

CHRONIC INFLAMMATION AS A PATHWAY LEADING TO COGNITIVE
DYSFUNCTION IN DEPRESSED YOUTH

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ABSTRACT

Cognitive functioning is disrupted during a depressive episode and cognitive dysfunction persists when depression is in remission. A subtype of depressed individuals who exhibit elevated inflammatory biomarkers may be at particular risk for cognitive dysfunction. We examined whether an elevated inflammatory biomarker (C-reactive protein: CRP) in acute and/or remitted depression was associated with specific deficits in executive functioning, episodic memory, and verbal fluency. Data were drawn from a population-based sample of Dutch adolescents (N = 1,066; 46% male) recruited at the age of 11 and followed over the course of eight years. We tested whether adolescents with either, (i) a history of depression (Wave 1 – 3) or (ii) current depression (Wave 4), *and* elevated levels of C-reactive protein measured in blood at Wave 3 performed worse on cognitive assessments at Wave 4. Eight measures of cognitive functioning were hypothesized to load on to one of three dimensions of cognitive functioning (executive functioning, episodic memory, and verbal fluency) within a structural equation model framework. Higher levels of CRP were associated with worse future executive functioning in adolescents with and without current/prior depression. A current depression diagnosis also was associated with worse future executive functioning. There was consistent evidence linking low socioeconomic status and health-related covariates (high body mass index/sedentary behavior) with worse performance across multiple measures of cognitive functioning and, importantly, the association of depression/CRP and executive functioning was no longer significant when controlling for these covariates. Future

studies may benefit from investigating whether specific depressogenic behaviors (e.g., sedentary behavior/substance use) mediate a relationship between depression and worse executive functioning, potentially via a prospective pathway through elevated inflammation.

DEDICATION

This dissertation is dedicated to my wife, Giselle, whose love and support made this process light and joyful. I couldn't ask for a better partner. To my son, Seosamh, who was eight months old when I wrote this dissertation, I smiled many times as I wrote this dissertation while listening to you babbling close by. Now as I prepare to defend it, you make me laugh more on and more as you start to say your first words. To my parents, Seán and Jean, who cultivated a love of learning, and to my brothers, Niall, Shane and Muiris, who were always quick to pick apart a lazy argument – you've made these last six years a lot easier.

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CHAPTER 1

**INVESTIGATING WHETHER DEPRESSED YOUTH EXHIBITING ELEVATED
C REACTIVE PROTEIN PERFORM WORSE ON MEASURES OF EXECUTIVE
FUNCTIONING, VERBAL FLUENCY AND EPISODIC MEMORY IN A LARGE,
POPULATION BASED SAMPLE OF DUTCH ADOLESCENTS.**

Introduction

Depression is a highly prevalent, recurrent, and burdensome disorder that typically first emerges during adolescence (Hasin et al., 2005; Hasin et al., 2018). Depression tends to follow a remitting, relapsing course: recurrent episodes occur for 50% of individuals who experience a first depressive episode and 80% of those who experience a second episode (Burcusa & Iacono, 2007; Kessler et al., 2003). The consequences of depression are severe; most depressed individuals (approximately 60%) report that the impact of symptoms on functioning is severe or very severe, particularly for social functioning, and depression is associated with increased risk of adverse outcomes, such as suicidal behavior and cardiovascular disease (Kessler et al., 2003; Oquendo et al., 2003; Ownby et al., 2006; Van der Kooy et al., 2007). It is the heavy disease burden of depression combined with its high prevalence, early onset, and recurrent course that makes it imperative to better understand the etiology of depression, particularly during adolescence when it typically first emerges.

Cognitive vulnerabilities, that are characterized by negative biases in the way individuals attend to, interpret, and recall information from their environment, have been shown to precede depression and predict its first onset in prospective, longitudinal studies and in high-risk designs (Abramson et al., 1989; Alloy et al., 2006; Beck, 1976; Gotlib & Joormann, 2010; N. Mac Giollabhui et al., 2018). However, in addition to the existence of negative cognitive biases in depression, there is accumulating evidence that cognitive processes (e.g., memory, attention, and executive functioning) are disrupted in

depression. Depressed individuals perform worse across a broad range of cognitive domains (e.g., episodic and working memory, sustained attention, psychomotor speed, and executive function) when compared to healthy controls (McDermott & Ebmeier, 2009; Rock et al., 2014; Snyder, 2013b; Wagner et al., 2012). These deficits are observed at first onset (Lee et al., 2012), in both medicated and unmedicated samples (Porter et al., 2003), and in both community and in-patient samples (Porter et al., 2007). Moreover, deficits across a range of cognitive domains persist in remitted depression (most consistently in psychomotor speed, attention, executive functioning, and verbal fluency) (Bora et al., 2013; Hasselbalch et al., 2011; Rock et al., 2014; Semkowska et al., 2019); deficits in episodic memory are typically confined to a current depressive state (Bora et al., 2009; Hasselbalch et al., 2011; Rock et al., 2014). There is growing interest in understanding why cognitive dysfunction is observed in depression, particularly given its major contribution to functional impairment (Jaeger et al., 2006; Whiteford et al., 2013; Woo et al., 2016).

The association between cognitive functioning and depression may be characterized by four relationships. First, cognitive dysfunction may be caused by the presence of depressive symptoms, with cognitive dysfunction limited to the duration of a depressive episode (McDermott & Ebmeier, 2009). Second, depression, particularly a more severe and/or chronic course, may lead to neuropsychological scarring, such that cognitive dysfunction persists beyond a depressive episode (Allott et al., 2016). Third, cognitive dysfunction may play a causal role in the onset of depression (Franz et al.,

2011; Gale et al., 2010; Koenen et al., 2009; Zammit et al., 2004) – for example, cognitive dysfunction may generate stressful life events (e.g., academic failure) precipitating a depressive episode. Finally, depression and cognitive functioning may not be causally related and, instead, observed associations may be due to common underlying causes (e.g., inflammation) (Naoise Mac Giollabhui et al., 2018; Mac Giollabhui et al., 2019; Mac Giollabhui, Swistun, et al., 2020). It should be noted that these relationships are not mutually exclusive, and instead, may exert reciprocal effects. To extend our previous example, cognitive dysfunction generates stressful life events (e.g., academic failure) leading to depression, which, in turn, leads to substance use that further worsens cognitive functioning and, exacerbated by further impairment in cognitive functioning, increases the likelihood of further academic failure, resulting in increasing depressive symptoms...). In fact, Mac Giollabhui et al. (2019) have shown in a single cohort that cognitive dysfunction worsens during a depressive episode, persists when depressive symptoms abate, and that stress exposure is longitudinally associated with both increased depressive symptoms and worse cognitive functioning. The lack of firm conclusions about the prospective associations of cognitive functioning and depression may be exacerbated by the relative dearth of longitudinal studies examining cognitive functioning prior to first onset of depression.

Difficulty in accurately characterizing the relationship between cognitive functioning and depression is exacerbated by heterogeneity within depression and variability in how cognitive functioning is assessed. Cognitive deficits in depressed

individuals vary based on a wide range of demographic (age, education, socioeconomic status) and clinical characteristics (pre-clinical dementia, severity of depressive symptoms, recurrence of depression, comorbid conditions, and medication status) (Engels et al., 2010; Keilp et al., 2008; McDermott & Ebmeier, 2009; Snyder, 2013b; Snyder et al., 2015; Sommerfeldt et al., 2016; Veiel, 1997). Thus, it may be that group differences observed in cognitive functioning within depressed samples are driven by specific demographic, clinical, and/or biologically-based phenotypes (Carvalho et al., 2014; Snyder et al., 2015). Second, discrepant results may be due to differences in the domains of cognitive functioning assessed in a given study and/or differences in the functional demands of a specific cognitive test; for example, some tasks assessing cognitive flexibility also capture variability in psychomotor speed while others also capture variability in problem-solving/rule learning. Moreover, most studies examine a relatively small number of cognitive domains, and typically, it is unclear whether cognitive deficits reported are specific to the domain assessed (e.g., differentially affecting episodic memory) or reflect difficulties in cognitive functioning that are more generalized in nature (e.g., affecting episodic memory and multiple other domains).

Meaningful progress toward understanding the relationship between cognitive functioning and depression may require a better understanding of the biological mechanism(s) underpinning cognitive dysfunction in depression, which, in turn, may identify for whom and under which conditions cognitive dysfunction emerges in depression. Multiple, overlapping biological pathways are implicated in the development

of cognitive dysfunction in depression (Carvalho et al., 2014). In particular, there is convergent evidence for inflammation as a neurobiological mechanism underpinning cognitive dysfunction in depression. Peripheral inflammation can act directly upon the central nervous system (Christine et al., 2015; Harrison et al., 2014; Hoogland, 2015; Lampa & Westman, 2012) and disrupt neuronal processes (e.g., long-term potentiation, synaptic plasticity, and neurogenesis) as well as affect brain regions and their respective cognitive associates (e.g., hippocampus: episodic memory; anterior cingulate cortex: executive function). Studies have linked inflammatory biomarkers with impaired cognition in medical (Crisan et al., 2014; Huang et al., 2016; Li et al., 2014), healthy elderly (Baune et al., 2008; Jenny et al., 2012; Noble et al., 2010), and healthy adult (Paine et al., 2015; Reichenberg et al., 2001; Yang et al., 2019) samples; however null results also are observed (Dik et al., 2005). Inflammatory biomarkers also have been prospectively associated with worse cognition in healthy middle-aged samples (Karlamangla et al., 2014; Singh-Manoux et al., 2014). Inflammation also is implicated in the development of ‘sickness’ behaviors that characterize depression (anhedonia, social withdrawal, psychomotor retardation) (Maes et al., 1995; Smith, 1991). Experimental induction of inflammation is associated with the onset of depressive symptoms (Dantzer, 2001) and it also prospectively predicts depression in community samples (Au et al., 2015; Gimeno et al., 2009; Khandaker et al., 2014). It is noteworthy that elevated peripheral biomarkers of inflammation are likely present in just a subgroup (approximately 30%) of individuals with MDD (Dowlati et al., 2010; Haapakoski et al.,

2015; Howren et al., 2009; Kohler et al., 2017; Osimo et al., 2019). Thus, there is strong evidence linking inflammatory physiology in both cognitive dysfunction and depression.

A small, emerging body of research has examined the relationship between inflammatory biomarkers and cognitive functioning in major depression (MDD) (Misiak et al., 2018), and there is convergent evidence linking inflammatory biomarkers with structural and functional brain abnormalities observed in MDD as well as cognitive dysfunction (Carvalho et al., 2014; Drevets et al., 2008; McAfoose & Baune, 2009). Elevated inflammatory biomarkers have been associated with psychomotor retardation, memory deficits, and impaired executive functioning in adults with current MDD (Chang et al., 2012; Goldsmith et al., 2016; Grassi-Oliveira et al., 2011; Krogh et al., 2014); however, it is notable that, although inflammatory biomarkers are associated with cognitive functioning in the depressed group, they also are associated with cognitive dysfunction in healthy controls (Grassi-Oliveira et al., 2011; Krogh et al., 2014). Other studies have shown that inflammatory biomarkers may be indirectly associated with worse working memory via higher body mass (Yang et al., 2019), and longitudinal data indicate that higher body mass prospectively predicts both worse executive functioning and more severe depressive symptoms in a diverse, community sample of adolescents, with interleukin-6 as the mediator of the body mass-executive functioning association (Mac Giollabhui, Swistun, et al., 2020). These studies provide initial evidence implicating inflammatory biomarkers in the etiology of cognitive dysfunction in depression. However, many outstanding questions exist – two of which will be

investigated in this study. First, are depression and inflammatory biomarkers independent risk factors for cognitive dysfunction or do these factors compound so that individuals with elevated depression and inflammatory biomarkers experience greater difficulties than individuals with either depression or an elevated inflammatory biomarker alone? Second, is the association between an elevated inflammatory biomarker and cognitive dysfunction limited to depressive episodes, or might the presence of persistently elevated inflammatory biomarkers explain why cognitive dysfunction is observed outside of depressive episodes?

This study examined these two central questions using four waves of data from a population-based sample of Dutch adolescents ($N = 1,066$). Specifically, we tested whether adolescents with either (1) a history of depression (self-reported symptoms at Waves 1 - 3 or retrospective diagnosis at W4) or (2) current depression (self-reported symptoms or diagnosis at Wave 4) *and* elevated levels of an inflammatory biomarker (C-reactive protein: CRP) measured in blood at Wave 3 performed differentially worse on cognitive tests at Wave 4. In addition, we investigated whether CRP and/or depression were associated with specific deficits in executive functioning, episodic memory, and verbal fluency or whether they were associated with a more generalized pattern of cognitive dysfunction. These three dimensions of cognitive functioning were estimated using a structural equation model framework based on eight measures of cognitive functioning: executive functioning, episodic memory, and verbal fluency.

We hypothesized that:

(1) Individuals with current depression at Wave 4 *and* elevated CRP at Wave 3 will perform worse on tests of executive functioning, episodic memory, and verbal fluency at Wave 4 than individuals with either current depression or elevated CRP alone.

(2) Individuals with a history of depression (Waves 1 – 3) and elevated CRP (Wave 3) will perform worse on tests of executive functioning and verbal fluency (but not episodic memory) at Wave 4 than individuals with either current depression or elevated CRP alone.

These hypotheses are generally in line with previous findings of cognitive deficits in current depression/depression history (Ahern & Semkowska, 2017; Bora et al., 2013; Hasselbalch et al., 2011; Rock et al., 2014; Snyder, 2013b). It should be noted that, because this study only measured CRP and cognitive functioning at a single timepoint, we only investigated a single dimension of the possible associations of CRP, cognitive functioning and depression. For example, it is equally plausible that CRP may lead to difficulties in self-regulatory behavior, which may, in turn, leads to stress generation and depression (Shields et al., 2017).

Materials and Methods

Participants

Data were drawn from the TRacking Adolescents' Individual Lives Survey (TRAILS), a prospective cohort study examining psychosocial development and mental

health during adolescence and early adulthood. Adolescents aged 11 years were recruited and attended regular follow-up assessments every 2-3 years. Two separate cohorts were followed by TRAILS: one population-based and another clinic-based (Huisman et al., 2008). This study is based on data from the TRAILS population-based cohort. Adolescents were recruited from 135 schools in five municipalities in the north of The Netherlands, which included both urban and rural areas. Eligible participants were required to be enrolled in primary school, and of 2935 youth who met this criterion, 2230 (76%) provided informed consent from both parent and child to participate.

The current study utilized data from Waves 1 – 4. From the baseline sample, 1,231 adolescents' blood was assayed at Wave 3 (W3), of whom 18 participants were excluded because $CRP > 10\text{mg/L}$ and they also reported either experiencing illness, injury, or a doctor visit/hospitalization during the prior week. From the 1,213 remaining participants, 1,066 had complete data available on all measures of cognitive functioning. The analytic sample of 1,066 participants had a mean age of 11.09 years ($SD = .56$) at W1, 13.52 years ($SD = .52$) at W2, 16.19 years ($SD = .65$) at W3 and 19.00 years ($SD = .57$) at W4. In this study, depressive symptoms were measured at each assessment (W1 – W4), depression diagnosis (lifetime and 30-day prevalence) was assessed via a semi-structured interview at W4, a battery of neuropsychological measures were administered at W4 to measure cognitive functioning, and a range of covariates used in this study were assessed at W1 (socio-economic status, age, sex) or W3 (sedentary behavior, body mass index, and substance use).

The analytic sample was less likely than the complete TRAILS sample enrolled at baseline to include individuals of low socioeconomic status (SES), mean difference = .41, $p < .001$, and males, $\chi^2(1, 2228) = 7.89$, $p = .005$. No difference in baseline age was observed ($p = .12$).

Measures

Depressive Disorder.

Depressive disorders were assessed at W4 using the Composite International Diagnostic Interview, version 3.0 (CIDI) (Kessler & Üstün, 2004). The CIDI is a structured diagnostic interview that uses criteria from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition to identify individuals meeting criteria for a major or dysthymic depressive diagnosis during their lifetime or during the 30 days prior to interview (current). The CIDI is a valid, reliable, and widely used instrument to assess depression (Haro et al., 2006; Kessler et al., 2009; Wittchen, 1994).

Depressive Symptoms.

Depressive symptoms were assessed at W1 – W4. During the first three waves, depressive symptoms were measured using the Withdrawn/Depressed scale of the Youth Self-Report (YSR) (Achenbach, 1991). The scale has demonstrable reliability at W1 (8 items; $\alpha = .72$), W2 (14 items; $\alpha = .74$), and W3 (14 items; $\alpha = .77$). At W4, the Withdrawn/Depressed scale (14 items; $\alpha = .76$) from the Adult Self-Report form was administered (Achenbach & Rescorla, 2003).

C-Reactive Protein.

C reactive protein (CRP) is a liver-based protein used as an indicator of systemic inflammation. The current study used a high sensitivity CRP assay capable of reliably measuring CRP at lower levels of detection. At Wave 3, 39.5 ml of blood was drawn from fasting participants and breakfast was subsequently provided – 89.9% of participants endorsed fasting at the time of the blood draw. CRP was assayed using an immunonephelometric method, BN2 of Siemens Medical Solutions USA (Malvern, PA, USA) with a lower detection limit of 0.175 mg l^{-1} . Intra-assay coefficients of variance ranged from 2.1 to 4.4 mg l^{-1} , and inter-assay coefficients of variance ranged from 1.1 to 4.0 mg l^{-1} . CRP values were relatively low, as might be expected in a community sample of adolescents, with 90% of participants exhibiting hsCRP values $< 3.2 \text{ mg/L}$.

Cognitive Functioning.

Reliable and valid measures of cognitive functioning were administered at W4. Measures administered are discussed briefly here and thorough descriptions are provided in Supplementary Information. Normative data were not used because Dutch norming data were not available across all measures. Cognitive data are described in Table 1.

Table 1. Descriptive Statistics For All Cognitive Measures.

Cognitive Measures	Mean	Standard Deviation	Min. Value	Max. Value	Skewness	Kurtosis
Digit Span Backwards	6.73	2.06	2	14	0.56	0.40
Self-Ordered Pointing Task	1.56	0.78	0	5	1.07	2.56
RCFT: Copy	31.44	3.07	19.5	36	-0.95	0.96
Block Design	44.38	15.04	3	68	-0.38	-0.73
Rey verbal Learning: Immediate	51.13	8.65	19	70	-0.53	0.34
Rey verbal Learning: Delay	10.55	2.63	2	15	-0.49	-0.10
Phonological Fluency	21.93	7.37	4	55	0.43	0.57
Semantic Fluency	36.44	8.33	13	62	0.22	-0.08

Min. = Minimum; Max. = Maximum; RCFT = Rey-Osterrieth Complex Figure Test

Auditory verbal working memory was measured using the ‘Digit Span Backwards’ from the Wechsler Adult Intelligence Scale, third edition (WAIS-III), Dutch version (Wechsler, 1997). Visual working memory was assessed using the Self-Ordered Pointing Task (Petrides & Milner, 1982); the average number of errors was used as the outcome variable for this task, given that it is the most sensitive outcome (Ross et al., 2007) and to be consistent with prior TRAILS studies (Jonker et al., 2014). Visual organization, a component of executive functioning, was assessed using the ‘Copy’ trial of the Rey-Osterrieth Complex Figure Test (Shin et al., 2006), in which participants were asked to draw a complex geometric shape. Visuo-constructional and non-verbal reasoning skills were assessed using the ‘Block Design’ subtest of the WAIS-III (Wechsler, 1997). Immediate (number of words recalled across five trials) and delayed

(number of target words recalled following a delay) verbal episodic memory was assessed using a list learning task (Rey Auditory Verbal Learning Test) (Van Der Elst et al., 2005). Verbal fluency (phonological and semantic) was measured using a modified version of the short test of semantic and phonological fluency

Three latent constructs were hypothesized to underpin these eight measures: executive functioning, episodic memory, and verbal fluency. It should be noted that important components of executive functioning were not available, such as inhibition and cognitive flexibility (Miyake & Friedman, 2012), and less commonly used measures were included, such as visual reasoning and visual organization. This decision was based upon the measures available, and when these four measures were separated into two latent factors of visual/verbal working memory (Self-Ordered Pointing Task/Digit Span Backward) and visual organization/reasoning (Rey-Osterrieth Complex Figure Test/Block Design), the correlation of the latent factors was .83. Although verbal fluency often is considered an index of executive functioning, more recent research has identified it as more closely linked with language skills and psychomotor speed (Henry & Crawford, 2005; Whiteside et al., 2016).

Covariates.

Sociodemographic variables. Participant sex was measured at W1 (male was coded as '1'). Age was assessed at all assessments, as was SES. SES was estimated using five indicators: family income, maternal educational level, paternal educational level, maternal occupational level and paternal occupational level using the International

Standard Classification of Occupations and has been consistently used in TRAILS (Ganzeboom & Treiman, 1996; Jonker et al., 2017). Height and weight were measured at W3 and used to calculate body mass index (kg/m^2).

Behavioral variables. Participant sedentary behavior measured at W3 was calculated as the mean number of hours: sitting at a computer (Monday-Friday); sitting at a computer (Saturday/Sunday); watching television or video (Monday-Friday); and watching television or video (Saturday/Sunday). Substance use was measured at W3 and calculated as the mean of the number of cigarettes smoked in the last week (0 = 'I don't smoke'; 1 = 'I haven't smoked in the last week'; 2 = '< 1 cigarette a day; 3 = '1-5 cigarettes a day'; 4 = '6-10 cigarettes a day; 5 = '11-20 cigarettes a day'; 6 = '>20 cigarettes a day') and number of days of the last week participant drank alcohol.

Analyses.

Analyses were conducted in Mplus (Version 7.4) and missing data were handled using Full Information Maximum Likelihood. We used growth mixture modelling to identify the smallest number of classes of individuals exhibiting different intercepts and trajectories of depressive symptoms measured at Waves 1 – 3, as described by Jung and Wickrama (2008). Latent class growth analysis, where the variance and covariance estimates of the growth factors are constrained to be zero within each class, was not selected because of the known heterogeneity in depressive symptoms. Estimated models were based on 500 random starts and 200 optimizations in the final stage. Depressive symptoms (W1-W3) do not exhibit evidence of skewness or kurtosis (all estimate <

1.02). We set out with a one-class solution and subsequent models were progressively added. Model identification was based upon theoretical interpretability of the classes estimated (i.e., latent classes being congruent with trajectories of depression in adolescence) and model fit. Model fit was assessed via commonly used indices of fit and likelihood-based statistical tests [Akaike information criterion (AIC), Bayesian information criterion (BIC), entropy, Vuong Lo-Mendell-Rubin likelihood ratio test] (Golden, 2000; Nylund et al., 2007).

Next, a structural equation model approach identified the model that best fit the cognitive data based on three possible models: single factor model, correlated factors model (three latent factors), or a bifactor model (one general factor/three specific factors). Three factors were generated from eight cognitive tasks thought to measure: executive functioning (verbal/visual working memory and visual organization/visuoconstructional abilities), verbal fluency (phonological/semantic fluency), and episodic memory (immediate/delayed recall). Although, verbal fluency often is considered an executive function, there is strong evidence that it indexes verbal abilities (Whiteside et al., 2016) and/or psychomotor speed (Henry & Crawford, 2005). The model that best fit our data was selected based on the Comparative Fit Index (CFI), Tucker Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA), AIC and BIC. The Chi-Square test of model fit was reported according to convention, but was not interpreted because it has limited utility in large samples (i.e., $N > 200$) (Chen, 2007; Cheung & Rensvold, 2002). For the CFI, good fit consisted of a value $> .90$ and excellent fit by a value $> .95$. A

RMSEA statistic between .05 and .10 was indicative of good fit, whereas a value $<.05$ was indicative of excellent fit (Schermelleh-Engel et al., 2003). Lower AIC and BIC values were considered indicative of better model fit.

Third, for predictive analyses, two models were fitted separately for the two measures of depression: (i) depressive symptoms measured at Waves 1 – 4 and (ii) lifetime and recent depression diagnosis measured at Wave 4. For both models, we examined whether depression and CRP were associated with cognitive functioning when controlling for demographic and behavioral variables. Subsequently, we included an interactive term of CRP by depression (both current and past). Demographic and behavioral variables were selected that are known correlates of depression, CRP, and/or cognitive functioning (Nolen-Hoeksema, 2001; O'Connor et al., 2009).

Sensitivity analyses [based on recommendations by Mac Giollabhui et al. (Mac Giollabhui, Ellman, et al., 2020)] evaluated the generalizability of results based on how extreme CRP values are handled in analyses. For the main analyses, 18 extreme CRP values were excluded where $CRP > 10\text{mg/L}$ and the participant reported experiencing illness, injury, or a doctor visit/hospitalization during the prior week. Sensitivity analyses were reported where all CRP values $> 10\text{mg/L}$ ($n = 40$) were both included and excluded.

Results

Bivariate correlations and descriptive statistics for the main study variables are presented in Table 2 for the analytic sample of 1,066 adolescents with complete data on cognitive measures, whose blood was assayed at Wave 3 (W3), and who did not exhibit

evidence of acute illness/injury. Notable associations are described below. Identifying as female (W1) was generally associated with higher depression across multiple waves, BMI (W3), CRP (W3), and episodic memory (W4). Higher SES (W1) also was consistently associated with: less severe depression across multiple waves; lower BMI, lower CRP, and sedentary behavior (W3); and better performance on all cognitive measures (W4). Depressive symptoms (W1 –W4) were generally associated with higher BMI, CRP, and sedentary behaviors. Elevated depression was generally associated with worse working memory, but not other aspects of cognitive functioning at W4 and both BMI and CRP were consistently associated with measures of executive functioning.

Variable	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1. W1 Age	.03	.04	.00	.00	.00	.01	-.03	.03	.04	.09**	.01	-.06*	-.04	.03	.00	-.05	-.03	-.03	.03	.03	.03
2. W1 Sex (Male = 1)	-	.03	-.02	-.15**	-.15**	-.04	-.12**	-.05	-.17**	-.12**	-.12**	-.03	.17**	.09**	-.07*	-.07*	-.05	-.17**	-.19**	-.04	-.01
3. W1 SES		-	-.07*	-.05	-.10**	-.09*	-.07*	-.07*	-.05	-.15**	-.10**	.06	-.18**	.26**	.16**	.13**	.24**	.17**	.10**	.22**	.28**
4. W1 Dep Sxs ^a			-	.45**	.33**	.26**	.28**	.09**	.18**	.11**	.07*	.03	.07*	.00	.02	.02	-.10**	-.01	-.02	-.01	-.06
5. W2 Dep. Sxs ^a				-	.53**	.37**	.52**	.14**	.27**	.06	.08**	.02	.04	-.01	.00	.06*	-.05	.04	.03	.01	-.02
6. W3 Dep. Sxs ^a					-	.53**	.76**	.14**	.31**	.08*	.01	-.03	.13**	-.02	.02	.04	-.07*	.03	.04	-.04	-.05
7. W4 Dep. Sxs ^b						-	.44**	.21**	.30**	.04	.01	-.02	.08*	-.01	-.03	.04	-.06	-.03	-.02	-.09*	-.03
8. W1 – 3 Depression Class							-	.11**	.24**	.06*	.01	.05	.07*	-.02	.02	.07*	-.07*	.02	.02	-.02	-.02
9. W4 Current Dep. Dx.								-	.37**	.03	.02	.02	.02	-.03	-.03	-.05	-.07*	-.01	-.02	-.06	.00
10. W4 Lifetime Dep. Dx.									-	.08**	.04	-.02	.06*	-.02	-.04	.00	-.05	.01	-.02	.00	.00
11. W3 BMI										-	.30**	-.03	.14**	-.06*	-.08**	-.07*	-.12**	-.08**	-.06	-.06	-.03
12. W3 CRP											-	-.04	-.02	-.09**	-.09**	-.02	-.07*	-.02	-.01	-.05	-.03
13. W3 Substance Use												-	.02	.05	.10**	.01	.05	.01	-.02	.03	.07*
14. W3 Sedentary													-	-.14**	-.11**	-.13**	-.14**	-.13**	-.10**	-.15**	-.14**
15. W4 Block Design														-	.30**	.21**	.29**	.24**	.17**	.28**	.27**
16. W4 RCFT: Copy															-	.12**	.23**	.23**	.21**	.13**	.15**
17. W4 SOPT																-	.21**	.27**	.23**	.17**	.15**
18. W4 DS: Back																	-	.35**	.27**	.22**	.34**
19. W4 Rey: Immediate																		-	.74**	.31**	.29**
20. W4 Rey: Delay																			-	.29**	.22**
21. W4 Fluency: Seman.																				-	.48**
22. W4 Fluency: Phono.																					-
Mean	.46	.16	.35	.35	.37	.23	.17	.03	.17	21.20	1.16 ^c	0.87	3.17	44.43	31.47	1.56	6.75	51.14	10.53	36.45	21.98
SD =	.50	.77	.29	.28	.32	.27	.38	.16	.38	3.08	2.47 ^c	1.08	1.29	15.11	3.06	0.78	2.06	8.65	2.64	8.37	7.38

W = Wave; Dep = Depressive; Sxs = Symptoms; Sxs^a = Measured using the Withdrawn/Depressed scale of the Youth Self Report; Sxs^b = Measured using the Withdrawn/Depressed scale from the Adult Self-Report; BMI = Body Mass Index; CRP = C-Reactive protein; RCFT = Rey-Osterrieth Complex Figure Test; SOPT = Self-ordered Pointing Task; Rey = Rey Verbal Learning Test; Seman. = Semantic; Phono. = Phonological; Fluency: Phono; Descriptive statistics for Age = .11.09, *SD* = 0.56; ^c = Mean and standard deviation reported for non-transformed raw C-Reactive Protein values (mg/L); * = $p < .05$; ** = $p < .001$

Latent Class Analysis of Depressive Symptoms

Latent-class analysis identified the best fitting model of depressive symptoms, based on depressive symptoms reported (W1 - W3). Fit statistics, latent class intercept and slope, and latent class size are provided in Table 3 for all models. A two-class solution was selected identifying a group with lower baseline depressive symptoms that decreased across waves 1 – 3 (intercept: .32, $p < .001$; slope: -.03, $p < .05$; $n = 883$) and a group with higher baseline depressive symptoms that increased across waves 1 – 3 (intercept: .49, $p < .001$; slope: .17, $p < .001$; $n = 183$). Complete detail on why a two-, rather than three- or four-, class solution is provided in supplementary material.

Table 3. Fit Statistics and Statistical Parameters for Four Latent Class Models: a One Class Model, a Two Class Model, a Three Class Model, and a Four Class Model (n = 1,066)

Fit Statistics	Model 1: One Class Model			Model 2: Two Class Model			Model 3: Three Class Model			Model 4: Four Class Model¹		
Log Likelihood	-333.79			-266.10			-221.14			-199.44		
AIC	683.59			554.20			470.28			432.89		
BIC	723.36			608.89			539.89			517.41		
Entropy	-			0.76			.77			.79		
LRT	-			$p < .001$			$p < .001$			$p = .11$		
	Model 1: One Class Model			Model 2: Two Class Model			Model 3: Three Class Model			Model 4: Four Class Model		
Classes	Intercept	Slope	N	Intercept	Slope	N	Intercept	Slope	N	Intercept	Slope	N
Class One	.35**	.01*	1066	.32**	-.03*	883	.25**	.01	800	.24**	.01	783
Class Two	Not estimated – one class model			.49**	.17*	183	.47**	.21**	136	.28**	.30**	75
Class Three				Not estimated – two class model			.81**	-.21**	130	.79**	-.25**	114
Class Four							Not estimated – three class model			.71**	.06	94

AIC = Akaike information criterion; BIC = Bayesian information criterion; LRT = adjusted Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (p value); * = $p < .05$; ** = $p < .001$; ¹ = Failed to reliably converge on a single solution.

Factor Models of Cognitive Variables

Fit indices for three potential models of the cognitive measures are presented in Table 4.

<i>Table 4. Fit Indices for Four Potential Measurement Models underlying Cognitive Measures (n = 1,066).</i>								
Model	χ^2	df	CFI	TLI	SRMR	RMSEA (90% CI)	AIC	BIC
Single Factor	442.98	20	.76	.66	.086	.14 (.13-.15)	22768.02	22887.34
Correlated Factors	78.27	17	.97	.94	.032	.06 (.05-.07)	22386.23	22520.46
Bifactor	Model failed to converge.							
df = degrees of freedom; CFI = Comparative Fit Index; TLI = Tucker Lewis Index; SRMR = Standardized Root Mean Square Residual; RMSEA = Root Mean Square Error of Approximation; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion								

A single factor solution fit the data poorly based on the CFI, TLI, and RMSEA and no reliable solution was found using a bifactor model. Instead, the correlated factors model demonstrated good to excellent fit across all indices. Visual depiction of the correlated factors model including factor loadings and path coefficients is presented in Figure 1. Factor loadings for each latent variable ranged from .40 to .96 and the measure of association ranged from .45 to .67.

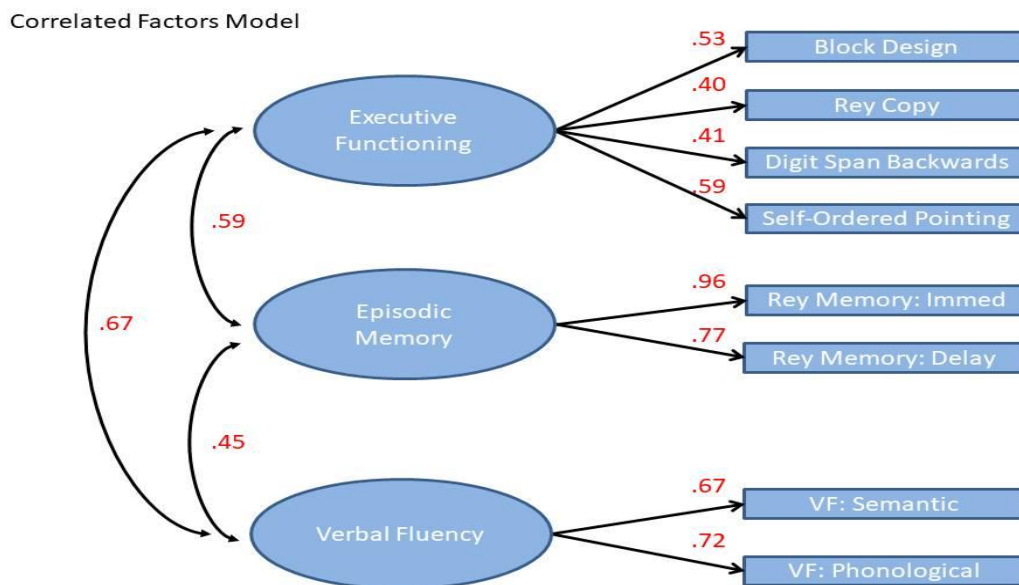


Figure 1. Visual depiction of the correlated factors and single hierarchical factor models

Structural Models Predicting Cognitive Functioning by CRP and prior depression

Following identification of a model that provided a satisfactory fit for the cognitive measures, we subsequently extended the correlated factors model to examine the associations of CRP and depression with domains of cognitive functioning within a structural equation modeling framework. We iteratively examined the following models: depression (current depression and history of depression; Model 1); depression, CRP, and demographic variables (sex, age, SES) (Model 2); depression, CRP, demographic, and biobehavioral variables (sedentary behavior, body mass index, substance use) (Model 3);

followed by the introduction of the interaction terms (CRP x current depression: Model 4; CRP x history of depression: Model 5). Fit indices for all models ranged from good to excellent – see Table 5 for complete information.

Model	Model Fit Indices			
	$\chi^2 =$	CFI	TLI	RMSEA (90% CI)
Depressive Sxs: Model 1	98.189**	.96	.94	.05 (.04, .06)
Depressive Sxs: Model 2	157.03**	.95	.91	.05 (.04, .06)
Depressive Sxs: Model 3	186.03**	.94	.90	.045 (.04, .05)
Depression Dx: Model 1	88.47**	.97	.94	.05 (.04, .06)
Depression Dx: Model 2	150.672**	.95	.92	.046 (.038, .054)
Depression Dx: Model 3	169.42**	.95	.91	.042 (.034, .049)

Sxs = Symptoms; Dx = Diagnosis; CFI = Comparative Fit Index; TLI = Tucker Lewis Index; RMSEA = Root Mean Square Error of Approximation.

The associations of depressive symptoms [latent trajectory (i.e., history)/current symptoms] and depression diagnostic status [history/current diagnosis (within last 30 days)] and CRP (in addition to important covariates) with cognitive functioning are reported in Table 6.

Models	Depressive Sxs – Child Report (n = 1044)			Depression Diagnosis (n = 1058)		
	Executive Functioning	Episodic Memory	Verbal Fluency	Executive Functioning	Episodic Memory	Verbal Fluency
Model 1						
Depression W4	-.04	-.05	-.09	-.50**	-.10	-.28
Depression W1 – W3	-.01	.11	.02	-.08	.06	.04
Model 2						
Depression W4	-.02	-.03	-.06	-.31	-.04	-.13
Depression W1 – W3	.01	.07	.07	-.07	-.05	.06
Log-transformed CRP	-.11*	-.03	-.04	-.11*	-.04	-.04
Age	-.06	-.01	.07*	-.06	-.01	.07*
Sex (1 = male)	-.08	-.40**	-.10	-.10	-.42**	-.10
Socio-economic status (Higher status = higher values)	.41**	.17**	.36**	.40**	.16**	.36**
Model 3						
Depression W4	.00	-.01	-.04	-.40	-.16	-.13
Depression W1 – W3	-.01	.07	.01	.07	.12	.00
Log-transformed CRP	-.08	.00	-.02	-.07	-.01	-.02
Age	-.07	-.02	.07	-.07	-.01	.07
Sex (1 = male)	-.04	-.20**	-.05	-.03	-.42**	-.02
Socio-economic status (Higher status = higher values)	.37**	.14**	.33**	.37**	.13**	.33**
Sedentary Behavior	-.20**	-.06	-.13*	-.19**	-.05	-.14**
Body Mass Index	-.08	-.07*	.03	-.09	-.08*	.03
Substance Use	-.07	-.06	-.07	-.05	-.05	-.07*
Model 4 / Model 3 + Interactions						
Log-transformed CRP*Depression W4	.01	.05	.02	-.01	-.01	.00
Log-transformed CRP*Depression W1 - W3	.01	.06	.06	-.03	.08	.01

*= p <.05; **= p <.001; Sxs = Symptoms; Dx = Diagnosis; CRP = C-reactive protein

In Model 1, where both current and prior depression were entered, only a current depression diagnosis was associated with worse executive functioning. When adjusting for demographic covariates and depression (past/current), higher CRP was associated with worse executive functioning. Higher SES consistently was associated with higher performance on all measures of cognitive functioning. When additional biobehavioral covariates were introduced in Model 3, the associations of higher CRP and worse executive functioning was no longer statistically significant. Higher levels of sedentary behavior were associated with worse executive functioning and verbal fluency, whereas higher levels of BMI were associated with worse episodic memory. CRP did not interact with trajectories of depressive symptoms or prior depression diagnosis (Model 4) to predict differential performance in any domain of cognitive functioning. It should be noted that, in the case of a current depression diagnosis, all 29 individuals who met criteria for acute depression had previously experienced a depressive episode and consequently it is not possible to disentangle current from recurrent depression.

Sensitivity analyses and Exploratory Analyses

No meaningful differences were observed in analyses in which all CRP values greater than or equal to 10 mg/L were either removed or included. We conducted additional exploratory analyses to estimate whether the observed association of CRP and executive functioning differed in individuals with current depression/history of depression compared to individuals without depression replicating the analysis presented in Table 6 for depressive symptoms (Depressive symptoms: Model 2). Models were specified separately by group ('History/current depression diagnosis' vs. 'No diagnosis history') and the parameters for executive functioning regressed on log-transformed CRP did not differ by group (wald test statistic = .541, $p = .46$).

Discussion

In a population-based sample of 1,066 Dutch adolescents who were recruited aged 11 years and assessed on three subsequent occasions, spaced approximately 2.5 years apart, we found that higher levels of CRP at Wave 3 were associated with worse future executive functioning at Wave 4, irrespective of whether they had a history of depression or not (Waves 1 – 4). In addition, adolescents experiencing a current depressive episode exhibited worse executive functioning than non-depressed peers. There was no evidence of an additive effect whereby those with depression *and* elevated CRP performed worse on measures of cognitive functioning than individuals with depression or elevated CRP alone. There was consistent evidence linking low socioeconomic status and health-related covariates (high body mass index/sedentary behavior) with worse performance across

multiple measures of cognitive functioning and, importantly, the association of depression/CRP and executive functioning was no longer significant when controlling for these covariates. These results provide evidence that, in depression, higher CRP is associated with worse executive functioning, but that these associations are not unique to depression.

CRP was prospectively associated with worse future executive functioning independent of age, sex, SES, and depression. This finding is consistent with concurrent and prospective associations observed in middle-aged or elderly samples (Jenny et al., 2012; Noble et al., 2010; Teunissen et al., 2003; Zheng & Xie, 2018). The strength of the association between CRP and executive functioning did not differ depending on whether adolescents had experienced depression (either a current diagnosis or a prior diagnosis), suggesting that an inflammatory subtype of depression characterized by worse cognitive functioning may exist, but that this association is not unique to depression. This finding is generally consistent with previous work, although few studies have been conducted in community or youth samples. Similar to this study, salivary CRP was concurrently associated with worse performance on some executive functioning tasks in a risk-enriched sample of 107 young adolescents (Cullen et al., 2017), irrespective of the level of internalizing, externalizing, or subclinical psychotic symptoms present. However, CRP was not associated with two measures of cognitive functioning (visual working memory/verbal episodic memory) in a prior TRAILS study investigating the cognitive sequelae of herpes viruses (Jonker et al., 2014) and was not associated with episodic

memory or verbal fluency in this study. These results should be considered within a literature where: null results also have been observed, there is marked heterogeneity in the domains of cognition implicated, and effect sizes are frequently attenuated following adjustment for covariates, such as BMI (Alley et al., 2008; Cohen-Manheim et al., 2015; Dik et al., 2005; Palta et al., 2015; Singh-Manoux et al., 2014). Indeed, the magnitude of the association of CRP and future executive functioning was small, although this is generally characteristic of effect sizes in the psychological science (Button et al., 2013).

The core hypotheses of this study, namely that individuals with depression *and* higher levels of CRP would perform worse across multiple measures of cognitive functioning, was not supported. Only one other study has tested a similar hypothesis in a community sample; Cullen et al. (2017) examined a risk-enriched sample of 107 children (56% of children had a history of developmental delays; social/emotional/behavioral problems; psychotic-like experiences or a family history of psychosis) and found that children with internalizing symptomology *and* elevated salivary CRP did not perform worse on measures of cognitive functioning, although CRP was associated with worse performance on verbal fluency and executive functioning tasks – a pattern of results that is broadly in line with the results of this study. A consistent pattern also was observed in clinical studies of adults with a current major depression diagnosis. Across these studies, elevated inflammatory biomarkers were associated with worse cognitive functioning, so that depressed individuals with higher levels of inflammatory biomarkers performed worse across tests of cognitive functioning, including executive functioning (Chang et al.,

2012; Goldsmith et al., 2016; Grassi-Oliveira et al., 2011; Krogh et al., 2014). Significantly and consistent with our results, the two studies that included control groups reported that elevated inflammatory biomarkers also were associated with cognitive dysfunction in the control condition (Grassi-Oliveira et al., 2011; Krogh et al., 2014). It is important to note, however, that, despite the large sample, this sample may not have been adequately powered to detect a cumulative association of depression and C reactive protein on cognitive functioning given the relative low number of depressed individuals with elevated CRP. If we use diagnostic status as our indicator of depression, only 3 of 29 individuals with a current diagnosis and 22 out of 182 individuals with a lifetime diagnosis have C reactive protein values ≥ 3 mg/L.

When examining the association of depression with individual measures of cognitive functioning, depression, particularly current depression, was consistently associated with visual and verbal working memory and more severe current depressive symptoms (but not current diagnosis) were associated with worse verbal fluency (see Table 2). In primary analyses, the concurrent associations of depression (current and past) with three latent cognitive variables (executive functioning, verbal fluency, and episodic memory) were estimated and current depression alone was associated with worse executive functioning. These findings were generally consistent with prior meta-analyses that have observed worse working memory, and worse executive functioning more broadly, in individuals with acute depression, although such difficulties are also typically observed in remitted depression (Ahern & Semkowska, 2017; Rock et al., 2014;

Semkovska et al., 2019; Snyder, 2013a). Depressed adults (Ahern & Semkovska, 2017; Snyder, 2013b; Veiel, 1997; Zakzanis et al., 1998) and youth (Baune et al., 2014) frequently perform worse on tests of verbal fluency, which also can be observed in remitted depression (Semkovska et al., 2019). In this study, consistent verbal fluency differences were not observed and, as a result, these results are more congruent with the considerable heterogeneity in effect size as well as null results that are observed (Henry & Crawford, 2005). It may be that such deficits are less commonly observed in youth, where relatively fewer studies examining verbal fluency have been carried out (Ahern & Semkovska, 2017; Semkovska et al., 2019).

Neither past nor current depression was associated with deficits in episodic memory, measured using a verbal list-learning task, in the current study. Worse episodic memory has long been recognized as impaired in depression (Burt et al., 1995) and is consistent with reduced hippocampal volumes that are consistently observed in depression (Videbech & Ravnkilde, 2004). However, reduced hippocampal volumes is often associated with recurrent, prolonged or repeated bouts of depression (Sheline et al., 1999; Sheline et al., 1996; Videbech & Ravnkilde, 2004) and, more importantly, deficits in episodic memory are typically not observed in youth with a history of depression (Bora et al., 2009; Hasselbalch et al., 2011; Rock et al., 2014). It may be that the type of episodic memory tasks matters when detecting deficits in depression because memory difficulties typically are not observed on list-learning tasks during the first-episode of depression and, instead, are more likely to be observed when participants are asked to

recall narratives (Ahern & Semkowska, 2017). In addition, deficits in episodic memory are typically not observed in early onset depression but are pronounced in older adults (Bora et al., 2013). Thus, the null results observed in the current study reflect a broader pattern of findings that episodic memory, at least as assessed using a list-learning task, is not impaired in depressed youth.

The association of CRP and future executive function was substantially attenuated following the inclusion of covariates; however, this does not necessarily imply that CRP is unrelated to cognitive functioning. For example, there is strong theory as well as empirical data to suggest that inflammation may mediate the association between body mass and cognitive functioning (Spyridaki et al., 2016; Yang et al., 2018; Yang et al., 2019). For instance, in a longitudinal study of adolescents, Mac Giollabhui et al. found that an inflammatory biomarker (interleukin-6), which is closely related to CRP, mediated the association between BMI and worse future executive functioning, although CRP itself did not (Mac Giollabhui, Swistun, et al., 2020). It does, however, highlight the need for further studies to disentangle the association of multiple overlapping risk or causal factors, such as SES, BMI, inflammation, stress, diet, with both depression and cognitive functioning (Mac Giollabhui et al., 2019; Mac Giollabhui, Swistun, et al., 2020; Shields et al., 2017). For instance, low SES is generally associated with greater risk of depression (Reiss, 2013) and risk factors for both depression and cognitive dysfunction, including BMI (Mac Giollabhui, Swistun, et al., 2020; Yang et al., 2018), inflammatory biomarkers (Muscatell et al., 2018; O'Connor et al., 2009), and diet (Darmon &

Drewnowski, 2008; Nyaradi et al., 2014). An important limitation of this study is that it was only capable of examining the association of depression with future cognition when it is known that the relationship between depression and cognition is more complex (34). Further, a recent meta-analysis by Mac Giollabhui et al. (Mac Giollabhui et al., In Press) has shown that CRP is associated with future depression and that depression is associated with future CRP, highlighting the multiple potential ways that depression, inflammation and cognitive functioning may be associated. For instance, it also is plausible that, rather than depression leading to cognitive dysfunction, inflammation leads to executive dysfunction, which in turn leads to depression via stress generation (Shields et al., 2017; Snyder & Hankin, 2016).

There is compelling evidence that SES, greater body mass, and increased sedentary behaviors are linked with cognitive dysfunction and similar results were observed in this study. In particular, there is a striking difference in youth performance on tests of executive functioning, memory, and language based on SES (Duncan & Magnuson, 2012; Hackman et al., 2015). Strong evidence also exists linking higher body mass (Cheke et al., 2016; Tabriz et al., 2015; Yang et al., 2018) and increased sedentary behavior (Carson et al., 2015; Fedewa & Ahn, 2011) with cognitive dysfunction. Since all of these factors are inter-related (Hanson & Chen, 2007; O'Dea & Wilson, 2006; Paine et al., 2015; Reichenberg et al., 2001; Singh-Manoux et al., 2014) and, moreover, also are associated with both depression and inflammatory biomarkers (Mac Giollabhui, Swistun, et al., 2020; Matthews et al., 2016; Muscatell et al., 2018), an ongoing challenge

for researchers is better characterizing the causal relationships between these variables and better understanding whether, for example, SES is associated with depression and cognitive dysfunction via the impact of SES on inflammation via increased BMI or, alternatively whether other variables, such as diet or genotype, play an important role (Baym et al., 2014; Beydoun et al., 2014; Darmon & Drewnowski, 2008; Francis & Stevenson, 2011; Junger & van Kampen, 2010; Molteni et al., 2002; Nyaradi et al., 2014; Retterstol et al., 2003; Su et al., 2009). Rather than dissociable risk factors, it may also be that some of these factors represent expressions of shared biological pathways (Carvalho et al., 2014).

This study contained a number of notable strengths. Inflammation was assessed in serum using a widely-used inflammatory biomarker (CRP) and three domains of cognitive functioning were estimated from a large battery of reliable, valid, and widely-used behavioral assessments. Moreover, the use of a structural equation modeling approach reduced the risk of type I error caused by the increased number of statistical tests that is a frequent limitation of many studies examining cognitive dysfunction in depression (Hasselbalch et al., 2011). An SEM approach also increased confidence that observed associations were related to the constructs being measured, rather than task-specific variance. Finally, the use of a large, population-based, representative sample of adolescents likely increases the generalizability of these results.

These results also should be considered in the context of important limitations. Cognitive functioning was only assessed at a single occasion, and therefore, we cannot

exclude the possibility that, for example, worse cognitive functioning (e.g., verbal fluency) is a risk factor for depression, and consequently, the true temporal relationship is the reverse of that observed in this study (Sculth et al., 2017). Similarly, CRP was only assessed at a single timepoint and the possibility of reverse temporal relations cannot be excluded. Tests of cognitive functioning typically use standardized scores that are age and/or gender-normed; however, norms were not available for all tests of cognitive functioning used in this study. Thus, we cannot exclude the possibility that subtle effects of age or gender bias results, although this possibility is minimized by our same age cohort, a roughly equal number of male and female participants, and by controlling for these variables in all analyses. Finally, biased attrition may limit the generalizability of results because the analytic sample was less likely to retain individuals of low SES and males.

Conclusions

Depression and CRP are already negatively associated with executive functioning early in development when cognitive abilities, critical for academic and psychosocial functioning, are still emerging. Importantly, these results do provide evidence that individuals who experience depression are more likely to exhibit executive functioning difficulties, although the underlying causes of these associations are unlikely to be unique to depression. Future research is needed to disentangle the effect of multiple, overlapping risk factors for cognitive dysfunction in youth by examining whether inflammatory biomarkers are risk markers or mediators for other deleterious processes, such as

adiposity, diet, substance use, sedentary behavior, physical activity, and/or low socioeconomic status.

REFERENCES CITED

Abramson, L. Y., Metalsky, G. I., & Alloy, L. B. (1989). Hopelessness depression: A theory-based subtype of depression. *Psychological Review*, *96*, 358-372. <https://doi.org/10.1037/0033-295x.96.2.358>

Achenbach, T., & Rescorla, L. (2003). Manual for the ASEBA adult forms & profiles. In Burlington, Vermont: University of Vermont Research Center for Children, Youth, & Families.

Achenbach, T. M. (1991). *Manual for the youth self-report and 1991 profile*. Department of Psychiatry, University of Vermont Burlington.

Ahern, E., & Semkovska, M. (2017). Cognitive functioning in the first-episode of major depressive disorder: A systematic review and meta-analysis. *Neuropsychology*, *31*(1), 52. <https://doi.org/https://doi.org/10.1037/neu0000319>

Alley, D. E., Crimmins, E. M., Karlamangla, A., Hu, P., & Seeman, T. E. (2008). Inflammation and rate of cognitive change in high-functioning older adults. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *63*(1), 50-55.

Allott, K., Fisher, C. A., Amminger, G. P., Goodall, J., & Hetrick, S. (2016). Characterizing neurocognitive impairment in young people with major depression: state, trait, or scar? *Brain and Behavior*, *6*(10), e00527. <https://doi.org/10.1002/brb3.527>

Alloy, L. B., Abramson, L. Y., Whitehouse, W. G., Hogan, M. E., Panzarella, C., & Rose, D. T. (2006). Prospective incidence of first onsets and recurrences of depression in individuals at high and low cognitive risk for depression. *Journal of Abnormal Psychology*, *115*(1), 145.

Au, B., Smith, K. J., Gariepy, G., & Schmitz, N. (2015). The longitudinal associations between C-reactive protein and depressive symptoms: evidence from the English Longitudinal Study of Ageing (ELSA). *International Journal of Geriatric Psychiatry*, *30*(9), 976-984. <https://doi.org/10.1002/gps.4250>

Baune, B., Ponath, G., Golledge, J., & Varga, G. (2008). Association between IL-8 cytokine and cognitive performance in an elderly general population—the MEMO-Study. *Neurobiology of Aging*, *29*(6), 937-944.

Baune, B. T., Fuhr, M., Air, T., & Hering, C. (2014). Neuropsychological functioning in adolescents and young adults with major depressive disorder – A review. *Psychiatry Research*, *218*(3), 261-271. <https://doi.org/10.1016/j.psychres.2014.04.052>

Baym, C. L., Khan, N. A., Monti, J. M., Raine, L. B., Drollette, E. S., Moore, R. D., Scudder, M. R., Kramer, A. F., Hillman, C. H., & Cohen, N. J. (2014). Dietary lipids are differentially associated with hippocampal-dependent relational memory in prepubescent children. *American Journal of Clinical Nutrition*, *99*(5), 1026-1032. <https://doi.org/10.3945/ajcn.113.079624>

Beck, A. T. (1976). *Cognitive therapy of depression*. International Universities Press.

Beydoun, M. A., Gamaldo, A. A., Beydoun, H. A., Tanaka, T., Tucker, K. L., Talegawkar, S. A., Ferrucci, L., & Zonderman, A. B. (2014). Caffeine and alcohol intakes and overall nutrient adequacy are associated with longitudinal cognitive performance among U.S. adults. *Journal of Nutrition*, *144*(6), 890-901. <https://doi.org/10.3945/jn.113.189027>

Bora, E., Harrison, B. J., Yücel, M., & Pantelis, C. (2013). Cognitive impairment in euthymic major depressive disorder: a meta-analysis. *Psychological Medicine*, *43*, 2017-2026. <https://doi.org/10.1017/s0033291712002085>

Bora, E., Yucel, M., & Pantelis, C. (2009). Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *Journal of Affective Disorders*, *113*(1-2), 1-20.

Burcusa, S. L., & Iacono, W. G. (2007). Risk for recurrence in depression. *Clinical Psychology Review*, *27*, 959-985. <https://doi.org/10.1016/j.cpr.2007.02.005>

Burt, D. B., Zembar, M. J., & Niederehe, G. (1995). Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychological Bulletin*, *117*, 285-305. <https://doi.org/10.1037/0033-2909.117.2.285>

Button, K. S., Ioannidis, J. P., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S., & Munafò, M. R. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience*, *14*(5), 365-376.

Carson, V., Kuzik, N., Hunter, S., Wiebe, S. A., Spence, J. C., Friedman, A., Tremblay, M. S., Slater, L. G., & Hinkley, T. (2015). Systematic review of sedentary behavior and cognitive development in early childhood. *Preventive Medicine*, *78*, 115-122.

Carvalho, A. F., Miskowiak, K. K., Hyphantis, T. N., Kohler, C. A., Alves, G. S., Bortolato, B., PM, G. S., Machado-Vieira, R., Berk, M., & McIntyre, R. S. (2014). Cognitive dysfunction in depression - pathophysiology and novel targets. *CNS &*

Neurological Disorders Drug Targets, 13(10), 1819-1835.
<https://doi.org/10.2174/1871527313666141130203627>

Chang, H. H., Lee, I. H., Gean, P. W., Lee, S. Y., Chi, M. H., Yang, Y. K., Lu, R. B., & Chen, P. S. (2012). Treatment response and cognitive impairment in major depression: association with C-reactive protein. *Brain Behavior and Immunity*, 26(1), 90-95. <https://doi.org/10.1016/j.bbi.2011.07.239>

Cheke, L. G., Simons, J. S., & Clayton, N. S. (2016). Higher body mass index is associated with episodic memory deficits in young adults. *Quarterly Journal of Experimental Psychology* (2006), 69(11), 2305-2316. <https://doi.org/10.1080/17470218.2015.1099163>

Chen, F. F. (2007). Sensitivity of Goodness of Fit Indexes to Lack of Measurement Invariance. *Structural Equation Modeling: A Multidisciplinary Journal*, 14(3), 464-504. <https://doi.org/10.1080/10705510701301834>

Cheung, G. W., & Rensvold, R. B. (2002). Evaluating Goodness-of-Fit Indexes for Testing Measurement Invariance. *Structural Equation Modeling: A Multidisciplinary Journal*, 9(2), 233-255. https://doi.org/10.1207/s15328007sem0902_5

Christine, M. S., Jean-Dominique, G., Brian, P., Nabeel, N., Keunpoong, L., Shu-Fei, L., David, M., Jae-Yun, L., Kevin, C. O. c., Yiyun, H., Richard, E. C., Jonas, H., & Kelly, P. C. (2015). Imaging robust microglial activation after lipopolysaccharide administration in humans with PET. *Proceedings of the National Academy of Sciences*, 112(40), 12468. <https://doi.org/10.1073/pnas.1511003112>

Cohen-Manheim, I., Doniger, G. M., Sinnreich, R., Simon, E. S., Pinchas-Mizrachi, R., Otvos, J. D., & Kark, J. D. (2015). Increase in the Inflammatory Marker GlycA over 13 Years in Young Adults Is Associated with Poorer Cognitive Function in Midlife. *PloS One*, 10(9), e0138036-e0138036. <https://doi.org/10.1371/journal.pone.0138036>

Crisan, A. F., Oancea, C., Timar, B., Fira-Mladinescu, O., Crisan, A., & Tudorache, V. (2014). Cognitive impairment in chronic obstructive pulmonary disease. *PloS One*, 9(7), e102468. <https://doi.org/10.1371/journal.pone.0102468>

Cullen, A. E., Tappin, B. M., Zunszain, P. A., Dickson, H., Roberts, R. E., Nikkheslat, N., Khondoker, M., Pariante, C. M., Fisher, H. L., & Laurens, K. R. (2017). The relationship between salivary C-reactive protein and cognitive function in children aged 11–14years: Does psychopathology have a moderating effect? *Brain, Behavior, and Immunity*, 66, 221-229. <https://doi.org/10.1016/j.bbi.2017.07.002>

Dantzer, R. (2001). Cytokine-induced sickness behavior: where do we stand? *Brain Behavior and Immunity*, *15*(1), 7-24. <https://doi.org/10.1006/brbi.2000.0613>

Darmon, N., & Drewnowski, A. (2008). Does social class predict diet quality? *American Journal of Clinical Nutrition*, *87*(5), 1107-1117. <https://doi.org/10.1093/ajcn/87.5.1107>

Dik, M., Jonker, C., Hack, C., Smit, J., Comijs, H., & Eikelenboom, P. (2005). Serum inflammatory proteins and cognitive decline in older persons. *Neurology*, *64*(8), 1371-1377.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctot, K. L. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry*, *67*(5), 446-457. <https://doi.org/https://doi.org/10.1016/j.biopsych.2009.09.033>

Drevets, W. C., Price, J. L., & Furey, M. L. (2008). Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression [journal article]. *Brain Structure and Function*, *213*(1), 93-118. <https://doi.org/10.1007/s00429-008-0189-x>

Duncan, G. J., & Magnuson, K. (2012). Socioeconomic status and cognitive functioning: moving from correlation to causation. *Wiley Interdisciplinary Reviews: Cognitive Science*, *3*(3), 377-386.

Engels, A. S., Heller, W., Spielberg, J. M., Warren, S. L., Sutton, B. P., Banich, M. T., & Miller, G. A. (2010). Co-occurring anxiety influences patterns of brain activity in depression. *Cognitive, Affective, & Behavioral Neuroscience*, *10*(1), 141-156. <https://doi.org/10.3758/CABN.10.1.141>

Fedewa, A. L., & Ahn, S. (2011). The effects of physical activity and physical fitness on children's achievement and cognitive outcomes: a meta-analysis. *Research Quarterly for Exercise and Sport*, *82*(3), 521-535.

Francis, H. M., & Stevenson, R. J. (2011). Higher reported saturated fat and refined sugar intake is associated with reduced hippocampal-dependent memory and sensitivity to interoceptive signals. *Behavioral Neuroscience*, *125*(6), 943-955. <https://doi.org/10.1037/a0025998>

Franz, C. E., Lyons, M. J., O'Brien, R., Panizzon, M. S., Kim, K., Bhat, R., Grant, M. D., Toomey, R., Eisen, S., Xian, H., & Kremen, W. S. (2011). A 35-year longitudinal assessment of cognition and midlife depression symptoms: the Vietnam era twin study of

aging. *American Journal of Geriatric Psychiatry*, 19, 559-570. <https://doi.org/10.1097/JGP.0b013e3181ef79f1>

Gale, C. R., Batty, G. D., Tynelius, P., Deary, I. J., & Rasmussen, F. (2010). Intelligence in early adulthood and subsequent hospitalization for mental disorders. *Epidemiology*, 21(1), 70-77. <https://doi.org/10.1097/EDE.0b013e3181c17da8>

Ganzeboom, H. B., & Treiman, D. J. (1996). Internationally comparable measures of occupational status for the 1988 International Standard Classification of Occupations. *Social Science Research*, 25(3), 201-239.

Gimeno, D., Kivimaki, M., Brunner, E. J., Elovainio, M., De Vogli, R., Steptoe, A., Kumari, M., Lowe, G. D., Rumley, A., Marmot, M. G., & Ferrie, J. E. (2009). Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychological Medicine*, 39(3), 413-423. <https://doi.org/10.1017/S0033291708003723>

Golden, R. M. (2000). Statistical tests for comparing possibly misspecified and nonnested models. *Journal of Mathematical Psychology*, 44(1), 153-170.

Goldsmith, D. R., Haroon, E., Woolwine, B. J., Jung, M. Y., Wommack, E. C., Harvey, P. D., Treadway, M. T., Felger, J. C., & Miller, A. H. (2016). Inflammatory markers are associated with decreased psychomotor speed in patients with major depressive disorder. *Brain Behavior and Immunity*, 56, 281-288. <https://doi.org/10.1016/j.bbi.2016.03.025>

Gotlib, I. H., & Joormann, J. (2010). Cognition and depression: current status and future directions. *Annual Review of Clinical Psychology*, 6, 285-312. <https://doi.org/10.1146/annurev.clinpsy.121208.131305>

Grassi-Oliveira, R., Bauer, M. E., Pezzi, J. C., Teixeira, A. L., & Brietzke, E. (2011). Interleukin-6 and verbal memory in recurrent major depressive disorder. *Neuro Endocrinology Letters*, 32(4), 540-544. <https://www.ncbi.nlm.nih.gov/pubmed/21876502>

Haapakoski, R., Mathieu, J., Ebmeier, K. P., Alenius, H., & Kivimäki, M. (2015). Cumulative meta-analysis of interleukins 6 and 1 β , tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. *Brain Behavior and Immunity*, 49, 206-215.

Hackman, D. A., Gallop, R., Evans, G. W., & Farah, M. J. (2015). Socioeconomic status and executive function: developmental trajectories and mediation. *Developmental Science*, 18, 686-702. <https://doi.org/10.1111/desc.12246>

Hanson, M. D., & Chen, E. (2007). Socioeconomic status, race, and body mass index: the mediating role of physical activity and sedentary behaviors during adolescence. *Journal of Pediatric Psychology*, 32(3), 250-259. <https://doi.org/10.1093/jpepsy/jsl024>

Haro, J. M., Arbabzadeh-Bouchez, S., Brugha, T. S., De Girolamo, G., Guyer, M. E., Jin, R., Lepine, J. P., Mazzi, F., Reneses, B., & Vilagut, G. (2006). Concordance of the Composite International Diagnostic Interview Version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health surveys. *International Journal of Methods in Psychiatric Research*, 15(4), 167-180.

Harrison, J. E., Buxton, P., Husain, M., & Wise, R. (2000). Short test of semantic and phonological fluency: Normal performance, validity and test-retest reliability. *British Journal of Clinical Psychology*, 39(2), 181-191.

Harrison, N. A., Doeller, C. F., Voon, V., Burgess, N., & Critchley, H. D. (2014). Peripheral inflammation acutely impairs human spatial memory via actions on medial temporal lobe glucose metabolism. *Biological Psychiatry*, 76, 585-593. <https://doi.org/10.1016/j.biopsych.2014.01.005>

Hasin, D. S., Goodwin, R. D., Stinson, F. S., & Grant, B. F. (2005). Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. *Archives of General Psychiatry*, 62(10), 1097-1106.

Hasin, D. S., Sarvet, A. L., Meyers, J. L., Saha, T. D., Ruan, W. J., Stohl, M., & Grant, B. F. (2018). Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. *JAMA psychiatry*, 75(4), 336-346. <https://doi.org/10.1001/jamapsychiatry.2017.4602>

Hasselbalch, B. J., Knorr, U., & Kessing, L. V. (2011). Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. *Journal of Affective Disorders*, 134, 20-31. <https://doi.org/https://doi.org/10.1016/j.jad.2010.11.011>

Henry, J. D., & Crawford, J. R. (2005). A Meta-Analytic Review of Verbal Fluency Deficits in Depression. *Journal of Clinical and Experimental Neuropsychology*, 27(1), 78-101. <https://doi.org/10.1080/138033990513654>

Hoogland, I. (2015). Systemic inflammation and microglial activation: systematic review of animal experiments. *Journal of Neuroinflammation*, 12, 1-13.

Howren, M. B., Lamkin, D. M., & Suls, J. (2009). Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosomatic Medicine*, 71(2), 171-186. <https://doi.org/10.1097/PSY.0b013e3181907c1b>

Huang, Y. S., Guilleminault, C., Hwang, F. M., Cheng, C., Lin, C. H., Li, H. Y., & Lee, L. A. (2016). Inflammatory cytokines in pediatric obstructive sleep apnea. *Medicine*, 95(41), e4944. <https://doi.org/10.1097/MD.0000000000004944>

Huisman, M., Oldehinkel, A. J., de Winter, A., Minderaa, R. B., de Bildt, A., Huizink, A. C., Verhulst, F. C., & Ormel, J. (2008). Cohort profile: The dutch 'TRacking adolescents' individual lives' survey'; TRAILS. *International Journal of Epidemiology*, 37(6), 1227-1235.

Jaeger, J., Berns, S., Uzelac, S., & Davis-Conway, S. (2006). Neurocognitive deficits and disability in major depressive disorder. *Psychiatry Research*, 145(1), 39-48. <https://doi.org/10.1016/j.psychres.2005.11.011>

Jenny, N. S., French, B., Arnold, A. M., Strotmeyer, E. S., Cushman, M., Chaves, P. H., Ding, J., Fried, L. P., Kritchevsky, S. B., Rifkin, D. E., Sarnak, M. J., & Newman, A. B. (2012). Long-term assessment of inflammation and healthy aging in late life: the Cardiovascular Health Study All Stars. *The Journals of Gerontology: Series A*, 67(9), 970-976. <https://doi.org/10.1093/gerona/qlr261>

Jonker, I., Klein, H. C., Duivis, H. E., Yolken, R. H., Rosmalen, J. G., & Schoevers, R. A. (2014). Association between exposure to HSV1 and cognitive functioning in a general population of adolescents. The TRAILS study. *PloS One*, 9(7), e101549.

Jonker, I., Rosmalen, J., & Schoevers, R. (2017). Childhood life events, immune activation and the development of mood and anxiety disorders: the TRAILS study. *Translational Psychiatry*, 7(5), e1112.

Jung, T., & Wickrama, K. A. (2008). An introduction to latent class growth analysis and growth mixture modeling. *Social and Personality Psychology Compass*, 2(1), 302-317.

Junger, M., & van Kampen, M. (2010). Cognitive ability and self-control in relation to dietary habits, physical activity and bodyweight in adolescents. *The International Journal of Behavioral Nutrition and Physical Activity*, 7, 22. <https://doi.org/10.1186/1479-5868-7-22>

Karlamangla, A. S., Miller-Martinez, D., Lachman, M. E., Tun, P. A., Koretz, B. K., & Seeman, T. E. (2014). Biological correlates of adult cognition: midlife in the United States (MIDUS). *Neurobiology of Aging*, 35(2), 387-394. <https://doi.org/10.1016/j.neurobiolaging.2013.07.028>

Keilp, J. G., Gorlyn, M., Oquendo, M. A., Burke, A. K., & Mann, J. J. (2008). Attention deficit in depressed suicide attempters. *Psychiatry Research, 159*(1-2), 7-17. <https://doi.org/10.1016/j.psychres.2007.08.020>

Kessler, R. C., Avenevoli, S., Green, J., Gruber, M. J., Guyer, M., He, Y., Jin, R., Kaufman, J., Sampson, N. A., & Zaslavsky, A. M. (2009). National comorbidity survey replication adolescent supplement (NCS-A): III. Concordance of DSM-IV/CIDI diagnoses with clinical reassessments. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*(4), 386-399.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., Rush, A. J., Walters, E. E., Wang, P. S., & National Comorbidity Survey, R. (2003). The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA, 289*(23), 3095-3105. <https://doi.org/10.1001/jama.289.23.3095>

Kessler, R. C., & Üstün, T. B. (2004). The world mental health (WMH) survey initiative version of the world health organization (WHO) composite international diagnostic interview (CIDI). *International Journal of Methods in Psychiatric Research, 13*(2), 93-121.

Khandaker, G. M., Pearson, R. M., Zammit, S., Lewis, G., & Jones, P. B. (2014). Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. *JAMA psychiatry, 71*(10), 1121-1128.

Koenen, K. C., Moffitt, T. E., Roberts, A. L., Martin, L. T., Kubzansky, L., Harrington, H., Poulton, R., & Caspi, A. (2009). Childhood IQ and adult mental disorders: A test of the cognitive reserve hypothesis. *American Journal of Psychiatry, 166*, 50-57. <https://doi.org/10.1176/appi.ajp.2008.08030343>

Kohler, C. A., Freitas, T. H., Maes, M., de Andrade, N. Q., Liu, C. S., Fernandes, B. S., Stubbs, B., Solmi, M., Veronese, N., Herrmann, N., Raison, C. L., Miller, B. J., Lanctot, K. L., & Carvalho, A. F. (2017). Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. *Acta Psychiatrica Scandinavica, 135*(5), 373-387. <https://doi.org/10.1111/acps.12698>

Krogh, J., Benros, M. E., Jørgensen, M. B., Vesterager, L., Elfving, B., & Nordentoft, M. (2014). The association between depressive symptoms, cognitive function, and inflammation in major depression. *Brain Behavior and Immunity, 35*, 70-76. <https://doi.org/10.1016/j.bbi.2013.08.014>

Lampa, J., & Westman, M. (2012). Peripheral inflammatory disease associated with centrally activated IL-1 system in humans and mice. *Proceedings of the National Academy of Sciences*, *109*, 12728-12733.

Lee, R., Hermens, D. F., Porter, M. a., & Redoblado-Hodge, M. A. (2012). A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *Journal of Affective Disorders*, *140*, 113-124. <https://doi.org/https://doi.org/10.1016/j.jad.2011.10.023>

Li, X., Robertson, C. M., Yu, X., Cheypesh, A., Dinu, I. A., & Li, J. (2014). Early postoperative systemic inflammatory response is an important determinant for adverse 2-year neurodevelopment-associated outcomes after the Norwood procedure. *The Journal of Thoracic and Cardiovascular Surgery*, *148*(1), 202-206. <https://doi.org/10.1016/j.jtcvs.2013.07.079>

Mac Giollabhui, N., Ellman, L. M., Coe, C. L., Byrne, M. L., Abramson, L. Y., & Alloy, L. B. (2020). To exclude or not to exclude: Considerations and recommendations for C-reactive protein values higher than 10 mg/L. *Brain, Behavior, and Immunity*, *87*, 898-900. <https://doi.org/https://doi.org/10.1016/j.bbi.2020.01.023>

Mac Giollabhui, N., Hamilton, J. L., Nielsen, J., Connolly, S. L., Stange, J. P., Varga, S., Burdette, E., Olino, T. M., Abramson, L. Y., & Alloy, L. B. (2018). Negative cognitive style interacts with negative life events to predict first onset of a major depressive episode in adolescence via hopelessness. *Journal of Abnormal Psychology*, *127*(1), 1-11. <https://doi.org/10.1037/abn0000301>

Mac Giollabhui, N., Ng, T. H., Ellman, L. M., & Alloy, L. B. (In Press). The longitudinal associations of inflammatory biomarkers and depression revisited: systematic review, meta-analysis, and meta-regression. *Molecular Psychiatry*. <https://doi.org/https://doi.org/10.1038/s41380-020-00867-4>

Mac Giollabhui, N., Nielsen, J., Seidman, S., Olino, T. M., Abramson, L. Y., & Alloy, L. B. (2018). The development of future orientation is associated with faster decline in hopelessness during adolescence. *Journal of Youth and Adolescence*, 1-14.

Mac Giollabhui, N., Olino, T. M., Nielsen, J., Abramson, L. Y., & Alloy, L. B. (2019). Is Worse Attention a Risk Factor for or a Consequence of Depression, or Are Worse Attention and Depression Better Accounted for by Stress? A Prospective Test of Three Hypotheses. *Clinical Psychological Science*, *7*(1), 93-109.

Mac Giollabhui, N., Swistun, D., Murray, S., Moriarity, D. P., Kautz, M. M., Ellman, L. M., Olino, T. M., Coe, C. L., Abramson, L. Y., & Alloy, L. B. (2020). Executive dysfunction in depression in adolescence: the role of inflammation and higher

body mass. *Psychological Medicine*, 50(4), 683-691.
<https://doi.org/https://doi.org/10.1017/S0033291719000564>

Maes, M., Meltzer, H. Y., Bosmans, E., Bergmans, R., Vandoolaeghe, E., Ranjan, R., & Desnyder, R. (1995). Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. *Journal of Affective Disorders*, 34(4), 301-309. <https://www.ncbi.nlm.nih.gov/pubmed/8550956>

Matthews, K. A., Chang, Y., Bromberger, J. T., Karvonen-Gutierrez, C. A., Kravitz, H. M., Thurston, R. C., & Montez, J. K. (2016). Childhood Socioeconomic Circumstances, Inflammation, and Hemostasis among Midlife Women: Study of Women's Health across the Nation (SWAN). *Psychosomatic Medicine*, 78(3), 311.

McAfoose, J., & Baune, B. T. (2009). Evidence for a cytokine model of cognitive function. *Neuroscience and Biobehavioral Reviews*, 33, 355-366.
<https://doi.org/10.1016/j.neubiorev.2008.10.005>

McDermott, L. M., & Ebmeier, K. P. (2009). A meta-analysis of depression severity and cognitive function. *Journal of Affective Disorders*, 119, 1-8.
<https://doi.org/10.1016/j.jad.2009.04.022>

Misiak, B., Beszlej, J. A., Kotowicz, K., Szewczuk-Boguslawska, M., Samochowiec, J., Kucharska-Mazur, J., & Frydecka, D. (2018). Cytokine alterations and cognitive impairment in major depressive disorder: From putative mechanisms to novel treatment targets. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 80(Pt C), 177-188. <https://doi.org/10.1016/j.pnpbp.2017.04.021>

Miyake, A., & Friedman, N. P. (2012). The nature and organization of individual differences in executive functions: Four general conclusions. *Current Directions in Psychological Science*, 21(1), 8-14.

Molteni, R., Barnard, R. J., Ying, Z., Roberts, C. K., & Gomez-Pinilla, F. (2002). A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. *Neuroscience*, 112(4), 803-814.
<https://www.ncbi.nlm.nih.gov/pubmed/12088740>

Muscatell, K. A., Brosso, S. N., & Humphreys, K. L. (2018). Socioeconomic status and inflammation: a meta-analysis. *Molecular Psychiatry*, 25(9), 1.
<https://doi.org/https://doi.org/10.1038/s41380-018-0259-2>

Noble, J. M., Manly, J. J., Schupf, N., Tang, M. X., Mayeux, R., & Luchsinger, J. A. (2010). Association of C-reactive protein with cognitive impairment. *Archives of Neurology*, 67(1), 87-92. <https://doi.org/10.1001/archneurol.2009.308>

Nolen-Hoeksema, S. (2001). Gender differences in depression. *Current Directions in Psychological Science*, *10*(5), 173-176.

Nyaradi, A., Foster, J. K., Hickling, S., Li, J., Ambrosini, G. L., Jacques, A., & Oddy, W. H. (2014). Prospective associations between dietary patterns and cognitive performance during adolescence. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *55*(9), 1017-1024. <https://doi.org/10.1111/jcpp.12209>

Nylund, K. L., Asparouhov, T., & Muthén, B. O. (2007). Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. *Structural equation modeling: A multidisciplinary Journal*, *14*(4), 535-569.

O'Connor, M. F., Bower, J. E., Cho, H. J., Creswell, J. D., Dimitrov, S., Hamby, M. E., Hoyt, M. A., Martin, J. L., Robles, T. F., Sloan, E. K., Thomas, K. S., & Irwin, M. R. (2009). To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. *Brain, Behavior, and Immunity*, *23*(7), 887-897. <https://doi.org/10.1016/j.bbi.2009.04.005>

O'Dea, J. A., & Wilson, R. (2006). Socio-cognitive and nutritional factors associated with body mass index in children and adolescents: possibilities for childhood obesity prevention. *Health Education Research*, *21*(6), 796-805. <https://doi.org/10.1093/her/cyl125>

Oquendo, M. A., Friend, J. M., Halberstam, B., Brodsky, B. S., Burke, A. K., Grunebaum, M. F., Malone, K. M., & Mann, J. J. (2003). Association of Comorbid Posttraumatic Stress Disorder and Major Depression With Greater Risk for Suicidal Behavior. *American Journal of Psychiatry*, *160*, 580-582. <https://doi.org/10.1176/appi.ajp.160.3.580>

Osimo, E. F., Baxter, L. J., Lewis, G., Jones, P. B., & Khandaker, G. M. (2019). Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. *Psychological Medicine*, *49*(12), 1958-1970. <https://doi.org/https://doi.org/10.1017/S0033291719001454>

Ownby, R. L., Crocco, E., Acevedo, A., John, V., & Loewenstein, D. (2006). Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Archives of General Psychiatry*, *63*, 530-538. <https://doi.org/10.1001/archpsyc.63.5.530>

Paine, N. J., Bosch, J. a., Ring, C., Drayson, M. T., & Veldhuijzen van Zanten, J. J. C. S. (2015). Induced mild systemic inflammation is associated with impaired ability to

improve cognitive task performance by practice. *Psychophysiology*, *52*, 333-341. <https://doi.org/10.1111/psyp.12360>

Palta, P., Xue, Q.-L., Deal, J. A., Fried, L. P., Walston, J. D., & Carlson, M. C. (2015). Interleukin-6 and C-reactive protein levels and 9-year cognitive decline in community-dwelling older women: the Women's Health and Aging Study II. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, *70*(7), 873-878.

Petrides, M., & Milner, B. (1982). Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia*, *20*(3), 249-262. [https://doi.org/10.1016/0028-3932\(82\)90100-2](https://doi.org/10.1016/0028-3932(82)90100-2)

Porter, R. J., Bourke, C., & Gallagher, P. (2007). Neuropsychological impairment in major depression: its nature, origin and clinical significance. *Australian and New Zealand Journal of Psychiatry*, *41*(2), 115-128.

Porter, R. J., Gallagher, P., Thompson, J. M., & Young, A. H. (2003). Neurocognitive impairment in drug-free patients with major depressive disorder. *The British Journal of Psychiatry*, *182*(3), 214-220.

Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., Morag, A., & Pollmacher, T. (2001). Cytokine-associated emotional and cognitive disturbances in humans. *Archives of General Psychiatry*, *58*(5), 445-452. <https://doi.org/doi:10.1001/archpsyc.58.5.445>

Reiss, F. (2013). Socioeconomic inequalities and mental health problems in children and adolescents: A systematic review. *Social Science and Medicine*, *90*, 24-31. <https://doi.org/https://doi.org/10.1016/j.socscimed.2013.04.026>

Retterstol, L., Eikvar, L., & Berg, K. (2003). A twin study of C-Reactive Protein compared to other risk factors for coronary heart disease. *Atherosclerosis*, *169*(2), 279-282. [https://doi.org/https://doi.org/10.1016/S0021-9150\(03\)00192-8](https://doi.org/https://doi.org/10.1016/S0021-9150(03)00192-8)

Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2014). Cognitive impairment in depression: a systematic review and meta-analysis. *Psychological Medicine*, *44*(10), 2029-2040. <https://doi.org/https://doi.org/10.1017/S0033291713002535>

Ross, T. P., Hanouskova, E., Giarla, K., Calhoun, E., & Tucker, M. (2007). The reliability and validity of the self-ordered pointing task. *Archives of Clinical Neuropsychology*, *22*(4), 449-458.

Schermelleh-Engel, K., Moosbrugger, H., & Müller, H. (2003). Evaluating the fit of structural equation models: Tests of significance and descriptive goodness-of-fit measures. *Methods of Psychological Research Online*, 8(2), 23-74.

Scult, M. A., Paulli, A. R., Mazure, E. S., Moffitt, T. E., Hariri, A. R., & Strauman, T. J. (2017). The association between cognitive function and subsequent depression: a systematic review and meta-analysis. *Psychological Medicine*, 47(1), 1-17. <https://doi.org/10.1017/s0033291716002075>

Semkowska, M., Quinlivan, L., O'Grady, T., Johnson, R., Collins, A., O'Connor, J., Knittle, H., Ahern, E., & Glod, T. (2019). Cognitive function following a major depressive episode: a systematic review and meta-analysis. *The Lancet Psychiatry*, 6(10), 851-861. [https://doi.org/https://doi.org/10.1016/S2215-0366\(19\)30291-3](https://doi.org/https://doi.org/10.1016/S2215-0366(19)30291-3)

Sheline, Y. I., Sanghavi, M., Mintun, M. A., & Gado, M. H. (1999). Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *Journal of Neuroscience*, 19(12), 5034-5043.

Sheline, Y. I., Wang, P. W., Gado, M. H., Csernansky, J. G., & Vannier, M. W. (1996). Hippocampal atrophy in recurrent major depression. *Proceedings of the National Academy of Sciences*, 93(9), 3908-3913.

Shields, G. S., Moons, W. G., & Slavich, G. M. (2017). Inflammation, self-regulation, and health: an immunologic model of self-regulatory failure. *Perspectives on Psychological Science*, 12(4), 588-612.

Shin, M.-S., Park, S.-Y., Park, S.-R., Seol, S.-H., & Kwon, J. S. (2006). Clinical and empirical applications of the Rey–Osterrieth complex figure test. *Nature Protocols*, 1(2), 892.

Singh-Manoux, A., Dugravot, A., Brunner, E., Kumari, M., Shipley, M., Elbaz, A., & Kivimaki, M. (2014). Interleukin-6 and C-reactive protein as predictors of cognitive decline in late midlife. *Neurology*, 83(6), 486-493. <https://doi.org/10.1212/WNL.0000000000000665>

Smith, R. S. (1991). The macrophage theory of depression. *Medical Hypotheses*, 35(4), 298-306. [https://doi.org/https://doi.org/10.1016/0306-9877\(91\)90272-Z](https://doi.org/https://doi.org/10.1016/0306-9877(91)90272-Z)

Snyder, H. R. (2013a). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychological Bulletin*, 139(1), 81.

Snyder, H. R. (2013b). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychological Bulletin*, *139*, 81-132. <https://doi.org/10.1037/a0028727>

Snyder, H. R., & Hankin, B. L. (2016). Spiraling out of control: Stress generation and subsequent rumination mediate the link between poorer cognitive control and internalizing psychopathology. *Clinical Psychological Science*, *4*(6), 1047-1064.

Snyder, H. R., Miyake, A., & Hankin, B. L. (2015). Advancing understanding of executive function impairments and psychopathology: Bridging the gap between clinical and cognitive approaches. *Frontiers in Psychology*, *6*, 328. <https://doi.org/10.3389/fpsyg.2015.00328>

Sommerfeldt, S. L., Cullen, K. R., Han, G., Fryza, B. J., Houri, A. K., & Klimes-Dougan, B. (2016). Executive Attention Impairment in Adolescents With Major Depressive Disorder. *Journal of Clinical Child and Adolescent Psychology*, *45*(1), 69-83. <https://doi.org/10.1080/15374416.2015.1072823>

Spyridaki, E. C., Avgoustinaki, P. D., & Margioris, A. N. (2016). Obesity, inflammation and cognition. *Current Opinion in Behavioral Sciences*, *9*, 169-175.

Su, S., Miller, A. H., Snieder, H., Bremner, J. D., Ritchie, J., Maisano, C., Jones, L., Murrah, N. V., Goldberg, J., & Vaccarino, V. (2009). Common genetic contributions to depressive symptoms and inflammatory markers in middle-aged men: the Twins Heart Study. *Psychosomatic Medicine*, *71*(2), 152-158. <https://doi.org/10.1097/PSY.0b013e31819082ef>

Tabriz, A. A., Sohrabi, M. R., Parsay, S., Abadi, A., Kiapour, N., Aliyari, M., Ahmadi, F., & Roodaki, A. (2015). Relation of intelligence quotient and body mass index in preschool children: a community-based cross-sectional study. *Nutrition & Diabetes*, *5*(8), e176-e176. <https://doi.org/10.1038/nutd.2015.27>

Teunissen, C., Van Boxtel, M., Bosma, H., Bosmans, E., Delanghe, J., De Bruijn, C., Wauters, A., Maes, M., Jolles, J., & Steinbusch, H. (2003). Inflammation markers in relation to cognition in a healthy aging population. *Journal of Neuroimmunology*, *134*(1-2), 142-150.

Van Der Elst, W., Van Boxtel, M. P., Van Breukelen, G. J., & Jolles, J. (2005). Rey's verbal learning test: normative data for 1855 healthy participants aged 24–81 years and the influence of age, sex, education, and mode of presentation. *Journal of the International Neuropsychological Society*, *11*(3), 290-302.

Van der Kooy, K., van Hout, H., Marwijk, H., Marten, H., Stehouwer, C., & Beekman, A. (2007). Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *International Journal of Geriatric Psychiatry*, 22, 613-626. <https://doi.org/10.1002/gps.1723>

Veiel, H. O. F. (1997). A preliminary profile of neuropsychological deficits associated with major depression. *Journal of Clinical and Experimental Neuropsychology*, 19, 587-603. <https://doi.org/10.1080/01688639708403745>

Videbech, P., & Ravnkilde, B. (2004). Hippocampal volume and depression: a meta-analysis of MRI studies. *The American journal of psychiatry*, 161, 1957-1966. <https://doi.org/10.1176/appi.ajp.161.11.1957>

Wagner, Doering, B., Helmreich, I., Lieb, K., & Tadić, A. (2012). A meta-analysis of executive dysfunctions in unipolar major depressive disorder without psychotic symptoms and their changes during antidepressant treatment. *Acta Psychiatrica Scandinavica*, 125, 281-292. <https://doi.org/10.1111/j.1600-0447.2011.01762.x>

Wechsler, D. (1997). Wechsler Adult Intelligence Scale, third edition, Dutch version. Swets & Zeitlinger.

Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., Charlson, F. J., Norman, R. E., Flaxman, A. D., Johns, N., Burstein, R., Murray, C. J. L., & Vos, T. (2013). Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet*, 382, 1575-1586. [https://doi.org/10.1016/s0140-6736\(13\)61611-6](https://doi.org/10.1016/s0140-6736(13)61611-6)

Whiteside, D. M., Kealey, T., Semla, M., Luu, H., Rice, L., Basso, M. R., & Roper, B. (2016). Verbal Fluency: Language or Executive Function Measure? *Applied Neuropsychology: Adult*, 23(1), 29-34. <https://doi.org/10.1080/23279095.2015.1004574>

Wittchen, H.-U. (1994). Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): a critical review. *Journal of Psychiatric Research*, 28(1), 57-84.

Woo, Y. S., Rosenblat, J. D., Kakar, R., Bahk, W. M., & McIntyre, R. S. (2016). Cognitive Deficits as a Mediator of Poor Occupational Function in Remitted Major Depressive Disorder Patients. *Clinical Psychopharmacology and Neuroscience*, 14(1), 1-16. <https://doi.org/10.9758/cpn.2016.14.1.1>

Yang, Y., Shields, G. S., Guo, C., & Liu, Y. (2018). Executive function performance in obesity and overweight individuals: A meta-analysis and review. *Neuroscience and Biobehavioral Reviews*, 84, 225-244.

Yang, Y., Shields, G. S., Wu, Q., Liu, Y., Chen, H., & Guo, C. (2019). The association between obesity and lower working memory is mediated by inflammation: Findings from a nationally representative dataset of US adults. *Brain, Behavior, and Immunity*.

Zakzanis, K., Leach, L., & Kaplan, E. (1998). On the nature and pattern of neurocognitive function in major depressive disorder. *Cognitive and Behavioral Neurology*, *11*(3), 111-119.

Zammit, S., Allebeck, P., David, A. S., Dalman, C., Hemmingsson, T., Lundberg, I., & Lewis, G. (2004). A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Archives of General Psychiatry*, *61*(4), 354-360.

Zheng, F., & Xie, W. (2018). High-sensitivity C-reactive protein and cognitive decline: the English Longitudinal Study of Ageing. *Psychological Medicine*, *48*(8), 1381-1389. <https://doi.org/10.1017/S0033291717003130>

CHAPTER 2

SUPPLEMENTARY MATERIAL

Methods

Cognitive Functioning – More Detailed Information

Reliable and valid measures of cognitive functioning were administered in TRAILS at Wave 4. Where appropriate, tasks were administered in Dutch or using Dutch versions of the task. Normative data were not used because they were not available for all measures, Dutch norming data typically are normed based on a substantially smaller sample than the current analytic sample, and because the narrow age range of the TRAILS cohort limit the risk of age-related bias. Thus, raw data from all neuropsychological measures were used in analyses rather than normed data.

Given the large number of measures of cognitive functioning administered and their common use in research and clinical settings, they only are briefly discussed here. Auditory, verbal working memory was measured using the ‘Digit Span Backwards’ subtest from the ‘Digit Span’ on the Wechsler Adult Intelligence Scale, third edition (WAIS-III), Dutch version (Wechsler, 1997), which required the respondent to recall a series of numbers presented out loud by the examiner and repeat them in reverse order. Visual working memory was assessed using the Self-Ordered Pointing Task (Petrides & Milner, 1982). For this task, participants selected a picture from several pictures on the computer screen. The participant was not allowed to select the same picture twice or to select the same place on the computer screen twice. The task consisted of four parts, with nine or twelve pictures and with abstract or concrete pictures. The average number of errors was used as the outcome variable for this task, given that it is the most sensitive

outcome (Ross et al., 2007) and to be consistent with prior TRAILS studies (Jonker et al., 2014). Given that the overall mean number of errors was low ($M = 1.57$; $SD = .85$), the values of five individuals with extreme values (5.25, 6.25, 7.0, 8.75, 9.5) were winsorized to be equal to five.

Visual organization, a component of executive functioning, was assessed using the ‘Copy’ trial of the Rey-Osterrieth Complex Figure Test (Shin et al., 2006), in which participants were asked to draw a complex geometric shape. Visuo-constructional and non-verbal reasoning skills were assessed using the ‘Block Design’ subtest of the WAIS-III (Wechsler, 1997). On this task, participants were asked to arrange and assemble blocks that have three color patterns so that they match a picture.

Verbal episodic memory was assessed using a list learning task (Rey Auditory Verbal Learning Test) in which participants are asked to recall as many target words as they can from 15 common words that are repeated over five trials (Van Der Elst et al., 2005). Immediate recall (number of words recalled across five trials) and delayed recall (number of target words recalled following a delay) were used as outcomes.

Verbal fluency was measured using a modified version of the short test of semantic and phonological fluency (Harrison et al., 2000). In the phonological condition, participants were asked to name as many words as they could, except for the names of people, starting with a given letter across two trials lasting one minute each. In the semantic condition, participants were asked to generate as many words as they could that were the names of animals across two minutes. The outcome of semantic fluency was the

correct number of words generated per minute and the outcome of phonological fluency was the average number of unique words generated across both trials.

Three latent constructs were hypothesized to underpin these eight measures: executive functioning, episodic memory, and verbal fluency. It should be noted that important components of executive functioning were not available, such as inhibition and cognitive flexibility (Miyake & Friedman, 2012), and less commonly used measures were included, such as visual reasoning and visual organization. This decision was based upon the measures available, and when these four measures were separated into two latent factors of visual/verbal working memory (Self-Ordered Pointing Task/Digit Span Backward) and visual organization/reasoning (Rey-Osterrieth Complex Figure Test/Block Design), the correlation of the latent factors was .83. Although verbal fluency often is considered an index of executive functioning, more recent research has identified it as more closely linked with language skills and psychomotor speed (Henry & Crawford, 2005; Whiteside et al., 2016).

Results

Latent Class Analysis of Depressive Symptoms

Although a four-class solution performed better than other classes based on fit statistics, a four-class model was unable to reliably converge on a single solution and, thus, was not considered. A three-class solution performed better than a one- or two-class solution when examining log likelihood, AIC, and BIC. Similarly, the adjusted Vuong-Lo-Mendell-Rubin Log Ratio Test was statistically significant in the three-class solution,

suggesting that the three-class solution represented a significant improvement in model fit. However, it was difficult to reconcile all of the classes identified by a three-class solution with our theoretical understanding of depression. In particular, because this study was interested in identifying individuals with a history of depression, the distinction of two of the groups in Model Three [(Class Two: intercept: .49, $p < .001$; slope: .17, $p < .001$) and (Class Three: intercept: .81, $p < .001$; slope: -.21, $p < .001$)] did not appear to be theoretically meaningful and may rather reflect the timing of a depressive period. Consequently, a two-class solution was selected on the basis of better performance when examining log-likelihood, AIC, and BIC compared with a one-class solution and the clear interpretability consistent with empirical and theoretical understanding of depression.

CHAPTER 3

**THE LONGITUDINAL ASSOCIATIONS OF INFLAMMATORY BIOMARKERS
AND DEPRESSION REVISITED: SYSTEMATIC REVIEW, META-ANALYSIS,
AND META-REGRESSION.**

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 58,306 participants, with up to 27 studies included in random-effects meta-analysis. Higher CRP and 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 CRP and future depression 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.

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 (Borcusa & Iacono, 2007; Erskine et al., 2015; Kessler et al., 2003). Although the cardinal symptoms of depression are low mood and anhedonia (American Psychiatric Association, 2013), depression typically 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 (Zimmerman et al., 2015), and in a study of 2,154 depressed individuals, 137 entirely unique symptom profiles were observed (Olbert et al., 2014). 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 (Kunugi et al., 2015), which may explain why one in three depressed patients do not respond to conventional treatments (Rush et al., 2006). Since the early 1990s, accumulating evidence suggests that dysregulated immune functioning may characterize one subtype of depression (Raison & Miller, 2011; Smith, 1991).

There is now 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 (Irwin & Miller, 2007)]. 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 (Haroon et al., 2012; Miller et al., 2009; Raison et al., 2006). In particular, there is strong evidence that activation of the innate immune system leads to “sickness behaviors” (e.g., anhedonia, fatigue, psychomotor retardation) that are characteristic of depression (Dantzer et al., 2008). 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 (Dowlati et al., 2010) and community (Howren et al., 2009) 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 (Udina et al., 2012), unless prophylactically treated with an antidepressant (Haroon et al., 2012; Musselman et al., 2001). Less powerful activation of the innate immune response through administration of a purified endotoxin or vaccination also reliably induces depressive symptoms (Dantzer et al., 2008; Schedlowski et al., 2014).

It has not been completely established, however, whether inflammation is a cause (Chiu et al., 2017; Dantzer et al., 2008), consequence (Berk et al., 2013), or correlate of depression (Haroon et al., 2012). 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) (Mac Giollabhui, Swistun, et al., 2020; Su et al., 2009). 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 (Bonnie Au et al., 2015; Khandaker et al., 2014), depression predicting inflammation (Copeland et al., 2012; Stewart et al., 2009), bidirectional associations (Deverts et al., 2010; Matthews et al., 2010), and null results (Niles et al., 2018; Simanek et al., 2014). 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 (Valkanova et al., 2013) or (ii) in elderly samples (Smith et al., 2018). Equally importantly, despite widespread knowledge of the many covariates that can influence circulating levels of inflammatory biomarkers (Valkanova et al., 2013) 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.

Material and 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 assay, 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, community 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 (Peterson et al., 2011) and based on a prior meta-analysis (Smith et al., 2018).

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 assay method/fasting status/time of blood draw/CRP values ≥ 10 removed from analyses; covariates included in statistical models; exclusion criteria, and kit used to assay inflammatory biomarkers.

Statistical Analysis

Meta-analyses were conducted in R (R Core Team, 2019) using ‘metafor’ (Viechtbauer, 2010). 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 Cochran 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 – see Table 7 for quality assessment scores and Table 8 for quality assessment protocol.

Author	1.Representative sampling procedure	2.Same reference group	3.Outcome not present at start	4.Adequacy of follow-up	5.Adequate sample size	6.Comparable cohorts	7. Controls for infection or injury	Score
Khandaker et al.	1	1	1	1	1	1	1	7
Adriaensen et al.	1	1	0	1	1	1	0	5
Deverts et al.	1	1	0	1	1	1	1	6
Elovainio et al.	1	1	0	0	1	1	1	5
Simanek et al.	1	1	1	0	1	1	0	5
Au et al.	1	1	0	0	1	1	1	5
Copeland et al.	0	1	0	1	1	1	1	5
Brown et al.	1	1	0	0	1	1	0	4
Hiles et al.	1	1	0	0	1	1	1	5
Milaneschi et al.	1	1	1	1	1	1	0	6
de Mello Franco et al.	0	1	1	0	1	1	1	5
Das et al.	1	1	0	1	1	1	1	6
Stewart et al.	1	1	0	1	1	1	1	6
Kern et al.	1	1	1	0	0	1	0	4
Zalli et al.	1	1	0	1	1	1	1	6
Simanek et al.	1	1	1	1	1	1	0	6
Matthews et al.	1	1	0	1	1	1	1	6
Baune et al.	1	1	0	1	1	1	0	5
Duivis et al.	1	1	0	1	1	1	1	6
Jonker et al.	1	1	0	1	1	1	1	6
Casaletto et al.	1	1	0	0	0	1	1	4
Kim et al.	1	1	0	1	1	1	0	5
Luciano et al.	1	1	0	1	1	1	1	6
Luukinen et al.	1	1	0	1	1	0	1	5
Matsushima et al.	1	1	0	1	0	0	0	3
Nelson et al.	0	1	1	0	0	1	0	3
Niles et al.	1	1	0	0	1	1	1	5
Pasco et al.	1	1	1	1	1	1	0	6
Tully et al.	1	1	0	1	1	1	0	5
Walss-Bass et al.	0	1	1	1	0	0	0	3
Oddy et al.	0	1	0	1	1	1	1	5
Jones et al.	1	1	0	0	1	1	1	5

<i>Table 7. (continued)</i>								
Chiang et al.	1	1	0	1	0	1	1	5
van den Biggelaar et al.	1	1	1	1	1	1	0	6
Glaus et al.	1	1	1	1	1	1	1	7
Caserta et al.	0	1	0	1	0	1	0	3
Mac Giollabhui et al.	1	1	0	1	1	1	1	6
Forti et al.	1	1	0	1	1	1	0	5

Table 8. Modified Quality Assessment Scale used to Appraise Study Quality for all Included Studies.

<p>Selection</p> <p>1) <u>Representative sampling procedure of participants in community base</u> a) Yes - truly representative of the average _____ (describe) in the community * b) Somewhat - somewhat representative of the average _____ in the community * c) No selected group - selected group of users (e.g. nurses, volunteers) d) No - no description of the derivation of the cohort</p> <p>2) <u>People with depression and reference group from same community</u> a) Yes - drawn from the same community as the exposed cohort * b) Different - drawn from a different source c) No - no description of the derivation of the non exposed cohort</p> <p>3) <u>Demonstration that outcome of interest was not present at start of study</u> a) Yes – individuals with prior history of depression excluded * b) No</p> <p>4) <u>Adequacy of follow-up of cohorts</u> a) Yes - Follow-up > 75% * b) Yes - >50% and min. bias - Retention considerable (>50%) and unlikely to introduce bias as examined in paper via attrition analysis * c) No - Increased risk of bias via substantial attrition and absence of analysis</p> <p>5) <u>Adequate sample size (analytic sample)</u> a) Yes - Longitudinal Analysis based on > 200 participants * b) No - Longitudinal Analysis based on < 200 participants</p>
<p>Comparability</p> <p>6) <u>Comparability of cohorts on the basis of the design or analysis</u> a) Yes - study controlled for at least two important confounds (baseline depression, baseline inflammation, BMI, sex) * b) No – at no point controls for two+ important confounds</p> <p>7) <u>Study controls for acute infection/injury</u> a) Yes - study controls use methodology to attempt to control for acute infection/injury either through covariation or exclusion * b) No - Study does not attempt to control either through exclusion or statistically for illness/injury</p> <p>Note: if data could not be extracted from article, score of 0 given. * indicates response where point awarded.</p>

Results

Study Selection

From 11,176 identified articles, 8,345 were removed following title review and 363 following abstract review, leaving 73 for full-text review. This led to 38 articles included for systematic review (Adriaensen et al., 2014; Au et al., 2015; Baune et al., 2012; Brown et al., 2016; Casaletto et al., 2018; Caserta et al., 2011; Chiang et al., 2019; Copeland et al., 2012; Deverts et al., 2010; Duivis et al., 2015; Elovainio et al., 2006; Forti et al., 2010; Glaus et al., 2018; Hiles et al., 2015; Jones et al., 2017; Jonker et al., 2017; Kern et al., 2014; Khandaker et al., 2014; Kim et al., 2018; Luciano et al., 2012; Luukinen et al., 2010; Mac Giollabhui, Swistun, et al., 2020; Matsushima et al., 2015; Matthews et al., 2010; Milaneschi et al., 2009; Nelson et al., 2018; Niles et al., 2018; Oddy et al., 2018; Pasco et al., 2010; Simanek et al., 2014; Simanek et al., 2018; Stewart et al., 2009; Tully et al., 2015; van den Biggelaar et al., 2007; Walss-Bass et al., 2018; Zalli et al., 2016) and 27 for meta-analysis (see Figure 2 for complete information). Details on the excluded 45 studies can be found in Table 9.

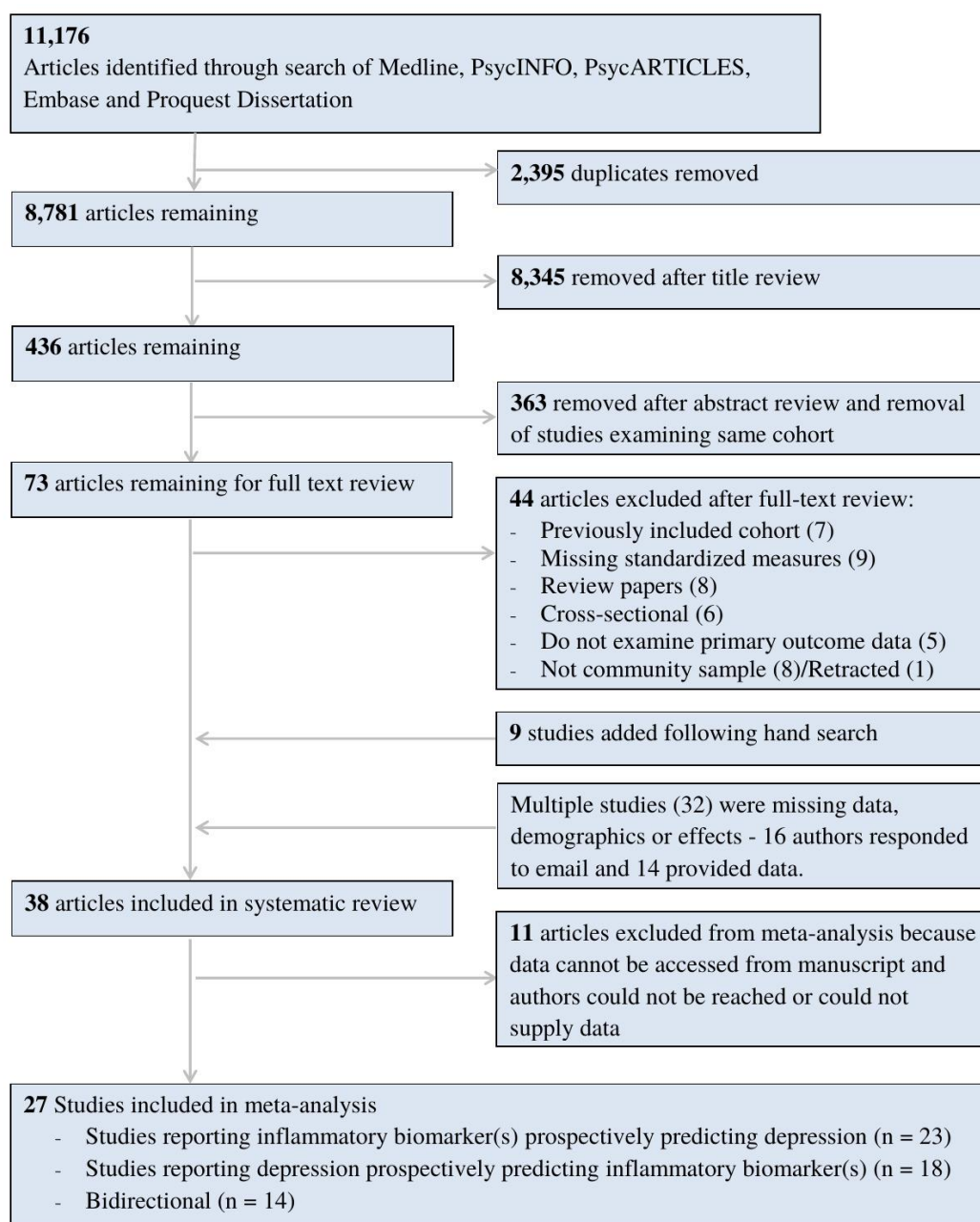


Figure 2. Flowchart detailing process by which studies were included in systematic review and meta-analysis.

Table 9. List of 45 Studies Excluded From Systematic Review.

Author	Year	Title	Reason for Exclusion
Rudaz et al.	2017	Partially distinct combinations of psychological, metabolic and inflammatory risk factors are prospectively associated with the onset of the subtypes of Major Depressive Disorder in midlife	Duplicate
Danese et al.	2008	Elevated inflammation levels in depressed adults with a history of childhood maltreatment	Not Longitudinal
Kern et al.	2013	Childhood violence victimisation predicts elevated inflammation levels in young women independent of latent genetic influences	Retracted
McBeth et al.	2018	The relationship between musculoskeletal pain, Inflammation and/or Depression in men	Could not access data
Pasquali et al.	2018	Peripheral biomarkers in new onset of major depressive disorder in midlife women: The harvard study of moods and cycles	Duplicate
Gurka et al.	2016	Depressive symptoms are associated with worsened severity of the metabolic syndrome in African American women independent of lifestyle factors: A consideration of mechanistic links from the Jackson heart study	Could not access data
Cohen-Manheim et al.	2015	Increase in the Inflammatory Marker GlycA over 13 Years in Young Adults Is Associated with Poorer Cognitive Function in Midlife	Unstandardized Measures of Inflammation and/or Depression
Freeman et al.	2016	Sex differences in associations between subjective social status and C-reactive protein in young adults	Not Longitudinal
Das	2017	Depression, Inflammation, and Physiological Risk in Late Life: A National Longitudinal Study	Not Longitudinal
Lamers et al.	2019	Longitudinal association between depression, depression characteristics and inflammatory markers: Results from the NESDA study	Not Community Sample
Vogelzangs et al.	2014	Inflammatory and metabolic dysregulation and the 2-year course of depressive disorders in antidepressant users	Duplicate
Chocano-Bedoya et al.	2014	C-reactive protein, interleukin-6, soluble tumor necrosis factor α receptor 2 and incident clinical depression	Unstandardized Measures of Inflammation and/or Depression
Moise et al.	2016	Demystifying the association between depressive symptoms and cardiovascular disease in black and white adults: The regards study	Unstandardized Measures of Inflammation and/or Depression

<i>Table 9 (continued)</i>			
De Berardis et al.	2009	The emerging role of C-reactive protein in affective and psychotic disorders	Review Paper
Kuo et al.	2005	Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: systematic review and meta-analysis	Review Paper
Martinac et al.	2014	Metabolic syndrome, activity of the hypothalamic-pituitary-adrenal axis and inflammatory mediators in depressive disorder	Review Paper
Martínez-Cengotitabengoa et al.	2017	Peripheral Inflammatory Parameters in Late-Life Depression: A Systematic Review	Review Paper
Smith et al.	2018	The association between C-reactive protein, Interleukin-6 and depression among older adults in the community: A systematic review and meta-analysis	Review Paper
Su et al.	2015	Nutrition, psychoneuroimmunology and depression: the therapeutic implications of omega-3 fatty acids in interferon- α -induced depression	Review Paper
Valkanova et al.	2013	CRP, IL-6 and depression: A systematic review and meta-analysis of longitudinal studies	Review Paper
Hughes & Kumari	2017	Associations of C-reactive protein and psychological distress are modified by antidepressants, supporting an inflammatory depression subtype: Findings from UKHLS	Unstandardized Measures of Inflammation and/or Depression
Beach et al.	2017	When Inflammation and/or Depression go together: The longitudinal effects of parent-child relationships	Not Longitudinal
Haarman Becking, Drexhage & Schoevers	2017	Immune dysregulation in unipolar and bipolar depression	Duplicate
Brody et al.	2014	Harsh parenting and adolescent health: A longitudinal analysis with genetic moderation	Not Longitudinal
Davis et al.	2019	Interleukin-6 and Depressive Mood Symptoms: Mediators of the Association Between Childhood Abuse and Cognitive Performance in Middle-Aged Adults	Not Longitudinal
De Berardis et al.	2006	The role of C-reactive protein in mood disorders	Review Paper
Dinan	2012	Cardiovascular outcome in major depression	Unstandardized Measures of Inflammation and/or Depression
Franco et al.	2017	Persistent Depressive Symptoms are Independent Predictors of Low-Grade Inflammation Onset Among Healthy Individuals	Duplicate

<i>Table 9 (continued)</i>			
Gu et al.	2017	Circulating inflammatory biomarkers in relation to brain structural measurements in a non-demented elderly population	Could not access data
Matthews et al.	2016	Childhood SES and age as moderators of changes in inflammatory markers over time among middle-age adults	Duplicate
Komulainen et al.	2007	Serum high sensitivity C-reactive protein and cognitive function in elderly women	Could not access data
Franco Laurinavicius et al.	2013	Depression is an independent predictor of subclinical inflammation onset among healthy individuals: A cohort study	Could not access data
Virtanen et al.	2015	Interleukin-6 as a predictor of symptom resolution in psychological distress: A cohort study	Unstandardized Measures of Inflammation and/or Depression
Wang et al.	2009	Inflammatory markers as predictors of depression and anxiety in adolescents: Statistical model building with component-wise gradient boosting	Unstandardized Measures of Inflammation and/or Depression
Naarding et al.	2005	A study on symptom profiles of late-life depression: The influence of vascular, degenerative and inflammatory risk-indicators	Unstandardized Measures of Inflammation and/or Depression
Gimeno et al.	2009	Dietary patterns, body mass index and inflammation: Pathways to depression and mental health problems in adolescents	Unstandardized Measures of Inflammation and/or Depression
Miller & Cole	2012	Prospective data from the Women's Health Initiative on depressive symptoms, stress, and inflammation	Not Community Sample
Tully et al.	2016	Prospective data from the Women's Health Initiative on depressive symptoms, stress, and inflammation	Duplicate
Rozing et al.	2019	Inflammation in older subjects with early- and late-onset depression in the NESDO study: a cross-sectional and longitudinal case-only design	Not Community Sample
Cizza et al.	2009	Inflammation in older subjects with early- and late-onset depression in the NESDO study: a cross-sectional and longitudinal case-only design	Not Community Sample
Dahl et al.	2014	The plasma levels of various cytokines are increased during ongoing depression and are reduced to normal levels after recovery	Not Community Sample

Dannehl et al.	2014	The predictive value of somatic and cognitive depressive symptoms for cytokine changes in patients with major depression	Not Community Sample
Lamers et al.	2018	Prospective data from the Women's Health Initiative on depressive symptoms, stress, and inflammation	Not Community Sample
Empana et al.	2005	Prospective data from the Women's Health Initiative on depressive symptoms, stress, and inflammation	Not Community Sample

Study characteristics (summarized in Table 10) indicate substantial variability in sample characteristics and study methodologies – see supplementary material ('Study Characteristics') for a complete discussion.

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
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

Author	Year	Country	N	Mean age	Female	Male	OR	CRP	CRP	Sample	Exclusion	Covariates	Exclusion	N
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
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

Inflammatory Biomarkers and Subsequent Depression

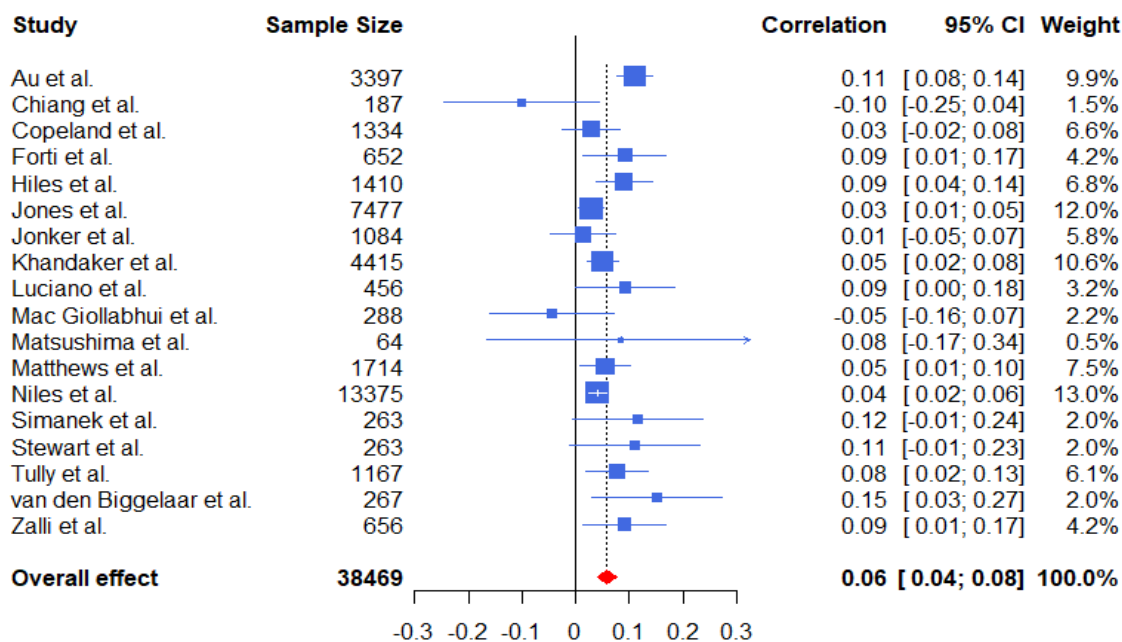
There were 32 studies that examined the association between at least one inflammatory biomarker (CRP: 25; IL-6: 17; TNF- α : 9) and subsequent depression. Baseline CRP was associated with future depressive symptoms in 52% ($k=12$) of all studies, which reduced to 20% ($k=5$) following adjustment for 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 3. 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 4. 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.

Figure 3. 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

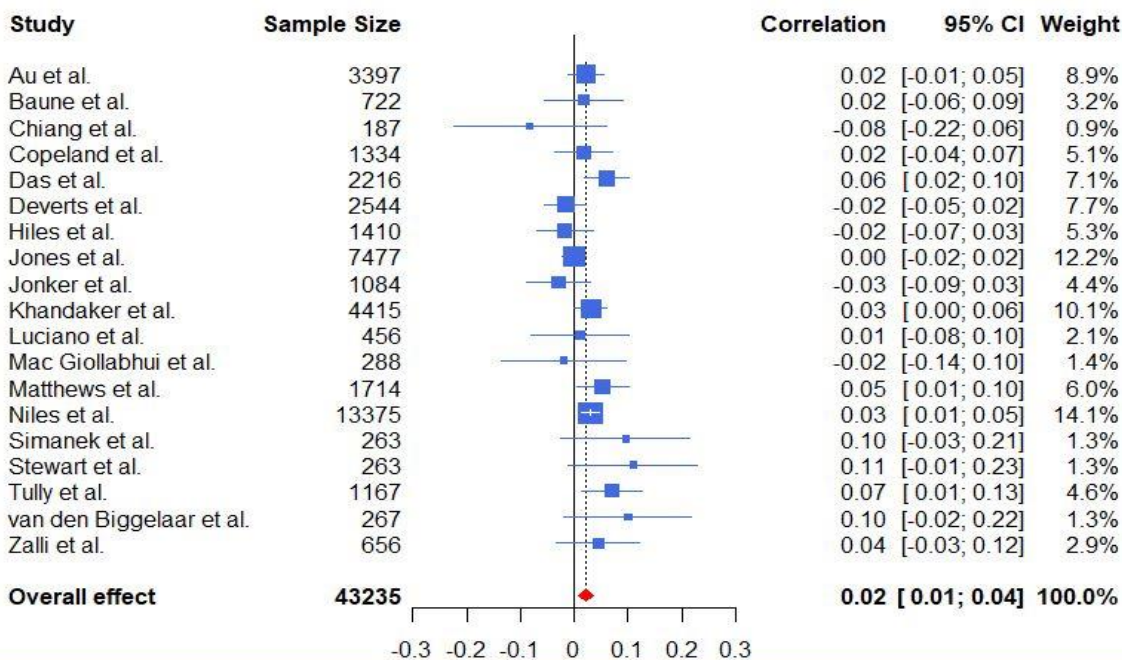
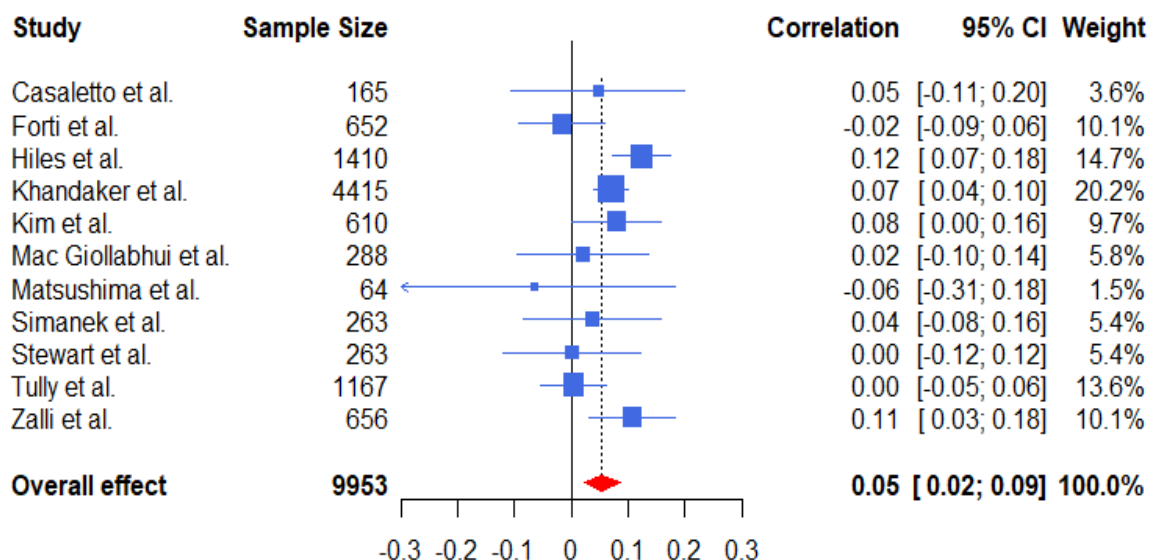
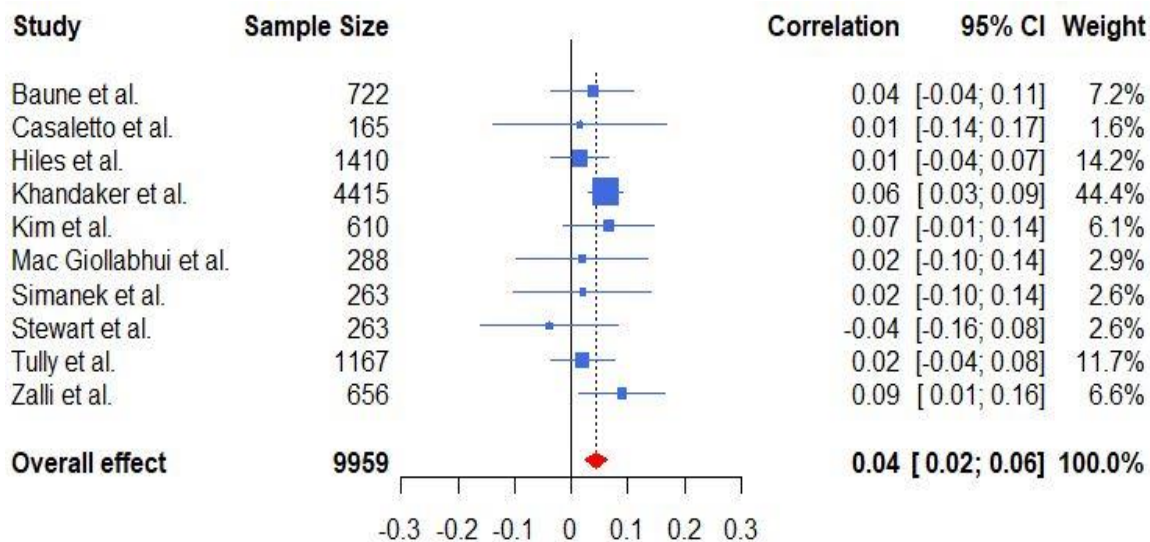


Figure 4. Forest Plots of Baseline IL-6 and Future Depressive Symptoms

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



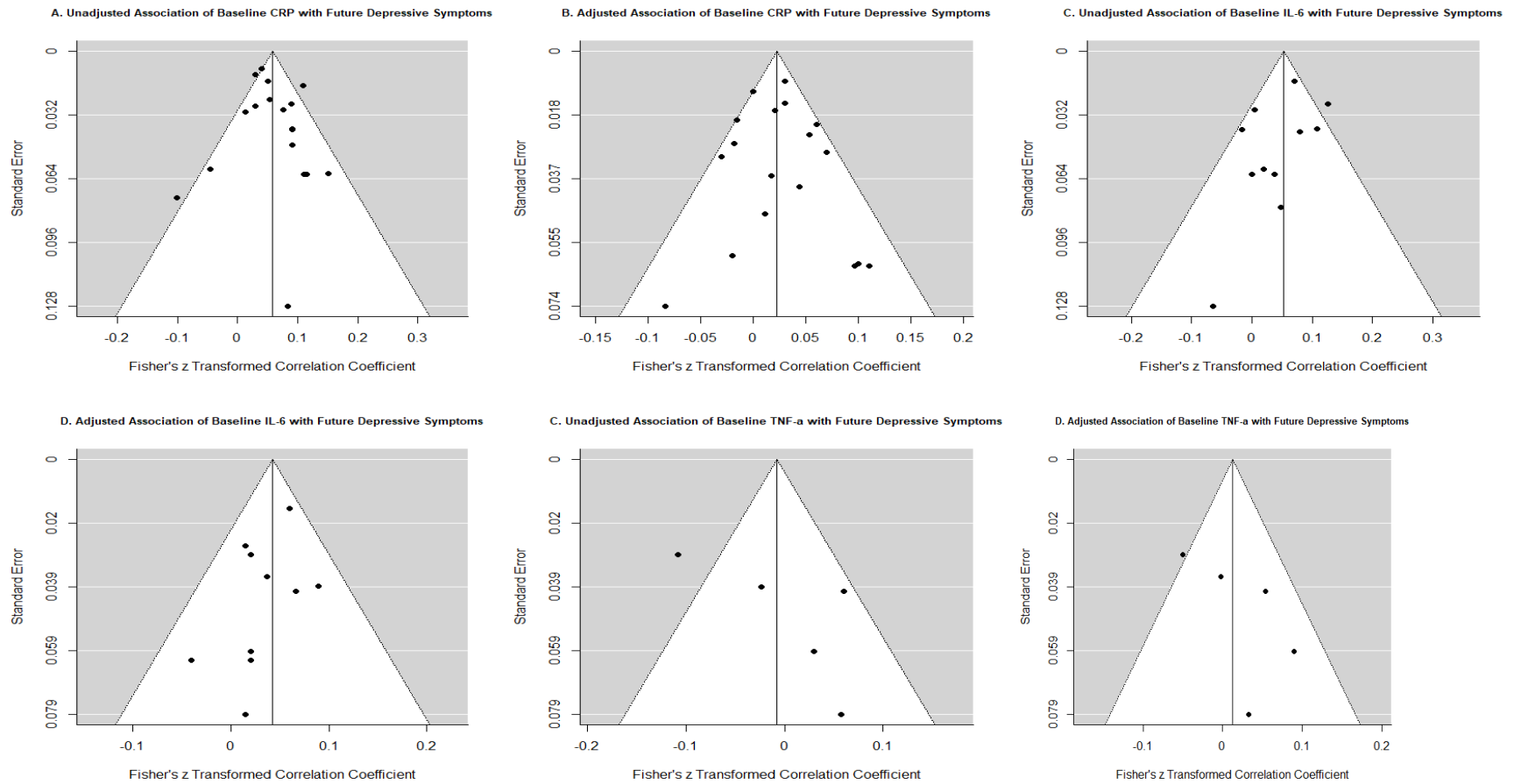
Meta-regression

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: $b=.032$, $p=.049$, $k=18$). Weaker associations for baseline CRP and future depression ($b=-.038$, $p=.007$, $k=18$), but not for IL-6 ($p=.36$), occurred when baseline inflammation was controlled. 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 Figure 5.

Figure 5. Funnel plots depicting the adjusted and unadjusted associations of inflammatory biomarkers and depressive symptoms.



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 Table 11 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

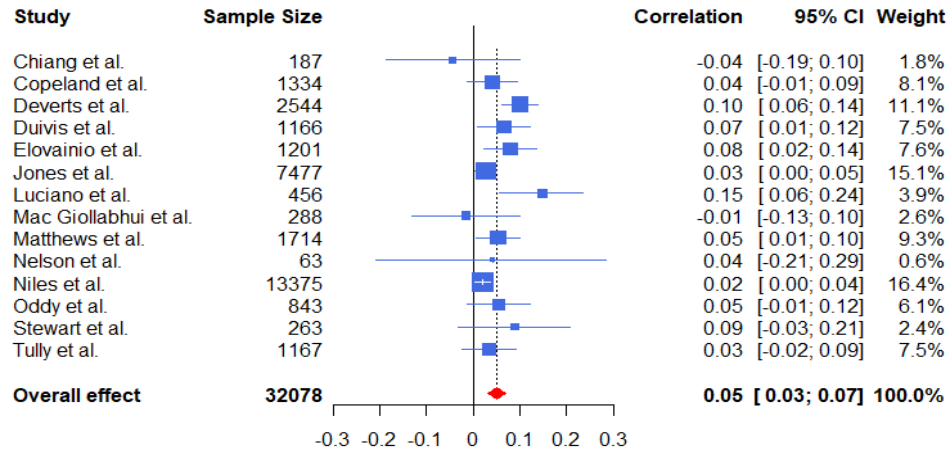
Baseline depression was associated with future CRP in unadjusted [$f(r)=.051$, $p < .0001$, $k=14$] and adjusted analyses [$f(r)=.011$, $p=.038$, $k=14$] and for IL-6 in unadjusted [$f(r)=.090$, $p < .0001$, $k=6$] and adjusted [$f(r)=.094$, $p=.016$, $k=5$] analyses – see Figure 6. Baseline depression 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.

Table 11. Results of Sensitivity Analyses for Inflammation Predicting Future Depression When (a) Community Samples Alone are Included, (b) Samples Using Data From Venous Blood Draws Are Included, (c) When Controlling for Baseline Depression, and (d) When Only High Quality Studies Are Included

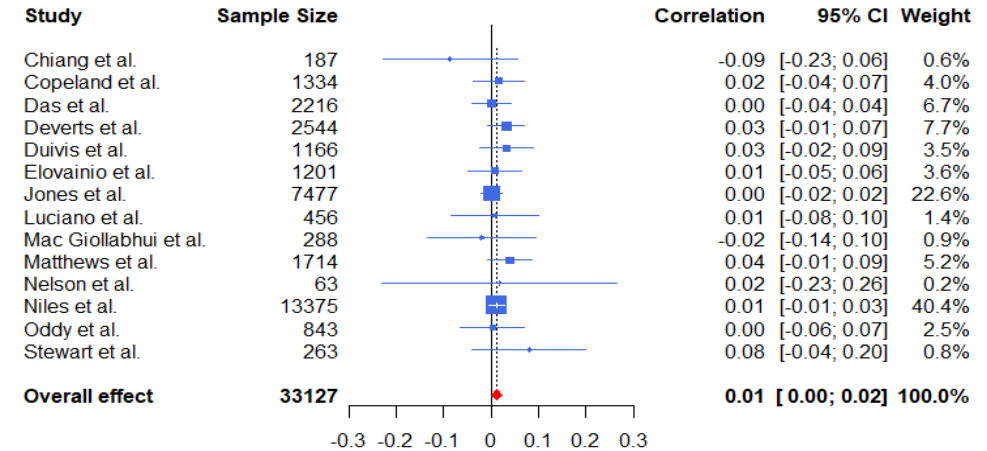
Inflammation predicting to depression				
	f(r)=	95% CI	p	k
Community Samples Only				
CRP -> Depression (LA)	.061	.041, .080	<.0001	17
CRP -> Depression (MA)	.023	.008, .038	.003	18
IL6 -> Depression (LA)	.053	.019, .087	.002	11
IL6 -> Depression (MA)	.043	.021, .064	<.0001	10
TNF- α -> Depression (LA)	-.008	-.078, .063	.828	5
TNF- α -> Depression (MA)	.013	-.040, .066	.637	5
Venous Blood Only				
CRP -> Depression (LA)	.067	.046, .088	<.0001	15
CRP -> Depression (MA)	.019	.002, .036	.031	15
IL6 -> Depression (LA)	.053	.019, .087	.002	11
IL6 -> Depression (MA)	.043	.021, .064	<.0001	10
TNF- α -> Depression (LA)	-.008	-.078, .063	.828	5
TNF- α -> Depression (MA)	.013	-.040, .066	.637	5
Controlling for Baseline Depression				
CRP -> Depression (LA)	.053	.031, .074	<.0001	13
CRP -> Depression (MA)	.019	.004, .034	.012	15
IL6 -> Depression (LA)	.080	.053, .108	<.0001	7
IL6 -> Depression (MA)	.047	.021, .073	.0004	7
TNF- α -> Depression (LA)	.052	-.009, .112	.095	3
TNF- α -> Depression (MA)	.061	.0002, .121	.049	3
In High Quality Studies				
CRP -> Depression (LA)	.058	.040, .077	<.0001	17
CRP -> Depression (MA)	.022	.001, .036	.002	19
IL6 -> Depression (LA)	.055	.019, .091	.003	9
IL6 -> Depression (MA)	.043	.021, .065	<.0001	9
TNF- α -> Depression (LA)	-.017	-.095, .061	.676	4
TNF- α -> Depression (MA)	.012	-.047, .071	.694	4
LA = Least Adjusted MA = Most Adjusted				

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

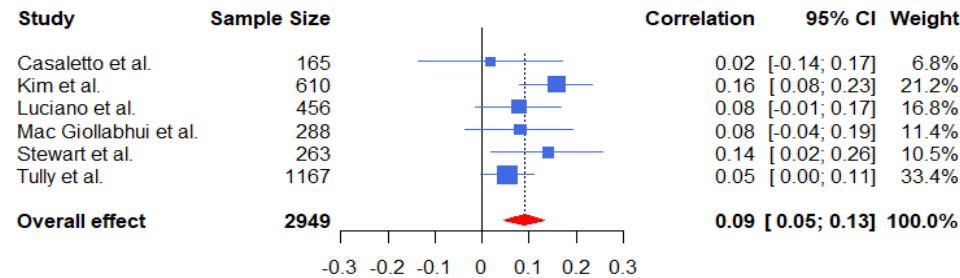
A1. Forest Plot Displaying Unadjusted Associations of Baseline Depressive Symptoms and Future CRP



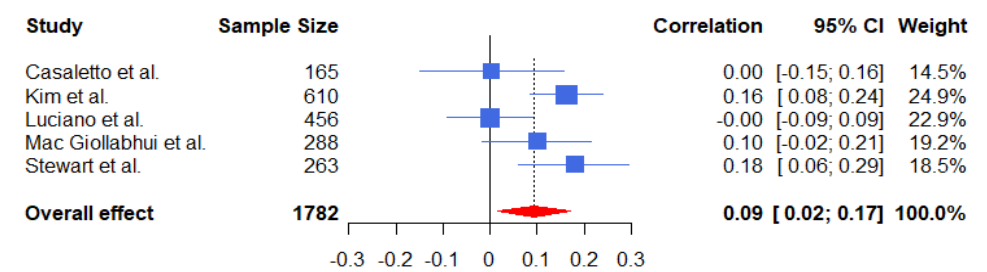
A2. Forest Plot Displaying Adjusted Associations of Baseline Depressive Symptoms and Future CRP



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



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 Figure 7.

Sensitivity analyses

Replication of analyses in community samples alone, in studies using venous blood draws, when controlling for baseline depression, 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 Table 12 for complete information.

Figure 7. Funnel Plots Depicting the Adjusted and Unadjusted Associations of Depressive Symptoms and Inflammatory Biomarkers.

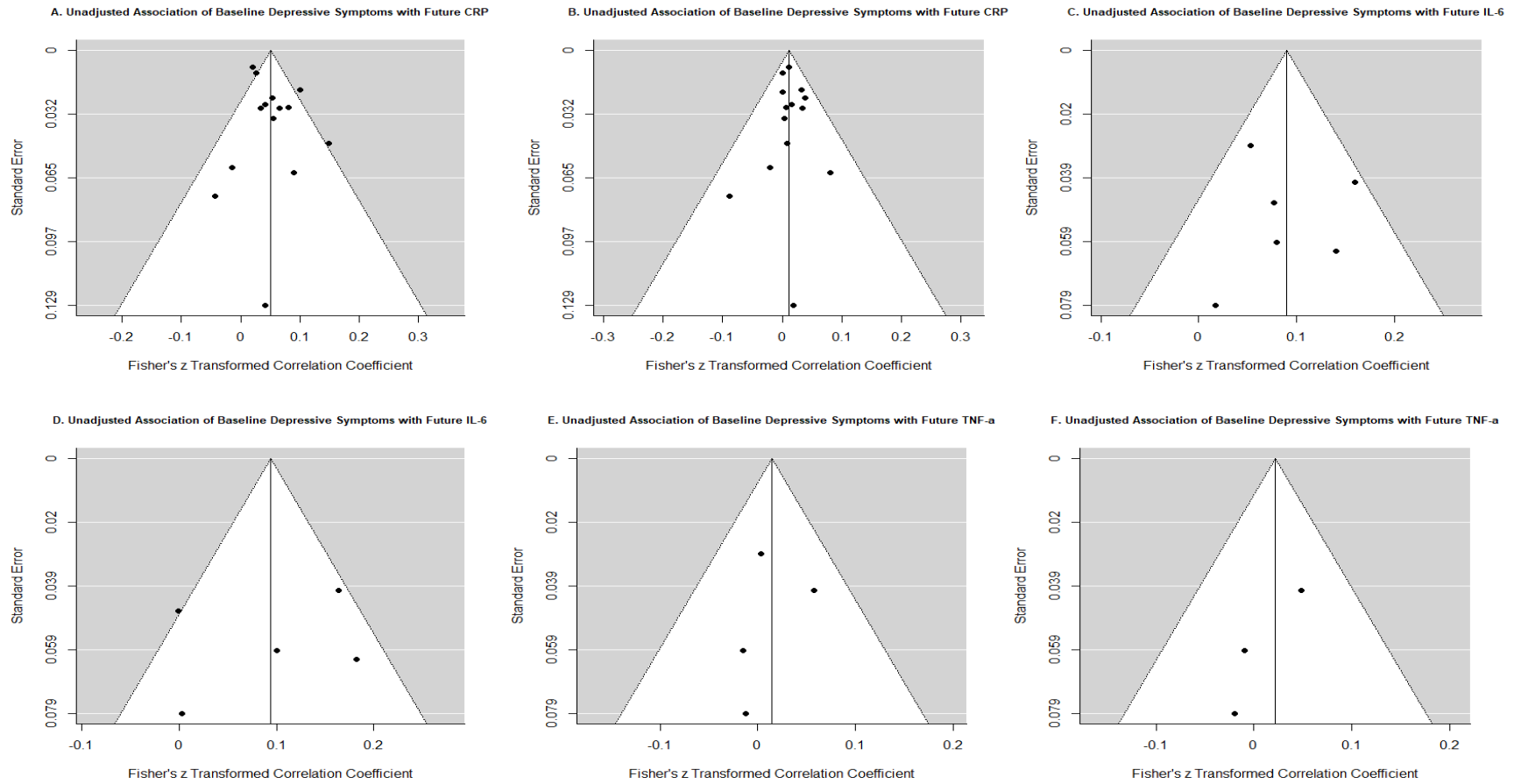


Table 12. Results Of Sensitivity Analyses For Depression Predicting Future Inflammation When (a) Community Samples Alone Are Included (b) Samples Using Data From Venous Blood Draws Are Included, (c) When Controlling For Baseline Inflammation, and (d) When Only High Quality Studies Are Included

Depression predicting to inflammation				
	f(r)=	95% CI	p	k
Community Samples Only				
Depression -> CRP (LA)	.053	.028, .077	<.0001	11
Depression -> CRP (MA)	.012	.0001, .023	.047	11
Depression -> IL6 (LA)	.090	.045, .135	<.0001	6
Depression -> IL6 (MA)	.094	.018, .171	.016	5
Depression -> TNF- α (LA)	.015	-.027, .056	.490	4
Depression -> TNF- α (MA)	.022	-.039, .082	.477	3
Venous Blood Only				
Depression -> CRP (LA)	.061	.037, .085	<.0001	10
Depression -> CRP (MA)	.015	-.002, .032	.076	9
Depression -> IL6 (LA)	.090	.045, .135	<.0001	6
Depression -> IL6 (MA)	.094	.018, .171	.016	5
Depression -> TNF- α (LA)	.015	-.027, .056	.490	4
Depression -> TNF- α (MA)	.022	-.039, .082	.477	3
Controlling for Baseline Inflammation				
Depression -> CRP (LA)	.045	.023, .067	<.0001	10
Depression -> CRP (MA)	.012	.0005, .023	.041	11
Depression -> IL6 (LA)	.119	.062, .176	<.0001	4
Depression -> IL6 (MA)	.130	.070, .191	<.0001	4
Depression -> TNF- α (LA)	.028	-.033, .088	.371	3
Depression -> TNF- α (MA)	.022	-.039, .082	.477	3
In High Quality Studies				
Depression -> CRP (LA)	.051	.030, .072	<.0001	13
Depression -> CRP (MA)	.011	.001, .022	.039	13
Depression -> IL6 (LA)	.096	.049, .144	<.0001	5
Depression -> IL6 (MA)	.109	.026, .193	.011	4
Depression -> TNF- α (LA)	.017	-.027, .060	.447	3
Depression -> TNF- α (MA)	.030	-.036, .095	.378	2

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 (Pasco et al., 2010), no association was observed in other studies (Copeland et al., 2012; Jonker et al., 2017). Similarly, inflammatory cytokines (IL-6/TNF- α) did not predict onset of future clinical depression in other studies (Glaus et al., 2018; Kern et al., 2014; Kim et al., 2018). 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 (Copeland et al., 2012). Incident depression, independent of relevant covariates, was significantly associated with increased IL-1 β , IL-6, and IL-8 levels in 732 Koreans aged 65+ assessed at two-year follow-up (Kim et al., 2018). 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 (Glaus et al., 2018). Details on kits used to measure inflammatory biomarkers provided in Table 13.

Table 13. Kits Used To Assay Inflammatory Biomarkers and Measures of Depression.		
Author	Kit	Depression Measure
Khandaker et al. 2014	Cytokines: enzyme-linked immunosorbent assay (R&D Systems) CRP: automated particle-enhanced immunoturbidimetric assay (Roche)	Clinical Interview Schedule–Revised/Mood and Feelings Questionnaire
Wim et al. 2014	Cytokines: Evidence Investigator Analyzer (IL) CRP: UniCel® DxC 800 Synchron	Geriatric Depression Scale -15
Deverts et al. 2010	CRP: BNII nephelometer	Center for Epidemiologic Studies Depression Scale
Elovainio et al. 2006	CRP: automated analyser (Olympus AU400; Olympus, USA) and a highly sensitive turbidimetric immunoassay kit ('CRP-UL' assay, Wako Chemicals, Neuss, Germany).	Beck Depression Inventory
Simanek et al. 2014	Cytokine: QuantiGlo Human IL-6 sandwich enzyme immunoassay kit (R & D Systems, USA) CRP: Ultra Wide Range Reagent Kit	Patient Health Questionnaire-9
Au et al. 2015	N Latex CRP mono Immunoassay on the Behring Nephelometer II Analyzer (Dade Behring, Milton Keynes, UK).	Center for Epidemiologic Studies Depression Scale
Copeland et al. 2012	CRP: Biotinstreptavidin based immunofluorometric system	Child and Adolescent Psychiatric Assessment
Brown et al. 2016	Cytokines: enzyme-linked immunosorbent assay kit from R&D Systems (Minneapolis, Minnesota)	Center for Epidemiologic Studies Depression Scale
Hiles et al. 2015	Cytokines: Magnetic bead/chemiluminescent immunoassay (Beckman Coulter, Fullerton, CA, USA, ref A16369) CRP: CRP Flex System on Dimension Vista System immunonephelometry (Siemens Healthcare Diagnostics, Newark, DE, USA).	Center for Epidemiologic Studies Depression Scale
Milaneschi et al. 2008	Serum levels of IL-6, soluble IL-6 receptor (sIL-6r) (80 kDa), IL-1 , IL-1 receptor antagonist (IL-1ra), tumor necrosis factor (TNF) - (kits from BIOSOURCE International, Camarillo, California), and IL-18 (kits from Quantikine HS, R&D Systems, Minneapolis, Minnesota) were measured by enzyme linked immuno-absorbent assays (ELISAs). Serum CRP (high-sensitivity) was measured in duplicate with an ELISA and colorimetric competitive immunoassay.	Center for Epidemiologic Studies Depression Scale

<i>Table 13. (continued)</i>		
de Mello Franco et al. 2017	CRP: immunonephelometry (Dade-Behring).	Beck Depression Inventory
Das et al. 2017	Not reported.	Center for Epidemiologic Studies Depression Scale
Stewart et al. 2009	Cytokines: Ultra-sensitive enzyme-linked immunosorbent assay kits (R&D Systems); CRP: BNII nephelometer utilizing a particle-enhanced immunonephelometric assay (Dade Behring, Deerfield, IL).	Beck Depression Inventory-II
Kern et al. 2014	Cytokines: Human Pro-inflammatory II 4-Plex Assay Ultra-Sensitive Kit (Meso Scale Discovery, Gaithersburg, MD, USA).	Montgomery-Åsberg Depression Rating Scale/Clinical Interview
Zalli et al. 2015	Cytokines: Quantitative enzyme-linked immunosorbent assay with a test kit from R&D systems (Minneapolis, MN). CRP: Nephelometric method (BN 100, Dade Behring, Marburg, Germany).	Center for Epidemiologic Studies Depression Scale
Simanek et al. 2018	Cytokines: Quantiglo Chemiluminescent Immunoassay, QTA00B and Q6000B (R&D Systems, Minneapolis, MN). CRP: Ultra Wide Range Reagent Kit latex-enhanced immunoassay (Equal Diagnostics, Exton, PA).	Center for Epidemiologic Studies Depression Scale
Matthews et al. 2010	CRP: Ultrasensitive rate immunonephelometry method (Dade-Behring, Marburg, Germany).	Center for Epidemiologic Studies Depression Scale
Baune et al. 2012	Cytokines: Cytometric bead array (CBA, BD Biosciences, San Diego, USA). CRP: turbidimetric method based on Near Infrared Particle Immunoassay rate methodology using the Beckman Coulter Synchron LXi analyser (Beckman Coulter, USA).	Geriatric Depression Scale - 15
Duivis et al. 2015	CRP: Immunonephelometric method of the Siemens BN2 Prospec system with a CardioPhase hsCRP assay.	Youth Self- Report
Jonker et al. 2017	CRP: Immunonephelometric method, BN2 of Siemens Medical Solutions USA (Malvern, PA, USA)	Adult Self-Report Questionnaire (ASR)/Composite International Diagnostic Interview (CIDI) Version 3.0

Casaletto et al. 2018	Cytokines: Human proinflammatory panel 1 V-PLEX kits provided by Meso Scale Diagnostics, LLC (Rockville, MD) and each multiplex array was scanned using the MESOQuickPlex SQ 120.	Geriatric Depression Scale
Kim et al. 2018	Cytokines: Solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) kit (Invitrogen, Camarillo, CA, USA)	Geriatric Mental State Schedule
Luciano et al. 2012	Cytokines: Automated Clauss assay (TOPS coagulometer, Instrumentation Laboratory, Warrington, UK) and high-sensitivity ELISA kits (R&D Systems, Oxon, UK). CRP: Dry-slide immuno-rate method on the OrthoFusion 5.1 F.S analyzers	Hospital Anxiety and Depression Scale
Luukinen et al. 2010	CRP: Innotracc Aio! analyzer (Innotracc Diagnostics Oy, Turku, Finland)	Short Zung Self-Rating Depression Scale
Matsushima et al. 2015	Cytokines: Sandwich enzyme-linked immunosorbent assay (ELISA) kits.	Beck Depression Inventory-II
Nelson et al. 2018	CRP: Bio-Plex multiplex bead array immunoassay system of human cytokine panel (Bio-Plex 200 System, Bio-Rad Laboratories, Inc., New South Wales, Australia).	Center for Epidemiologic Studies Depression Scale
Niles et al. 2018	CRP: Standard enzyme-linked immunosorbent assay (ELISA).	Center for Epidemiologic Studies Depression Scale
Pasco et al. 2010	CRP: Roche immunoturbidimetric .	Structured Clinical Interview for DSM-IV-TR Research Version
Tully et al. 2015	Cytokines: enzyme linked immunosorbent assay (ELISA) (Roche Diagnostics, Florham Park, New Jersey, US). CRP: Cobas autoanalyzer (Roche Diagnostics, Florham Park, New Jersey, US).	Center for Epidemiologic Studies Depression Scale/Beck Depression Inventory
Walss-Bass et al. 2018	Cytokines: Millipore bead-based flow immunoassays (Billerica, MA) in the Luminex FlexMap 3D system (Austin, TX),	Mood-Feelings Questionnaire-Child (MFQC)/ Schedule for Affective Disorders and Schizophrenia for School Aged Children - Present and Lifetime Version (K-SADS -PL)

<i>Table 13. (continued)</i>		
Oddy et al. 2018	CRP: Immunoturbidimetric method on the Architect c16000.	Beck Depression Inventory for Youth
Jones et al. 2017	Not reported.	Center for Epidemiological Studies Depression scale–short form
Chiang et al. 2019	CRP: High-sensitivity enzyme-linked immunosorbent assay.	Center for Epidemiological Studies Depression scale
van den Biggelaar et al. 2007	CRP: Fully automated Hitachi 747	Geriatric Depression Scale
Glaus et al. 2018	Cytokines: Multiplexed particle-based flow cytometric cytokine assay CRP: immunoassay and latex HS (IMMULITE 1000-High, Diagnostic Products Corporation, LA, CA, USA)	Diagnostic Interview for Genetic Studies (DIGS)
Caserta et al. 2011	Cytokines: Quantikine High Sensitivity ELISA kit for human interleukin 6 (IL-6) concentrations (R and D Systems, Minneapolis, MN).	Children’s Depression Inventory—Short Form
Mac Giollabhui et al. 2019	Cytokines were quantified by multi-cytokine array. CRP: Singleplex assay using an electrochemiluminescence platform and a QuickPlex SQ 120 imager for analyte detection (Meso Scale Discovery, Gaithersburg, MD, USA).	Children’s Depression Inventory
Forti et al. 2010	Cytokines: high-sensitivity ELISA kits (R&D Systems Inc., Minneapolis, Minn., USA). CRP: Latex-enhanced immunonephelometric assay on a BN II analyzer (Dade Behring, Milan, Italy).	Geriatric Depression Scale

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 study 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 CRP and future depressive symptoms 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 (Smith et al., 2018; Valkanova et al., 2013). This result is unsurprising because IL-6 is arguably the inflammatory biomarker most consistently associated with depression in humans (Baumeister et al., 2014) 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 (Khandaker et al., 2019).

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) (Berk et al., 2013). However, although statistically significant, depression was not substantially associated with future CRP ($r = .01$) once relevant covariates were included, a finding observed previously (Smith et al., 2018). 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 (Bonnie Au et al., 2015; Copeland et al., 2012; Elovainio et al., 2006) or mediating (Hiles et al., 2015; Mac Giollabhui, Swistun, et al., 2020) 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 (Mac Giollabhui, Swistun, et al., 2020). 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 (Dowlati et al., 2010), it is unclear 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 (Hiles et al., 2012; Strawbridge et al., 2015). 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 (Dantzer et al., 2008). Second, elevated inflammatory biomarkers typically are observed in a subset (25-30%) of depressed individuals, reducing the ability to detect mean level associations (Osimo et al., 2019; Raison & Miller, 2011). 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 (Alexopoulos & Morimoto, 2011). Finally, there is growing appreciation that elevated levels of IL-6 may not necessarily reflect a state of chronic, low-grade inflammation (Del Giudice & Gangestad, 2018), 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 Table 13)/exercise/substance-use/medication-use/medical status] (O'Connor et al., 2009). 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 (Leng et al., 2008), 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 (Mac Giollabhui, Ellman, et al., 2020)] and implementation of standardized approaches to assess acute illness is needed in addition to greater efforts to follow existing guidelines when controlling for covariates (O'Connor et al., 2009). 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.

REFERENCES CITED

Adriaensen, W., Matheï, C., Vaes, B., Van Pottelbergh, G., Wallemacq, P., & Degryse, J.-M. (2014). Interleukin-6 predicts short-term global functional decline in the oldest old: results from the BELFRAIL study. *Age*, *36*(6), 9723.

Alexopoulos, G. S., & Morimoto, S. S. (2011). The inflammation hypothesis in geriatric depression. *International Journal of Geriatric Psychiatry*, *26*(11), 1109-1118.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.).

Au, B., Smith, K. J., Gariépy, G., & Schmitz, N. (2015). The longitudinal associations between C-reactive protein and depressive symptoms: evidence from the English Longitudinal Study of Ageing (ELSA). *International Journal of Geriatric Psychiatry*, *30*(9), 976-984. <https://doi.org/10.1002/gps.4250>

Au, B., Smith, K. J., Gariépy, G., & Schmitz, N. (2015). The longitudinal associations between C-reactive protein and depressive symptoms: evidence from the English Longitudinal Study of Ageing (ELSA). *International Journal of Geriatric Psychiatry*, *30*(9), 976-984.

Baumeister, D., Russell, A., Pianta, C. M., & Mondelli, V. (2014). Inflammatory biomarker profiles of mental disorders and their relation to clinical, social and lifestyle factors [journal article]. *Social Psychiatry and Psychiatric Epidemiology*, *49*(6), 841-849. <https://doi.org/10.1007/s00127-014-0887-z>

Baune, B. T., Smith, E., Reppermund, S., Air, T., Samaras, K., Lux, O., Brodaty, H., Sachdev, P., & Trollor, J. N. (2012). Inflammatory biomarkers predict depressive, but not anxiety symptoms during aging: the prospective Sydney Memory and Aging Study. *Psychoneuroendocrinology*, *37*(9), 1521-1530.

Berk, M., Williams, L. J., Jacka, F. N., O'Neil, A., Pasco, J. a., Moylan, S., Allen, N. B., Stuart, A. L., Hayley, A. C., Byrne, M. L., & Maes, M. (2013). So depression is an inflammatory disease, but where does the inflammation come from? *BMC Medicine*, *11*, 200. <https://doi.org/10.1186/1741-7015-11-200>

Brown, P. J., Roose, S. P., Zhang, J., Wall, M., Rutherford, B. R., Ayonayon, H. N., Butters, M. A., Harris, T., Newman, A. B., & Satterfield, S. (2016). Inflammation, depression, and slow gait: a high mortality phenotype in later life. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, *71*(2), 221-227.

Burcusa, S. L., & Iacono, W. G. (2007). Risk for recurrence in depression. *Clinical Psychology Review*, 27, 959-985. <https://doi.org/https://doi.org/10.1016/j.cpr.2007.02.005>

Casaletto, K. B., Staffaroni, A. M., Elahi, F., Fox, E., Crittenden, P. A., You, M., Neuhaus, J., Glymour, M., Bettcher, B. M., & Yaffe, K. (2018). Perceived stress is associated with accelerated monocyte/macrophage aging trajectories in clinically normal adults. *The American Journal of Geriatric Psychiatry*, 26(9), 952-963.

Caserta, M. T., Wyman, P. A., Wang, H., Moynihan, J., & O'Connor, T. G. (2011). Associations among depression, perceived self-efficacy, and immune function and health in preadolescent children. *Development and Psychopathology*, 23(4), 1139-1147.

Chiang, J. J., Park, H., Almeida, D. M., Bower, J. E., Cole, S. W., Irwin, M. R., McCreath, H., Seeman, T. E., & Fuligni, A. J. (2019). Psychosocial stress and C-reactive protein from mid-adolescence to young adulthood. *Health Psychology*, 38(3), 259.

Chiu, W., Su, Y., Su, K., & Chen, P. (2017). Recurrence of depressive disorders after interferon-induced depression. *Translational Psychiatry*, 7(2), e1026.

Copeland, W. E., Shanahan, L., Worthman, C., Angold, A., & Costello, E. J. (2012). Cumulative depression episodes predict later C-reactive protein levels: a prospective analysis. *Biological Psychiatry*, 71(1), 15-21.

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Reviews Neuroscience*, 9(1), 46. <https://doi.org/https://doi.org/10.1038/nrn2297>

Del Giudice, M., & Gangestad, S. W. (2018). Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. *Brain, Behavior, and Immunity*, 70, 61-75.

Deverts, D. J., Cohen, S., DiLillo, V. G., Lewis, C. E., Kiefe, C., Whooley, M., & Matthews, K. A. (2010). Depressive symptoms, race, and circulating C-reactive protein: The Coronary Artery Risk Development in Young Adults (CARDIA) study. *Psychosomatic Medicine*, 72(8), 734-741. <https://doi.org/10.1097/PSY.0b013e3181ec4b98>

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctot, K. L. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry*, 67(5), 446-457.
<https://doi.org/https://doi.org/10.1016/j.biopsych.2009.09.033>

Duivis, H. E., Kupper, N., Vermunt, J. K., Penninx, B. W., Bosch, N. M., Riese, H., Oldehinkel, A. J., & de Jonge, P. (2015). Depression trajectories, inflammation, and lifestyle factors in adolescence: The TRacking Adolescents' Individual Lives Survey. *Health Psychology*, 34(11), 1047.

Elovainio, M., Keltikangas-Järvinen, L., Pulkki-Råback, L., Kivimäki, M., Puttonen, S., Viikari, L., Räsänen, L., Mansikkaniemi, K., Viikari, J., & TRAITAKARI, O. (2006). Depressive symptoms and C-reactive protein: the Cardiovascular Risk in Young Finns Study. *Psychological Medicine*, 36(6), 797-805.

Erskine, H. E., Moffitt, T. E., Copeland, W. E., Costello, E. J., Ferrari, A. J., Patton, G., Degenhardt, L., Vos, T., Whiteford, H. A., & Scott, J. G. (2015). A heavy burden on young minds: the global burden of mental and substance use disorders in children and youth. *Psychological Medicine*, 45(07), 1551-1563.
<https://doi.org/https://doi.org/doi:10.1017/S0033291714002888>

Forti, P., Rietti, E., Pisacane, N., Olivelli, V., Mariani, E., Chiappelli, M., Licastro, F., & Ravaglia, G. (2010). Blood inflammatory proteins and risk of incident depression in the elderly. *Dementia and Geriatric Cognitive Disorders*, 29(1), 11-20.

Glaus, J., von Känel, R., Lasserre, A., Strippoli, M.-P., Vandeleur, C., Castela, E., Gholam-Rezaee, M., Marangoni, C., Wagner, E.-Y., & Marques-Vidal, P. (2018). Mood disorders and circulating levels of inflammatory markers in a longitudinal population-based study. *Psychological Medicine*, 48(6), 961-973.

Haroon, E., Raison, C. L., & Miller, A. H. (2012). Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology*, 37(1), 137.

Hiles, S., Baker, A., De Malmanche, T., & Attia, J. (2012). Interleukin-6, C-reactive protein and interleukin-10 after antidepressant treatment in people with depression: a meta-analysis. *Psychological Medicine*, 42(10), 2015-2026.

Hiles, S. A., Baker, A. L., de Malmanche, T., McEvoy, M., Boyle, M., & Attia, J. (2015). Unhealthy lifestyle may increase later depression via inflammation in older women but not men. *Journal of Psychiatric Research*, 63, 65-74.

Howren, M. B., Lamkin, D. M., & Suls, J. (2009). Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosomatic Medicine*, *71*(2), 171-186. <https://doi.org/10.1097/PSY.0b013e3181907c1b>

Irwin, M. R., & Miller, A. H. (2007). Depressive disorders and immunity: 20 years of progress and discovery. *Brain, Behavior, and Immunity*, *21*(4), 374-383. <https://doi.org/https://doi.org/10.1016/j.bbi.2007.01.010>

Jones, S. M., Weitlauf, J., Danhauer, S. C., Qi, L., Zaslavsky, O., Wassertheil-Smoller, S., Brenes, G. A., & LaCroix, A. Z. (2017). Prospective data from the Women's Health Initiative on depressive symptoms, stress, and inflammation. *Journal of Health Psychology*, *22*(4), 457-464.

Jonker, I., Rosmalen, J., & Schoevers, R. (2017). Childhood life events, immune activation and the development of mood and anxiety disorders: the TRAILS study. *Translational Psychiatry*, *7*(5), e1112.

Kern, S., Skoog, I., Börjesson-Hanson, A., Blennow, K., Zetterberg, H., Östling, S., Kern, J., Gudmundsson, P., Marlow, T., & Rosengren, L. (2014). Higher CSF interleukin-6 and CSF interleukin-8 in current depression in older women. Results from a population-based sample. *Brain, Behavior, and Immunity*, *41*, 55-58.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., Rush, A. J., Walters, E. E., & Wang, P. S. (2003). The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*, *289*, 3095-3105. <https://doi.org/10.1001/jama.289.23.3095>

Khandaker, G. M., Pearson, R. M., Zammit, S., Lewis, G., & Jones, P. B. (2014). Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. *JAMA psychiatry*, *71*(10), 1121-1128.

Khandaker, G. M., Zuber, V., Rees, J. M., Carvalho, L., Mason, A. M., Foley, C. N., Gkatzionis, A., Jones, P. B., & Burgess, S. (2019). Shared mechanisms between coronary heart disease and depression: findings from a large UK general population-based cohort. *Molecular Psychiatry*, 1-10.

Kim, J.-M., Stewart, R., Kim, J.-W., Kang, H.-J., Bae, K.-Y., Kim, S.-W., Shin, I.-S., & Yoon, J.-S. (2018). Changes in pro-inflammatory cytokine levels and late-life depression: a two year population based longitudinal study. *Psychoneuroendocrinology*, *90*, 85-91.

Kunugi, H., Hori, H., & Ogawa, S. (2015). Biochemical markers subtyping major depressive disorder. *Psychiatry and Clinical Neurosciences*, 69(10), 597-608. <https://doi.org/https://doi.org/10.1111/pcn.12299>

Leng, S. X., McElhaney, J. E., Walston, J. D., Xie, D., Fedarko, N. S., & Kuchel, G. A. (2008). ELISA and multiplex technologies for cytokine measurement in inflammation and aging research. *The journals of gerontology. Series A, Biological sciences and medical sciences*, 63(8), 879-884. <https://doi.org/10.1093/gerona/63.8.879>

Luciano, M., Möttus, R., Starr, J. M., McNeill, G., Jia, X., Craig, L. C., & Deary, I. J. (2012). Depressive symptoms and diet: their effects on prospective inflammation levels in the elderly. *Brain, Behavior, and Immunity*, 26(5), 717-720.

Luukinen, H., Jokelainen, J., & Hedberg, P. (2010). The relationships between high-sensitivity C-reactive protein and incident depressed mood among older adults. *Scandinavian Journal of Clinical and Laboratory Investigation*, 70(2), 75-79.

Mac Giollabhui, N., Ellman, L. M., Coe, C. L., Byrne, M. L., Abramson, L. Y., & Alloy, L. B. (2020). To exclude or not to exclude: Considerations and recommendations for C-reactive protein values higher than 10 mg/L. *Brain, Behavior, and Immunity*, 87, 898-900. <https://doi.org/https://doi.org/10.1016/j.bbi.2020.01.023>

Mac Giollabhui, N., Swistun, D., Murray, S., Moriarity, D. P., Kautz, M. M., Ellman, L. M., Olino, T. M., Coe, C. L., Abramson, L. Y., & Alloy, L. B. (2020). Executive dysfunction in depression in adolescence: the role of inflammation and higher body mass. *Psychological Medicine*, 50(4), 683-691. <https://doi.org/https://doi.org/10.1017/S0033291719000564>

Matsushima, J., Kawashima, T., Nabeta, H., Imamura, Y., Watanabe, I., Mizoguchi, Y., Kojima, N., Yamada, S., & Monji, A. (2015). Association of inflammatory biomarkers with depressive symptoms and cognitive decline in a community-dwelling healthy older sample: a 3-year follow-up study. *Journal of Affective Disorders*, 173, 9-14.

Matthews, K. A., Schott, L. L., Bromberger, J. T., Cyranowski, J. M., Everson-Rose, S. A., & Sowers, M. (2010). Are there bi-directional associations between depressive symptoms and C-reactive protein in mid-life women? *Brain, Behavior, and Immunity*, 24(1), 96-101.

Milaneschi, Y., Corsi, A. M., Penninx, B. W., Bandinelli, S., Guralnik, J. M., & Ferrucci, L. (2009). Interleukin-1 receptor antagonist and incident depressive symptoms over 6 years in older persons: the InCHIANTI study. *Biological Psychiatry*, 65(11), 973-978.

Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biological Psychiatry*, *65*, 732-741. <https://doi.org/10.1016/j.biopsych.2008.11.029>

Musselman, D. L., Lawson, D. H., Gumnick, J. F., Manatunga, A. K., Penna, S., Goodkin, R. S., Greiner, K., Nemeroff, C. B., & Miller, A. H. (2001). Paroxetine for the Prevention of Depression Induced by High-Dose Interferon Alfa. *New England Journal of Medicine*, *344*(13), 961-966. <https://doi.org/10.1056/nejm200103293441303>

Nelson, B. W., Byrne, M. L., Simmons, J. G., Whittle, S., Schwartz, O. S., O'Brien-Simpson, N. M., Walsh, K. A., Reynolds, E. C., & Allen, N. B. (2018). Adolescent temperament dimensions as stable prospective risk and protective factors for salivary C-reactive protein. *British Journal of Health Psychology*, *23*(1), 186-207.

Niles, A. N., Smirnova, M., Lin, J., & O'Donovan, A. (2018). Gender differences in longitudinal relationships between depression and anxiety symptoms and inflammation in the health and retirement study. *Psychoneuroendocrinology*, *95*, 149-157.

O'Connor, M. F., Bower, J. E., Cho, H. J., Creswell, J. D., Dimitrov, S., Hamby, M. E., Hoyt, M. A., Martin, J. L., Robles, T. F., Sloan, E. K., Thomas, K. S., & Irwin, M. R. (2009). To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. *Brain, Behavior, and Immunity*, *23*(7), 887-897. <https://doi.org/10.1016/j.bbi.2009.04.005>

Oddy, W. H., Allen, K. L., Trapp, G. S., Ambrosini, G. L., Black, L. J., Huang, R.-C., Rzehak, P., Runions, K. C., Pan, F., & Beilin, L. J. (2018). Dietary patterns, body mass index and inflammation: pathways to depression and mental health problems in adolescents. *Brain, Behavior, and Immunity*, *69*, 428-439.

Olbert, C. M., Gala, G. J., & Tupler, L. A. (2014). Quantifying heterogeneity attributable to polythetic diagnostic criteria: theoretical framework and empirical application. *Journal of Abnormal Psychology*, *123*(2), 452.

Osimo, E. F., Baxter, L. J., Lewis, G., Jones, P. B., & Khandaker, G. M. (2019). Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels. *Psychological Medicine*, *49*(12), 1958-1970. <https://doi.org/https://doi.org/10.1017/S0033291719001454>

Pasco, J. A., Nicholson, G. C., Williams, L. J., Jacka, F. N., Henry, M. J., Kotowicz, M. A., Schneider, H. G., Leonard, B. E., & Berk, M. (2010). Association of high-sensitivity C-reactive protein with de novo major depression. *The British Journal of Psychiatry*, *197*(5), 372-377.

Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2011). The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *Ottawa: Ottawa Hospital Research Institute.*

R Core Team. (2019). *R: A language and environment for statistical computing.* In R Foundation for Statistical Computing.

Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in Immunology*, *27*, 24-31. <https://doi.org/10.1016/j.it.2005.11.006>

Raison, C. L., & Miller, A. H. (2011). Is depression an inflammatory disorder? *Current Psychiatry Reports*, *13*(6), 467-475. <https://doi.org/https://doi.org/10.1007/s11920-011-0232-0>

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Niederehe, G., Thase, M. E., Lavori, P. W., & Lebowitz, B. D. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. *American Journal of Psychiatry*, *163*(11), 1905-1917.

Schedlowski, M., Engler, H., & Grigoleit, J.-S. (2014). Endotoxin-induced experimental systemic inflammation in humans: A model to disentangle immune-to-brain communication. *Brain, Behavior, and Immunity*, *35*, 1-8. <https://doi.org/https://doi.org/10.1016/j.bbi.2013.09.015>

Simanek, A. M., Cheng, C., Yolken, R., Uddin, M., Galea, S., & Aiello, A. E. (2014). Herpesviruses, inflammatory markers and incident depression in a longitudinal study of Detroit residents. *Psychoneuroendocrinology*, *50*, 139-148.

Simanek, A. M., Zheng, C., Yolken, R., Haan, M., & Aiello, A. E. (2018). A Longitudinal Study of the Association Between Persistent Pathogens and Incident Depression Among Older US Latinos. *The Journals of Gerontology: Series A*, *74*(5), 634-641.

Smith, K. J., Au, B., Ollis, L., & Schmitz, N. (2018). The association between C-reactive protein, Interleukin-6 and depression among older adults in the community: a systematic review and meta-analysis. *Experimental Gerontology*, *102*, 109-132.

Smith, R. S. (1991). The macrophage theory of depression. *Medical Hypotheses*, *35*(4), 298-306. [https://doi.org/https://doi.org/10.1016/0306-9877\(91\)90272-Z](https://doi.org/https://doi.org/10.1016/0306-9877(91)90272-Z)

Stewart, J. C., Rand, K. L., Muldoon, M. F., & Kamarck, T. W. (2009). A prospective evaluation of the directionality of the depression–inflammation relationship. *Brain, Behavior, and Immunity*, *23*(7), 936-944.

Strawbridge, R., Arnone, D., Danese, A., Papadopoulos, A., Vives, A. H., & Cleare, A. (2015). Inflammation and clinical response to treatment in depression: a meta-analysis. *European Neuropsychopharmacology*, *25*(10), 1532-1543.

Su, S., Miller, A. H., Snieder, H., Bremner, J. D., Ritchie, J., Maisano, C., Jones, L., Murrah, N. V., Goldberg, J., & Vaccarino, V. (2009). Common genetic contributions to depressive symptoms and inflammatory markers in middle-aged men: the Twins Heart Study. *Psychosomatic Medicine*, *71*(2), 152-158. <https://doi.org/10.1097/PSY.0b013e31819082ef>

Tully, P. J., Baumeister, H., Bengel, J., Jenkins, A., Januszewski, A., Martin, S., & Wittert, G. A. (2015). The longitudinal association between inflammation and incident depressive symptoms in men: the effects of hs-CRP are independent of abdominal obesity and metabolic disturbances. *Physiology and Behavior*, *139*, 328-335.

Udina, M., Castellvi, P., Moreno-Espana, J., Navines, R., Valdes, M., Forns, X., Langohr, K., Sola, R., Vieta, E., & Martin-Santos, R. (2012). Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. *Journal of Clinical Psychiatry*, *73*(8), 1128-1138. <https://doi.org/10.4088/JCP.12r07694>

Valkanova, V., Ebmeier, K. P., & Allan, C. L. (2013). CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. *Journal of Affective Disorders*, *150*(3), 736-744.

van den Biggelaar, A. H., Gussekloo, J., de Craen, A. J., Frölich, M., Stek, M. L., van der Mast, R. C., & Westendorp, R. G. (2007). Inflammation and interleukin-1 signaling network contribute to depressive symptoms but not cognitive decline in old age. *Experimental Gerontology*, *42*(7), 693-701.

Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. *J Stat Softw*, *36*(3), 1-48.

Walss-Bass, C., Suchting, R., Olvera, R. L., & Williamson, D. E. (2018). Inflammatory markers as predictors of depression and anxiety in adolescents: statistical model building with component-wise gradient boosting. *Journal of Affective Disorders*, *234*, 276-281.

Zalli, A., Jovanova, O., Hoogendijk, W. J., Tiemeier, H., & Carvalho, L. A. (2016). Low-grade inflammation predicts persistence of depressive symptoms. *Psychopharmacology*, *233*(9), 1669-1678. <https://doi.org/10.1007/s00213-015-3919-9>

Zimmerman, M., Ellison, W., Young, D., Chelminski, I., & Dalrymple, K. (2015). How many different ways do patients meet the diagnostic criteria for major depressive

disorder? *Comprehensive Psychiatry*, 56, 29-34.
<https://doi.org/https://doi.org/10.1016/j.comppsy.2014.09.007>

CHAPTER 4

SUPPLEMENTARY MATERIAL

Supplementary material presented here as referenced in Chapter 3.

Results

Systematic Review: Study Characteristics

Characteristics of studies included in the systematic review are summarized in Table 10 (details on kit used to measure inflammatory biomarkers and depression measures provided in Table 13). These 38 studies represent 58,256 participants drawn from 13 countries between 2006 and 2019 who were assessed, on average, 4.19 years ($SD=3.80$) after baseline. Approximately 25% of studies involved children, 25% adults, and 50% elderly samples. Samples were, on average, 57.26% female (range: 0 – 100%). There was less variability in the racial/ethnic composition of samples, although a significant number of studies did not report race (47%), particularly studies conducted outside of the United States. The mean percentage of Caucasians in studies where race was reported ($k=20$) was 58.92% (range: 0 – 100%); this mean value was affected by three studies that did not include Caucasian participants (1-3) and 69.31% of the remaining 56,811 participants enrolled in studies reporting race were Caucasian. Across studies, participants were excluded based on: chronic medical conditions (e.g., autoimmune diseases) (33.33%), medication use (e.g., corticosteroids) (23.1%), a psychiatric or neurological disorder (38.46%), and evidence of possible acute infection (43.59%). Inflammatory biomarkers typically were assessed via venipuncture (84.21%). In 34 (of 38) studies reporting on CRP, 13 (44.12%) did not remove participants with CRP values greater than 10 mg/L, 15 removed participants with CRP values greater than 10 mg/L (38.23%), and 6 (17.64%) used an idiosyncratic approach to handle outliers (e.g., removed CRP values greater than 8.6 mg/L). There also was substantial

variability in time of day/fasting status of inflammation assessment, in measurement of depression (dichotomous/continuous; self-report/interview) and covariates included in analyses.

Heterogeneity and publication bias

Prospective Associations of Inflammatory Biomarkers and Subsequent Depression

Quantitative analysis of heterogeneity indicated high levels of heterogeneity for the unadjusted association of baseline CRP and future depressive symptoms ($I^2=52.87\%$; $Q(17)=36.31$, $p=.004$) and moderate levels for the adjusted association ($I^2=36.50\%$; $Q(18)=29.21$, $p=.046$). High levels of heterogeneity were observed for the unadjusted association of baseline IL-6 and future depressive symptoms ($I^2=51.28\%$; $Q(10)=18.07$, $p=.054$), but low levels were observed for the adjusted association ($I^2=5.89\%$; $Q(9)=6.97$, $p=.64$). High levels of heterogeneity were observed for the unadjusted association of baseline TNF- α and future depressive symptoms ($I^2=68.39\%$; $Q(4)=14.36$, $p=.006$) and moderate levels for the adjusted association ($I^2=46.76\%$; $Q(4)=7.18$, $p=.127$). Egger's regression intercept test did not indicate publication bias for the unadjusted ($p=.634$) or adjusted ($p=.575$) association of baseline CRP with future depressive symptoms nor for the unadjusted ($p=.200$) or adjusted ($p=.219$) association of baseline IL-6 with future depressive symptoms. There was no evidence of publication bias for the unadjusted ($p=.126$) or adjusted ($p=.071$) associations of baseline TNF- α with future depressive symptoms.

Prospective Associations of Depression and Subsequent Inflammatory Biomarkers

Quantitative analysis of heterogeneity indicated high levels of heterogeneity for the unadjusted association of baseline depressive symptoms and future CRP ($I^2=52.58\%$; $Q(13)=27.17$, $p=.012$) and low levels for the adjusted association ($I^2=0.00\%$; $Q(13)=7.50$, $p=.875$). Moderate levels of heterogeneity were observed for the unadjusted association of baseline depressive symptoms and future IL-6 ($I^2=26.51\%$; $Q(5)=6.12$, $p=.295$) and high levels were observed for the adjusted association ($I^2=59.78\%$; $Q(4)=10.28$, $p=.036$). Low levels of heterogeneity were observed both for the unadjusted association of baseline depressive symptoms and future TNF- α ($I^2=0.00\%$; $Q(3)=1.67$, $p=.644$) and for the adjusted association ($I^2=0.00\%$; $Q(2)=0.989$, $p=.610$). Egger's regression intercept test did not indicate publication bias for the association of baseline depressive symptoms and future CRP [unadjusted ($p=.617$), adjusted ($p=.848$)], IL-6 [unadjusted ($p=.947$), adjusted ($p=.615$)], or TNF- α [unadjusted ($p=.783$), adjusted ($p=.349$)].