10 may not capture acute illness [see Mac Giollabhui et al. for a review (75)] and implementation of standardized approaches to assess acute illness is needed in addition to greater efforts to follow existing guidelines when controlling for covariates (73). At the very least, reporting sensitivity analyses as supplementary material when different analytic strategies were pursued would improve comparability of studies.

Results should be interpreted within the limitations of this review. A meta-analysis draws conclusions based on the pooled results of comparable studies and it is abundantly clear that studies included in this review differ substantially based on a wide range of factors that

influence how we interpret results. Likewise, adjusted estimates were based on variables that clearly differed across studies and were limited to studies reported in English. However, this systematic review provides the first comprehensive picture of longitudinal research linking depression and inflammatory biomarkers, which allows us to evaluate and draw conclusions based on a comprehensive review of the literature and may prove useful in the design of future studies and informing our understanding of the etiology of depression.

There is growing consensus that innate immune system functioning is disrupted in clinical depression; however, a clear understanding of its role in the etiology of depression is lacking. The prospective associations of inflammation with future depression and depression with future inflammation (particularly in the case of IL-6) that were observed in this systematic review suggest that a complex relationship exists. For some, inflammation probably plays a causal role in the development of depression and, conversely, depressogenic behaviors likely lead to increases in future inflammation. Importantly, it is probable that both the strength and importance of this relationship is obscured by the heterogeneity inherent in depression as well as profound differences in study designs. Greater efforts to reduce variability in how we assess inflammatory biomarkers and include/exclude participant data are needed. Although the last two decades have seen enormous progress in identifying the biological mechanisms linking immune system dysregulation with depression, further work, particularly theoretical work, is needed to describe how the immune system relates to depression outside of depressive episodes. In particular, fine-grained longitudinal studies that assess inflammatory biomarkers and depression on multiple occasions over relatively short periods of time prior to first onset of depression are needed to disentangle the temporal relationship between depression and inflammatory biomarkers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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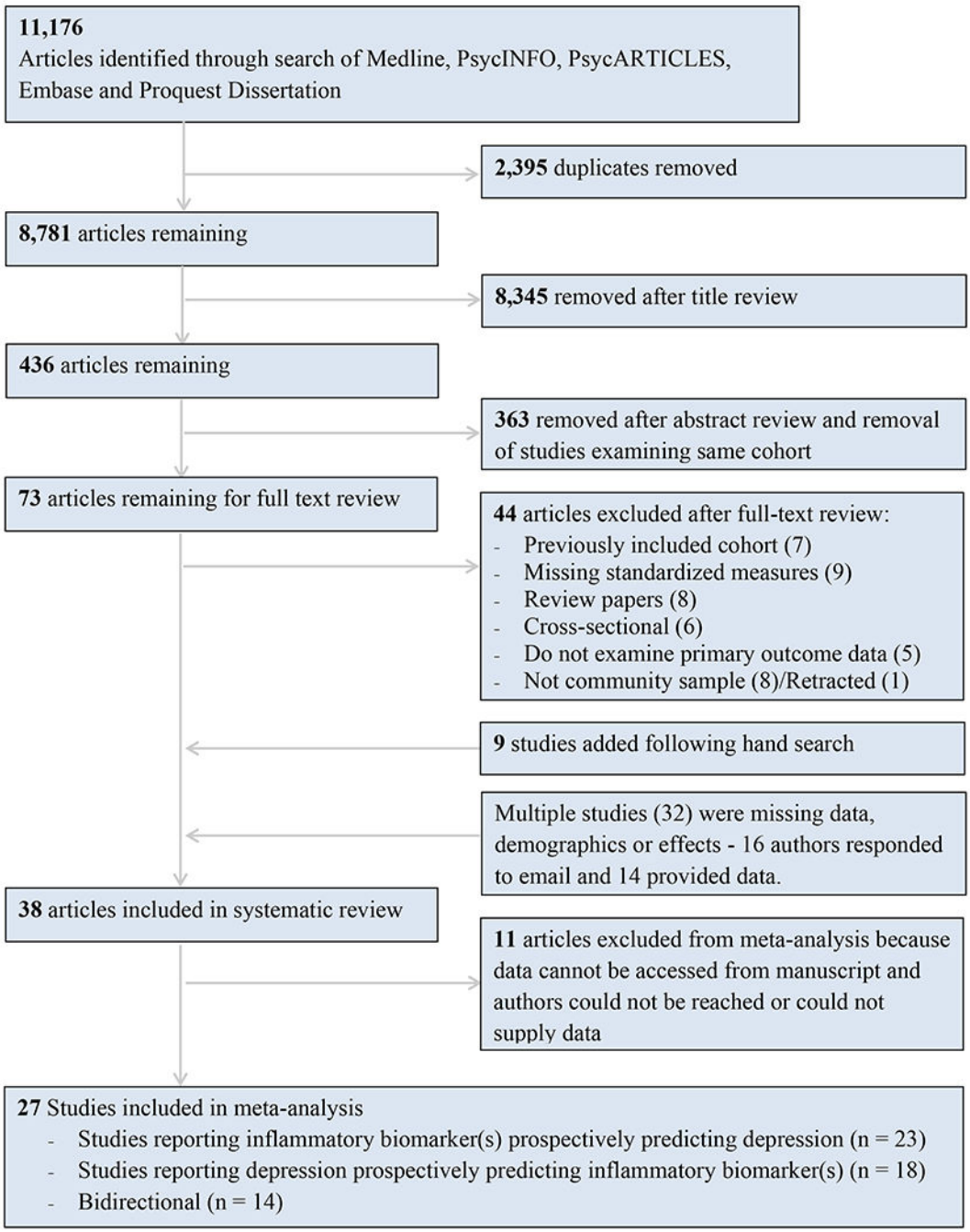

Figure 1.
Flowchart detailing process by which studies were included in systematic review and meta-analysis.

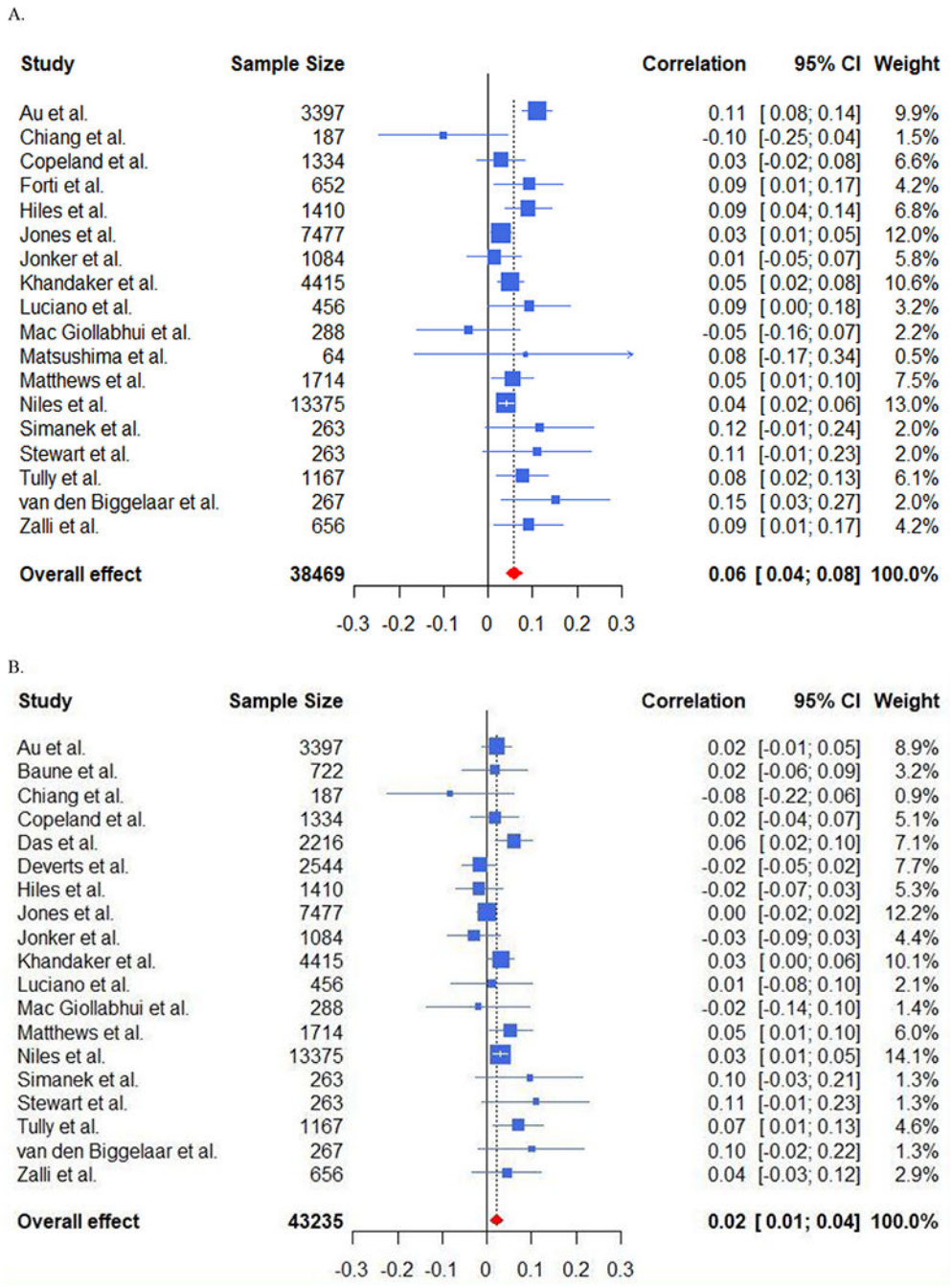

Figure 2. Forest Plots of Baseline CRP and Future Depressive Symptoms.

A. Forest Plot Displaying Unadjusted Associations of Baseline CRP and Future Depressive Symptoms.

B. Forest Plot Displaying Adjusted Associations of Baseline CRP and Future Depressive Symptoms.

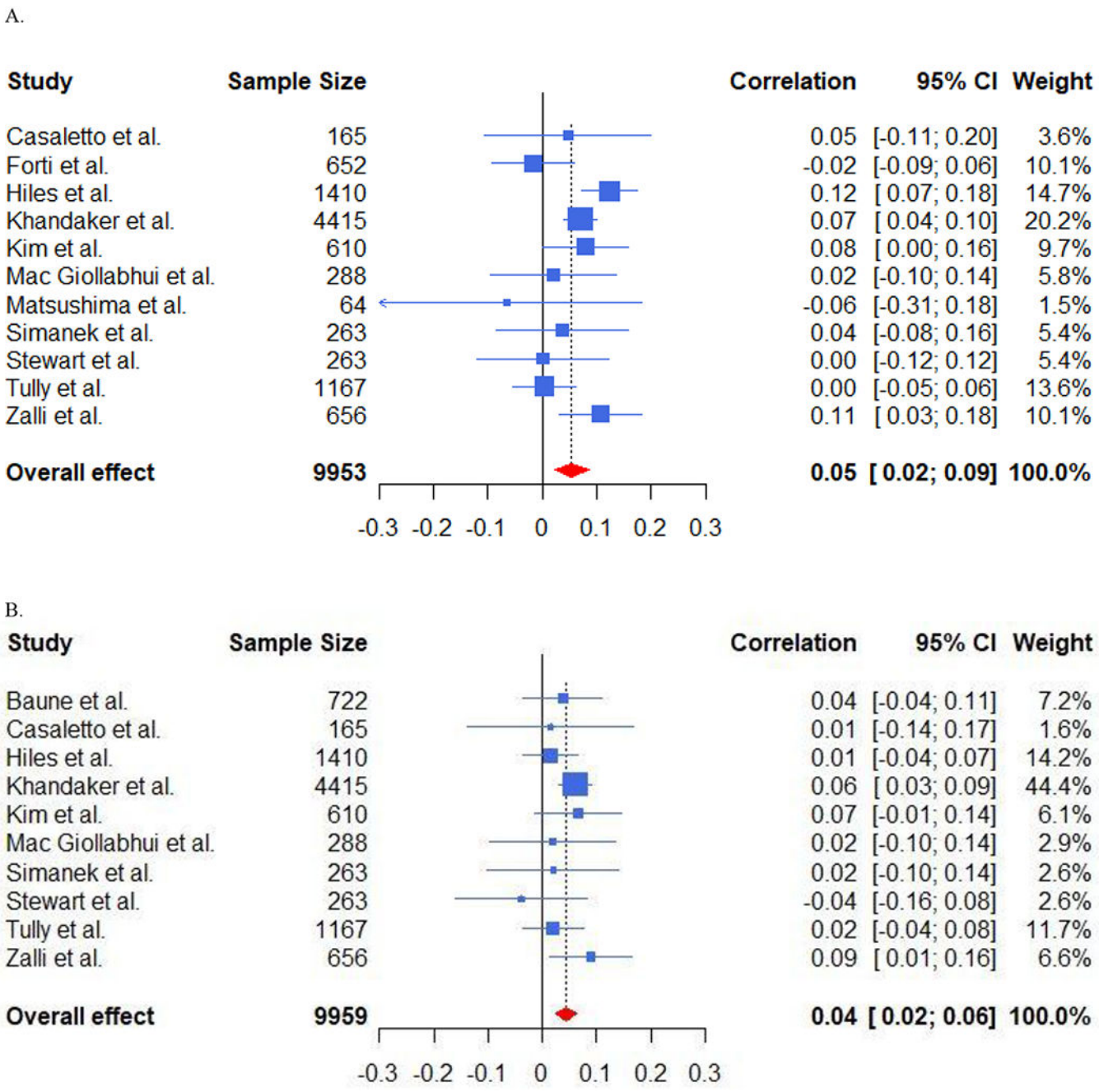

Figure 3. Forest Plots of Baseline IL-6 and Future Depressive Symptoms.

A. Forest Plot Displaying Unadjusted Associations of Baseline IL-6 and Future Depressive Symptoms.

B. Forest Plot Displaying Adjusted Associations of Baseline IL-6 and Future Depressive Symptoms.

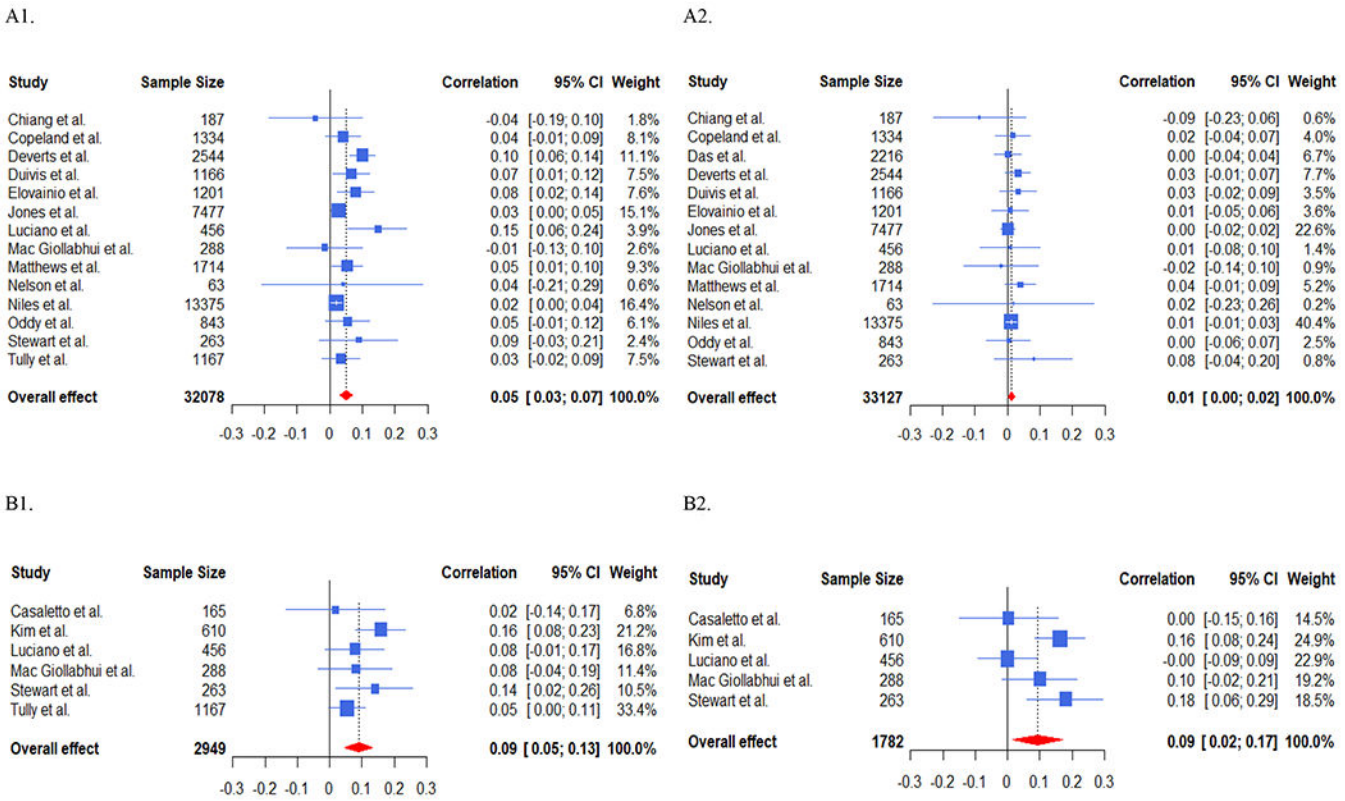

Figure 4. Forest Plots of Baseline Depressive Symptoms and Future CRP and Future IL-6.

A1. Forest Plot Displaying Unadjusted Associations of Baseline Depressive Symptoms and Future CRP.

A2. Forest Plot Displaying Adjusted Associations of Baseline Depressive Symptoms and Future CRP.

B1. Forest Plot Displaying Unadjusted Associations of Baseline Depressive Symptoms and Future IL-6.

B2. Forest Plot Displaying Adjusted Associations of Baseline Depressive Symptoms and Future IL-6.

Table 1.

Study characteristics for all studies examining prospective associations of inflammatory biomarkers and depression included in systematic review.

Author	Year	Country	Analytic Sample	Baseline Age	% Female	% White	Follow-up (Years)[a]	In Meta-analysis?	Depression assessed via interview?	Biomarkers Assessed (Method)	CRP>10[b]?	Covariates?	Exclusion Criteria[c]	Quality
Khandaker et al.	2014	UK	4415	9	48.0	98	8.8	Yes	No	Blood	No	a , b, c, d, e, f, s	d	7
Adriaensen et al.	2014	Belgium	303	84.3	62.7	nr	1.7	No	No	Blood	No	a, b, e, f, n, o, s	a	5
Deverts et al.	2010	USA	2544	40.2	55.0	58.2	5.0	Yes	No	Blood	Yes	a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, s	d	6
Elovainio et al.	2006	Finland	1201	22.5	59.4	nr	9.0	Yes	No	Blood	No	a, b, d, e, h, i, j, k, l, s	a	5
Simanek et al.	2014	USA	263	54	57.4	13.7	1.0	Yes	No	Blood	No	h, i, o, p	c	5
Au et al.	2015	UK	3397	64.6	56	99	4.0	Yes	No	Blood	No	a, b, d, e, f, h, j, k, l, n, o, s	none	5
Copeland et al.	2012	USA	1334	14.2	49	89.7	1.0	Yes	Yes	Finger	Yes	a, b, c, d, e, f, g, h, i, o, s	none	5
Brown et al.	2016	USA	3075	73.6	52	58.3	10.0	No	No	Blood	No CRP	a, b, e, n, o, q	d	4
Hiles et al.	2015	Australia	1410	65.6	50	nr	4.5	Yes	No	Blood	Yes	a, b, e, f, h, i, j, n, s	a, b, d	5
Milaneschi et al.	2009	Italy	550	75	56	nr	3.0	No	No	Blood	No		c	6
de Mello Franco et al.	2017	Brazil	1508	41.31	19	nr	2.2	No	No	Blood	Yes	a, b, e, h, j, n	a, d	5
Das et al.	2017	USA	2216	67.11	51	80.1	5.0	Yes	No	Finger	Yes*	a, b, c, d, e, f, g, n, o	none	6
Stewart et al.	2009	USA	263	61	52	86.7	6.3	Yes	No	Blood	Yes	a, b, c, d, e, f, g, h, i, j, k, l, m, n, s	a, b	6
Kern et al.	2014	Sweden	86	72.5	100	nr	16.5	No	Yes	CSF	No CRP	a, e, h	a	4
Zalli et al.	2016	Holland	656	73	60	nr	5.0	Yes	No	Blood	No	a, b, e, f, h, n, q	b, d	6
Simanek et al.	2019	USA	771	69.4	55	nr	1.5	No	No	Blood[2]	No	a, b, c, d, e, g, h, i, o	b, c	6

Author	Year	Country	Analytic Sample	Baseline Age	% Female	% White	Follow-up (Years)[a]	In Meta-analysis?	Depression assessed via interview?	Biomarkers Assessed (Method)	CRP>10[b]?	Covariates?	Exclusion Criteria[c]	Quality
Matthews et al.	2010	USA	1714	46.2	100	51	1.0	Yes	No	Blood	Yes	a, c, d, e, f, g, h, j, n, o, s	a, b, d	6
Baune et al.	2012	Australia	722	78.8	55	nr	2.0	Yes	No	Blood	No	a, b, d, e, h, n, o, q, s	a, c	5
Duivis et al.	2015	Holland	1166	11.1	54	nr	3.0	Yes	No	Blood	No*	a, b, d, e, h, j	d	6
Jonker et al.	2017	Holland	1084	16.2	54	nr	2.7	Yes	Yes	Blood	Yes	, b, c, d, e, h, i, s	c, d	6
Casaletto et al.	2018	USA	165	72.6	49	nr	1.9	Yes	No	Blood	No*	a, b, d, s	c, d	4
Kim et al.	2018	Korea	610	72.8	59	nr	2.4	Yes	Yes	Blood	No CRP	, b, f, g, j, n, s	c	5
Luciano et al.	2012	Scotland	456	69.5	50	nr	3.0	Yes	No	Blood	No*	a, b, e, j, o	a	6
Luukinen et al.	2010	Finland	404	nr	61	nr	2.5	No	No	Blood	Yes		c, d	5
Matsushima et al.	2015	Japan	64	72.05	74	nr	3.0	Yes	No	Blood	No		b, c	3
Nelson et al.	2018	Australia	63	14.84	41	77.8	0.6	Yes	No	Saliva	No	a, b, e, h, q, s	b, c	3
Niles et al.	2018	USA	13375	67.79	60	81.61	4.0	Yes	No	Finger	Yes	a, d, e, f, g, h, i, j, n, s	d	5
Pasco et al.	2010	Australia	644	47	100	nr	10.0	No	Yes	Blood	No	a, e, h, j, n, o	none	6
Tully et al.	2015	Australia	1167	54.13	0	nr	4.9	Yes	No	Blood	No	a, e, h, j, n	a, b, c	5
Walss-Bass et al.	2018	USA	195	13.37	54	58	0.9	No	No	Blood	No*	,	c, d	3
Oddy et al.	2018	Australia	843	14	51	88	3.0	Yes	No	Blood	Yes	a, c, d, e, h, i, j, s	d	5
Jones et al.	2017	USA	7477	63.47	100	53.8	15.4	Yes	No	Blood	No*	a, c, d, e, f, g, h, i, j, o, s	d	5
Chiang et al.	2019	USA	187	16.4	57	nr	2.0	Yes	No	Finger	Yes	a, b, d, e, h, i, n, o	d	5
van den Biggelaar et al.	2007	Holland	267	85	63	nr	1.0	Yes	No	Blood	No	e, f, h, n, q, s	b, c	6
Glaus et al.	2018	Switzerland	2580	43.94	61	96.39	5.8	No	Yes	Blood	Yes	a, b, c, d, e, h, j, n, o, s	d	7

Author	Year	Country	Analytic Sample	Baseline Age	% Female	% White	Follow-up (Years)[a]	In Meta-analysis?	Depression assessed via interview?	Biomarkers Assessed (Method)	CRP>10[b]?	Covariates?	Exclusion Criteria[c]	Quality
Caserta et al.	2011	USA	141	9.3[1]	46	47	0.5	No	No	Blood	No CRP	a, b, d, e, s	a	3
Mac Giollabhui et al.	2019	USA	288	16.34	51	41	1.2	Yes	No	Blood	Yes	e, f, g, q, s	a, c, d	6
Forti et al.	2010	Italy	652	74.54	55	nr	3.9	Yes	No	Blood	No	a, b, d, e, n, o, q, s	c	5

[a] = If more than two follow-up points of unequal length were included in the study, the average was calculated for the purpose of meta-regression.

[b] = Were CRP values greater than or equal to 10mg/L excluded. Where alternative cut-offs were used they are highlighted with "*" and marked "Yes" if they use a more conservative cut-off and "No" if they use a more liberal cut-off.

[c] = Represents a selection of the most important and common exclusion criteria used across studies.

[1] = Median age reported.

[2] = 32.4% assessed via venipuncture.

nr = not reported; Finger = Blood drawn via finger prick; CSF = cerebrospinal fluid;

Covariates: a = age, b = sex, c = race, d = socio-economic status, e = index of body mass/body fat, f = baseline depression, g = baseline inflammatory biomarker, h = smoking status, i = alcohol use, j = physical activity, k = triglycerides, l = cholesterol, m = glucose, n = medical diagnosis, o = medication use, p = stress, q = cognitive functioning, r = other

Exclusion criteria (non-exhaustive list): a = medical diagnosis, b = medication use, c = psychiatric diagnosis, d = acute infection.