

Bidirectional Associations Between Inflammatory Biomarkers and Depressive Symptoms in Adolescents: Potential Causal Relationships

Clinical Psychological Science
1–14

© The Author(s) 2020



Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/2167702620917458

www.psychologicalscience.org/CPS



Daniel P. Moriarity¹, Marin M. Kautz¹, Naoise Mac Giollabhui¹,
Joshua Klugman¹, Christopher L. Coe², Lauren M. Ellman¹,
Lyn Y. Abramson², and Lauren B. Alloy¹

¹Department of Psychology, Temple University, and ²Department of Psychology, University of Wisconsin

Abstract

There are inconsistent findings in the literature about the directionality and magnitude of the association between inflammation and depressive symptoms. This analysis separates predictors into between-persons and within-person components to gain greater clarity about this relationship. Blood samples were collected and depressive symptoms assessed in 140 adolescents (54% female, 59% Black; mean age = 16.1 years) with at least three blood draws and a total of 394 follow-up observations. Multilevel modeling indicated that the within-persons effect of tumor necrosis factor α predicted change in total depressive symptoms, which suggests a potential causal relationship. There were no significant within-persons effects of total depressive symptoms on change in biomarkers. Exploratory analyses examined associations between inflammatory biomarkers and subsets of depressive symptoms. These findings inform modeling decisions that may explain inconsistencies in the extant literature as well as suggest potential causal relationships between certain proteins with significant within-persons effects on depressive symptoms and vice-versa.

Keywords

affective disorders, causal analysis, causality, depression, health

Received 6/22/19; Revision accepted 1/15/20

Growing evidence implicates inflammatory processes in the pathophysiology of depressive symptoms; however, much is still unknown about the exact role that inflammation plays in the etiology of depression. In addition, increased levels of inflammatory proteins in the blood stream may be a downstream effect of depression. Initial evidence for the inflammation–depression relationship came from studies that found that depressive symptoms were more common in patients with medical conditions associated with increased inflammatory activity (Calder, 2006; Goodwin, Fergusson, & Horwood, 2004; Ohayon & Schatzberg, 2003; Pan et al., 2012; Whooley, 2006). In addition, many studies have found higher levels of pro-inflammatory cytokines, including interleukin (IL)-1 β , IL-6, IL-8 and tumor necrosis factor α (TNF- α), and acute phase reactants, such as C-reactive protein (CRP), in individuals with clinical depression compared with control

subjects (Dhabhar et al., 2009; Dowlati et al., 2010; Howren, Lamkin, & Suls, 2009). Proinflammatory cytokines normally function as intercellular signaling proteins and are up-regulated during infection or injury, but we now know that they can act through neuroimmune pathways to stimulate regions of the brain associated with emotionality, including limbic areas and the insular cortex (Eisenberger, Moieni, Inagaki, Muscatell, & Irwin, 2017; Janeway, 1989/2013). These findings also make sense within the larger theoretical framework of cytokines and sickness behavior, which is based on basic science studies showing that proinflammatory cytokines can evoke feelings of

Corresponding Author:

Lauren B. Alloy, Department of Psychology, Temple University, Weiss Hall, 1701 N. 13th St., Philadelphia, PA 19122

E-mail: lalloy@temple.edu

malaise, fatigue, anorexia, and an inability to concentrate (Hart, 1988). Anti-inflammatory cytokines (e.g., IL-10), which modulate the effects of proinflammatory biomarkers, also have been associated with depressive symptoms. However, the relationship between IL-10 and depressive symptoms may be complicated given that these proteins have been found to be associated with both higher (e.g., Meyer et al., 2011) and lower levels of depressive symptoms (e.g., Dhabhar et al., 2009).

When inflammatory pathways are activated, there also are effects on the endocrine system, including stimulation of the hypothalamic-pituitary-adrenal axis, resulting in a down-regulation of glucocorticoid receptors (which can result in a resistance to glucocorticoid actions) and less effective hormonal regulation of inflammatory activity. The resulting proinflammatory phenotype has been posited to be a risk factor for depressive symptoms (A. H. Miller, Maletic, & Raison, 2009; G. E. Miller, Cohen, & Ritchey, 2002). This association has gained considerable support (Howren et al., 2009; A. H. Miller et al., 2009); however, the vast majority of published studies have used cross-sectional designs. More longitudinal research is needed to evaluate causality and the direction of the relationship between inflammation and depressive symptoms.

Previous prospective studies have yielded inconsistent results regarding the association between inflammatory biomarkers and depressive symptoms, illustrated here with studies testing the association between both CRP and IL-6 (two of the most commonly studied biomarkers in depression research) and depressive symptoms in adult samples. Some studies have found that higher levels of CRP and IL-6 were associated with greater severity of future depressive symptoms (e.g., Gimeno et al., 2009; Zalli, Jovanova, Hoogendijk, Tiemeier, & Carvalho, 2016). Other studies have found that depressive symptoms predicted changes in IL-6, but not CRP, over time (e.g., Stewart, Rand, Muldoon, & Kamarck, 2009). Note that both Gimeno et al. (2009) and Stewart et al. (2009) tested bidirectional associations but obtained support only for the unidirectional effects described above, which were in opposite directions. Thus, there is inconsistency in published results with respect to the presence and direction of associations and for which biomarker the associations were observed.

Association Between Inflammation and Depressive Symptoms in Adolescence

There are relatively few prospective studies on inflammation and depression in adolescent samples, a critical period for the emergence of depressive symptoms (Hankin et al., 1998). In addition to the potential for depressive symptoms to progress to clinical diagnoses, even subclinical levels of depressive symptoms can

have problematic behavioral consequences, including suicide and poor school performance (Balázs et al., 2013; van Lang, Ferdinand, & Verhulst, 2007). Furthermore, adolescent-onset depression is associated with a recurrent course of depression throughout life (Gilman, Kawachi, Fitzmaurice, & Buka, 2003). Consequently, well-designed research on inflammatory processes that may underlie risk for depressive symptoms during this developmental period is needed.

Congruent with the adult literature, longitudinal research in adolescent samples also suggests the potential for a bidirectional association between inflammatory biomarkers and depressive symptoms. One study (G. E. Miller & Cole, 2012) reported a bidirectional relationship between inflammation and depression risk, albeit with different biomarkers, in a sample of adolescent females with a history of childhood adversity. G. E. Miller and Cole (2012) found that participants who experienced a depressive episode were more likely to have elevated CRP at a 6-month follow-up and that high levels of IL-6 were associated with increased depression risk at follow-up. Another study obtained similar results and found that high levels of IL-6 were associated with greater depression risk compared with low levels of IL-6 (Khandaker, Pearson, Zammit, Lewis, & Jones, 2014). Note that neither study found associations between CRP and later depression risk. Copeland, Shanahan, Worthman, Angold, and Costello (2012) did not find a significant association between CRP and later depression; however, consistent with G. E. Miller and Cole, this study found that more cumulative episodes of depression were prospectively associated with future CRP. In another study, Duivis et al. (2015) found that consistently moderate or high levels of depressive symptoms were associated with higher future CRP. These studies suggest a bidirectional relationship between inflammatory biomarkers and depressive symptoms in adolescents, which highlights the importance of collecting and analyzing longitudinal data with repeated measures of both biomarkers and symptoms.

Inflammation and Types of Depressive Symptoms

A potentially important source of the inconsistency in the research reviewed above may be differential relationships between inflammatory biomarkers and specific depressive symptoms (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Kuhlman et al., 2018). Because the vast majority of studies examined diagnostic status or analyzed total depressive symptoms, differences in particular symptom endorsement could drive discrepant results. Thus, testing symptom subtypes, or specific symptoms, might provide more replicable findings.

Recent commentaries have argued for the importance of investigating inflammatory phenotypes of depression (Felger, Haroon, & Miller, 2018; Krishnadas & Harrison, 2016). This interest inspired a recent review examining experimental evidence for the association between inflammation and depression, which concluded that increased inflammatory activity likely is associated with exaggerated reactivity to negative information, altered reward reactivity, and somatic symptoms but less likely to be associated with deficits in cognitive control (Dooley et al., 2018).

A Causal Relationship?

The majority of longitudinal studies supporting an association between inflammatory biomarkers and depressive symptoms do not allow for conclusions of causality because their analyses did not track how changes in one variable predicts changes in the other. Rather, they tested whether individuals with higher levels of *X* have higher levels of *Y*, also known as a between-persons effect. Consequently, the association between inflammation and depressive symptoms might be driven by shared risk factors that contribute to between-persons differences in both variables (e.g., gender). However, there is some evidence from quasi-experimental designs that supports the causal relationship between inflammation and depression.

Several studies have shown that inflammatory challenges (e.g., administering endotoxin) are associated with increases in depressive symptoms (e.g., Dantzer & Kelley, 2007; Watkins & Maier, 1999). Others have found that the use of anti-inflammatory medications is associated with reductions in depressive symptoms in some patients (e.g., Raison et al., 2013). In addition, a recent study found that IL-6 responses to flu vaccination were associated with depressive symptoms (Kuhlman et al., 2018). Specifically, greater increases in IL-6 after vaccination were associated significantly with increases in depressed mood, greater confusion, and lower average daily affect but not somatic symptoms, changes in sleep, or feelings of social disconnection. Thus, there is evidence from quasi-experimental designs involving acute inflammatory challenges/interventions that changes in inflammatory physiology may cause changes in depressive symptoms. However, designs using acute inflammatory challenges may differ from natural fluctuations in basal levels of inflammatory biomarkers. Consequently, there is still a need for longitudinal naturalistic studies that test the association between within-persons changes in inflammatory biomarkers and depressive symptoms and vice versa.

Although experimental designs are the “gold standard” for testing causal associations, this also can be done in

studies with repeated measures of both predictors and outcomes by using lagged models that separate a given predictor (e.g., IL-6) into between-persons and within-persons variance components (Falkenström, Finkel, Sandell, Rubel, & Holmqvist, 2017). Isolating between-persons variance is done by calculating the mean of IL-6 across all time points for an individual to compare differences between the participant’s average levels of IL-6. Then, to isolate within-persons variance over time, a second variable is created by centering the value of IL-6 at the mean for the individual at each time point. This is done by subtracting the average of IL-6 calculated in the previous step from the value at each time point to isolate changes in IL-6, controlling for a person’s average levels. The resulting within-persons variance component tests whether changes in the predictor are related to changes in an outcome, which tests possible causal relationships without potential confounding by unmeasured stable variables (Falkenström et al., 2017).

The Current Study

Our study examines the bidirectional longitudinal associations of five inflammatory biomarkers (CRP, IL-6, IL-8, IL-10, and TNF- α) and depressive symptoms in an ethnically diverse community sample of adolescents. The panel of inflammatory biomarkers was chosen because of their frequent use in depression research, which maximizes the ability of this study to inform the interpretation and design of studies. In addition, investigating the association between inflammation and depression in a community sample is important because most of the prior literature focused on at-risk or clinical samples (e.g., Dhabhar et al., 2009; Dowlati et al., 2010; Howren et al., 2009; Miller & Cole, 2012). The models tested in this study separated repeated measures predictors into both between-persons (average value for an individual across all time points) and within-persons (person-centered, or the average value for an individual subtracted from the value at each time point) variance components to isolate the levels of a predictor that are typical for a given participant and the effects of changes in a predictor over time, respectively. Specifically, the within-persons variance components can test potential causal relationships. The a priori hypothesis was that within-persons components of CRP and proinflammatory cytokine levels would be positively associated with subsequent change in depressive symptoms. Given mixed findings for the directionality of the association between IL-10 and depressive symptoms (Dhabhar et al., 2009; Meyer et al., 2011), no directional hypotheses were made. In addition, we hypothesized that within-persons components of depressive symptoms

would predict subsequent change in biomarker levels in the same directions described above. Because these are exploratory analyses, we also tested the prospective relationships between the five biomarkers and subtypes of depressive symptoms. Although the within-persons associations are the focus of this study because of their implications for causal relationships, between-persons associations will be reported in the Supplemental Results in the Supplemental Material available online to better facilitate comparison with the extant literature, which has primarily tested for between-persons differences.

Method

Participants

Participants were drawn from the Adolescent Cognition and Emotion (ACE) project at Temple University. A community sample of 641 adolescents ages 12 to 13 and their mothers or primary female caregivers were recruited from the greater Philadelphia area. Recruitment for this study involved a combination of mailings and follow-up calls to families with children attending Philadelphia public and private middle schools (68% of the total sample) and advertisement in local newspapers (32% of the sample). Inclusion criteria for Project ACE included (a) sufficient competence with the English language to complete the assessments and (b) identification as either White or African American because the investigation of differences in the etiology of depression comparing racial groups was one of the aims of Project ACE. Exclusion criteria for Project ACE included a history of severe psychiatric illness or developmental disorders (for further information, see Alloy et al., 2012). Informed written consent was obtained from mothers and written assent from adolescents before data collection. The Temple University Institutional Review Board approved the protocol (Protocol 6844).

A subsample of 315 adolescents from Project ACE volunteered to participate in an optional blood-draw protocol. This analytic sample included up to seven assessments (some had more blood draws than others because it was an optional part of annual assessments). Nineteen observations were excluded because participants were taking anti-inflammatory medications (e.g., ibuprofen) at the time of blood draw. An additional 78 observations were removed because CRP values were greater than 10 mg/L, which may indicate an acute infection (Bell et al., 2017; de Ferranti, Gauvreau, Ludwih, Newburger, & Rifai, 2006). After accounting for these exclusion criteria and missing data and removing the data from participants with fewer than three blood

draws, the final analytic sample included 534 observations (394 follow-ups after losing the first observation because of lagging predictors) across 140 participants (54% were female; 59% were Black; mean age at first blood draw = 16.1 years, $SD = 1.4$, range = 12.1–21.1 years). Because of differential missingness in covariates between models, sample size varied slightly between models (see Tables 1 and 2). An attrition analysis was conducted to determine whether any demographic variables were associated with the number of follow-ups after the first blood draw. Demographic variables and average depressive symptoms across time were not associated with number of follow-ups (all $ps > .05$). Across the study period, 21% of participants reported depressive symptom scores indicative of at least mild depression (Bang, Park, & Kim, 2015).

Measures

Depressive symptoms. Symptoms of depression were measured using the Children's Depression Inventory (CDI; Kovacs, 1985). It consists of 27 items reflecting affective, behavioral, and cognitive symptoms of depression. Items are rated on a scale from 0 (e.g., "I am sad once in a while") to 2 (e.g., "I am sad all of the time"); and total scores range from 0 to 54. The CDI has been demonstrated to be a reliable and valid measure of depressive symptoms in youth samples (Klein, Dougherty, & Olinio, 2005). Internal consistency in this sample was $\alpha = .88$ at the first study visit. The CDI was administered at all assessments. All items in the scale were summed to create the total CDI score. In addition, five depressive-symptom subscales were used, in accordance with a meta-analytic factor structure of the CDI in adolescents (Huang & Dong, 2014). The five subscales were somatic concerns (nine items; $\alpha = .63$), externalizing (six items; $\alpha = .69$), negative self-concept (seven items; $\alpha = .62$), lack of personal and social interest (five items; $\alpha = .73$), and dysphoric mood (four items; $\alpha = .75$).

Inflammatory physiology. Blood samples were obtained via antecubital venipuncture by a certified phlebotomist into a 10-mL vacutainer designed for freezing plasma separated from the cell fraction within the vial (BD Hemogard with K2 EDTA). Vacutainers were stored in an ultracold freezer at -80°C and later thawed on the day of assay. At each blood draw, the time of collection and participants' body mass indexes (BMIs), based on direct measurement of height and weight, were recorded. Four cytokines were quantified by multicytokine array (IL-6, IL-8, IL-10, and TNF- α), and high-sensitivity CRP was determined in a singleplex assay using an electrochemiluminescence platform and a QuickPlex SQ 120 imager for analyte detection (Meso Scale Discovery, Gaithersburg,

Table 1. Effects of Inflammatory Biomarkers on Change in Total Depressive Symptoms (as Measured by CDI)

Fixed effect	CRP			IL-6			Log IL-8			IL-10			Log TNF- α		
	Coefficient	β	<i>p</i>	Coefficient	β	<i>p</i>	Coefficient	β	<i>p</i>	Coefficient	β	<i>p</i>	Coefficient	β	<i>p</i>
Intercept	-0.962 (4.760)	0.000	.840	-1.102 (4.770)	0.000	.840	0.670 (6.014)	0.000	.911	-0.831 (4.755)	0.000	.861	1.789 (8.499)	0.000	.833
Effect of biomarker															
Within persons	-0.002 (0.211)	0.000	.993	0.545 (1.229)	0.029	.657	-0.232 (1.671)	-0.009	.890	-0.259 (1.363)	-0.132	.850	8.571 (3.265)	0.156	.0091**
Between persons	-0.109 (0.231)	-0.037	.637	-0.535 (1.313)	-0.030	.684	-0.712 (1.582)	-0.028	.653	-1.202 (1.274)	-0.064	.346	-1.465 (2.921)	-0.031	.616

Note: There were 130 participants and 310 observations in this analysis. In all cases, individual (person-level) variance was 0. Values in parentheses are standard errors. Residual (observation level) variance was as follows: for C-reactive protein (CRP), 19.90; for interleukin (IL)-6, 19.89; for Log IL-8, 19.90; for Log IL-10, 19.85; for Log tumor necrosis factor α (TNF- α), 19.42; all were significant at $p < .05$. CDI = Children's Depression Inventory (Kovacs, 1985).

** $p < .01$.

Table 2. Effects of Total Depressive Symptoms (as Measured by the CDI) on Change in Inflammatory Biomarkers

Fixed effect	Log CRP			Log IL-6			Log IL-8			Log IL-10			Log TNF- α		
	Coefficient	β	<i>p</i>	Coefficient	β	<i>p</i>	Coefficient	β	<i>p</i>	Coefficient	β	<i>p</i>	Coefficient	β	<i>p</i>
Intercept	0.078 (0.690)	0.000	.910	-0.264 (0.356)	0.000	.459	0.233 (0.282)	0.000	.409	-0.016 (0.307)	0.000	.959	-0.013 (0.151)	0.000	.930
Effect of biomarker															
Within persons	0.006 (0.013)	0.027	.671	0.012 (0.007)	0.103	.091	-0.005 (0.005)	-0.059	.341	0.007 (0.006)	0.068	.249	0.005 (0.003)	0.107	.077
Between persons	-0.006 (0.007)	-0.057	.383	0.000 (0.003)	-0.007	.903	0.001 (0.003)	0.018	.776	0.000 (0.003)	0.003	.964	-0.001 (0.001)	-0.038	.544

Note: There were 132 participants and 333 observations in this analysis. In all cases, individual (person-level) variance was 0. Values in parentheses are standard errors. Residual (observation level) variance was as follows: for Log C-reactive protein (CRP), 0.33; for Log interleukin (IL)-6, 0.09; for Log IL-8, 0.05; for Log IL-10, 0.06; for Log tumor necrosis factor α (TNF- α), 0.02; all were significant at $p < .05$. CDI = Children's Depression Inventory (Kovacs, 1985).

MD). Each specimen was assayed in duplicate, and the intraassay coefficients of variation averaged 5.36 and 2.29 for the cytokines and CRP, respectively. Plasma was diluted 1:2 for the cytokine assay and 1:1,000 for the CRP assay. CRP is present in blood at higher concentrations, and thus plasma was diluted to correspond to the standard curve. Values were calculated with respect to a standard curve generated from seven calibrators with known concentrations. The lower limit of detection (LLOD) for the cytokines was 0.1 pg/mL, with a large dynamic range up to 2,000 pg/mL. The LLOD for CRP was 0.1 mg/L. Values below the LLOD were set at the LLOD. Values were converted to milligrams per liter to be consistent with the clinical literature (Breen et al., 2011; Dabitaio, Margolick, Lopez, & Bream, 2011).

Procedure

All demographic information was self-reported during the first visit of the full Project ACE study. At each time point in the analytic sample, adolescents completed a blood draw and the CDI. All 140 participants had at least two follow-ups after the first blood draw and CDI assessment (Time 2: $M = 16.57$ months after Time 1, $SD = 6.84$; Time 3: $M = 13.46$ months after Time 2, $SD = 6.72$). Seventy-five had a third follow-up ($M = 12.74$ months after Time 3, $SD = 6.54$), 30 had a fourth follow-up ($M = 10.92$ months after Time 4, $SD = 5.13$), 8 had a fifth follow-up ($M = 11.52$ months after Time 5, $SD = 2.60$), and 1 had a sixth follow-up (8.28 months after Time 6). Note that the average length of these time lags is consistent with recent evidence that the association between inflammatory biomarkers and change in depressive symptoms is strongest for durations greater than 13 months (Moriarity et al., 2019).

Data analysis plan

All descriptive statistics, correlations, and preliminary analyses were conducted in IBM SPSS (Version 24.0). Primary analyses were conducted in the R programming environment (Version 3.5.2; R Core Team, 2018). Multilevel models with random intercepts and fixed slopes were estimated using the R packages *lmer4* (Version 1.1-21; Bates, Maechler, Bolker, & Walker, 2015) and *lmerTest* (Version 3.11; Kuznetsova, Brockhoff, & Christensen, 2017). Riverplots were created using the *riverplot* package (Version 0.5; Weiner, 2015) to visualize variance accounted for by predictors, which were calculated using the *r2MLM* function (Rights & Sterba, 2019). Five models were estimated with each protein predicting change in total depressive symptoms between each time point. To test for bidirectional effects, five additional models were run with total depressive symptoms predicting change in each biomarker between each time point.

Depression symptoms and biomarkers were lagged for temporal precedence. Gender, race, and family income were modeled as person-level predictors (Alanna et al., 2011; Deverts, Cohen, Kalra, & Matthews, 2012; Hankin et al., 1998). All repeated measures used as predictors—biomarkers, depressive symptoms, age at measurement of the outcome, BMI, time of blood draw, hormonal birth control use, and taking a medication that can influence inflammation (e.g., preventive asthma inhaler)—were separated into a within-persons component (person-centered) and a between-persons components (the mean across observations per individual; Dominguez-Rodriguez, Abreu-Gonzalez, & Kaski, 2009; Mills, Scott, Wray, Cohen-Woods, & Baune, 2013; Skovlund, Morch, Kessing, & Lidegaard, 2016). BMI was lagged in all models because it is prospectively associated with both inflammation and depression symptoms (Mac Giollaibhui et al., 2020). Medication status, birth control, and time of blood draw were used from the visit of the immune data (e.g., lagged when predicting depression, contemporaneous when predicting inflammatory biomarkers). In addition, the number of months between blood draws was used as an observation-level predictor. Given this study's longitudinal design, the number of months to follow-up was not centered or aggregated. Consequently, the number of months since blood draw is an estimate of a combination of within- and between-persons effects.

Inflammatory biomarker values more than 3 SD from the mean were winsorized. This resulted in the winsorization of 18 CRP, 9 IL-6, 8 IL-8, 4 IL-10, and 5 TNF- α values. All models were run with and without log-transformation ($\text{Log}(100 \times \text{value})$). For CRP, IL-6, IL-8, IL-10, and TNF- α values, skewness before log-transformation was 1.72, 2.93, 4.71, 7.80, and 1.14, respectively, and skewness after log-transformation was -0.04 , 0.50, 0.79, 1.80, and -0.22 , respectively. Plots of the resulting model residuals were checked visually, and the model that best satisfied the assumption of normality (i.e., residuals most closely followed the linear model) was interpreted. Both Level 1 and Level 2 residuals were investigated. Normality of Level 1 residuals was prioritized because of the current study's focus on time-varying predictors and the fact that the majority of the variance in the models was at the observation level. In cases of negligible differences in distribution of residuals, the log-transformed model was interpreted to be consistent with convention. To investigate the potential for covariances to differ over time, all models originally were tested with interaction terms between all predictors and the number of months to follow-up. To preserve degrees of freedom, only interaction terms with significant associations were included in the final models described below. In addition to the universal covariates described above, this resulted in the addition of

interaction terms (a) between time and the between-persons effect of birth control predicting change in IL-6, IL-8, and IL-10; (b) between time and gender predicting change in IL-8, IL-10, and TNF- α ; and (c) between time and the between-persons effect of medication status predicting change in IL-10. There were no significant interactions between number of months to follow-up and any of our key independent variables (biomarkers or symptoms) or in any of the models predicting change in symptoms.

Multilevel modeling was chosen because the data were clustered within individuals; using traditional regression techniques would result in greater probability of Type I error and less efficient estimates of coefficients for regression compared with multilevel modeling. Models were estimated using restricted maximum likelihood. Family-wise Holm-Bonferroni (Holm, 1979) corrections were used for all analyses. Exploratory analyses were run using identical models as the primary analyses, except that we substituted CDI subscales for total depressive symptoms. Although the American Statistical Association does not recommend selective reporting of results on the basis of p values (Wasserstein & Lazar, 2016), in the interest of space, only results significant at $p < .05$ will be described in the exploratory analyses below. Exact p values will be reported for all primary analyses regardless of significance.

Results

Preliminary analyses

Descriptive statistics and bivariate correlations for the main study variables at Time 1, including untransformed inflammation variables, are presented in Table S1 in the Supplemental Material available online. Correlations were calculated with log-transformed biomarker values to improve normality of the distributions, but descriptive statistics are reported using raw variables to increase interpretability. Independent-sample t tests tested whether average levels of total depressive symptoms or inflammatory biomarkers differed by race or sex. Significant sex differences were observed for CRP (males = 1.12, SD = 1.17; females = 1.77, SD = 1.79), $t(128.868) = -2.59$, $p = .01$; and for IL-6 (males = 0.32, SD = 0.21; females = 0.44, SD = .26), $t(138) = -2.95$, $p < .01$; but not for TNF- α , IL-8, IL-10, or depressive symptoms ($ps = .52, .23, .16$, and $.77$, respectively). Significant racial differences were observed for TNF- α (Whites = 1.55, SD = 0.33; African Americans = 1.38, SD = 0.29), $t(138) = 3.21$, $p < .01$, but not for CRP, IL-6, IL-8, IL-10, or depressive symptoms ($ps = .27, .83, .08, .16$, and $.08$, respectively). Independent-samples t tests (for continuous variables) and χ^2 tests (for categorical variables) found

no significant differences in total depression symptoms, income, race, gender, or any of the biomarkers between the total group of adolescents with at least one blood draw and the analytic sample. The analytic sample was significantly younger at their first blood draw than the total sample of participants with blood draws ($p < .01$; $Ms = 16.13$ years and 17.02 years, respectively), likely reflecting participants dropping out of the study as they transitioned into emerging adulthood. The analytic sample also was compared with the entire ACE sample, for which blood draws were an optional component, on demographics and baseline depression symptoms. The analytic and total samples did not differ on total depression symptoms at participant first study visit, household income, race, or gender (all $ps < .05$). Participants in the analytic sample were significantly older than the rest of the sample at their first study visit ($p = .02$, age: $Ms = 12.72$ years and 12.53 years, respectively).

Primary analyses

Inflammatory biomarkers predicting depressive symptoms. Log TNF- α had a small within-persons effect (following the guidelines for interpreting standardized regression coefficients as effect sizes; Acock, 2014) on change in total depressive symptoms ($\beta = 0.156$, $SE = 0.060$, $p = .009$; see Table 1 for model results and Fig. 1 for variance decomposition); increases in TNF- α predicted increases in depressive symptoms. The association between within-persons TNF- α and total depressive symptoms was robust to Holm-Bonferroni corrections (adjusted $p = .045$). Raw CRP, raw IL-6, log IL-8, and raw IL-10 had no significant within-persons effects on change in total depressive symptoms ($ps = .993, .657, .890$, and $.850$, respectively). Results with the between-persons variance components are provided in the Supplemental Material (no significant results).

Depressive symptoms predicting inflammatory biomarkers. Total depressive symptoms had no significant within-persons effect on change in log CRP, log IL-6, log IL-8, log IL-10, or log TNF- α ($ps = .671, .091, .341, .249$, and $.077$, respectively; see Table 2). Results with the between-persons variance components are provided in the Supplemental Material (no significant results).

Exploratory analyses

Inflammatory biomarkers predicting depressive symptom subtypes. There were small within-persons effects on changes in dysphoria for log TNF- α ($\beta = 0.168$, $SE = 0.059$, $p = .005$) and log IL-10 ($\beta = 0.166$, $SE = 0.063$, $p = .009$); increases in these cytokines predicted increases in

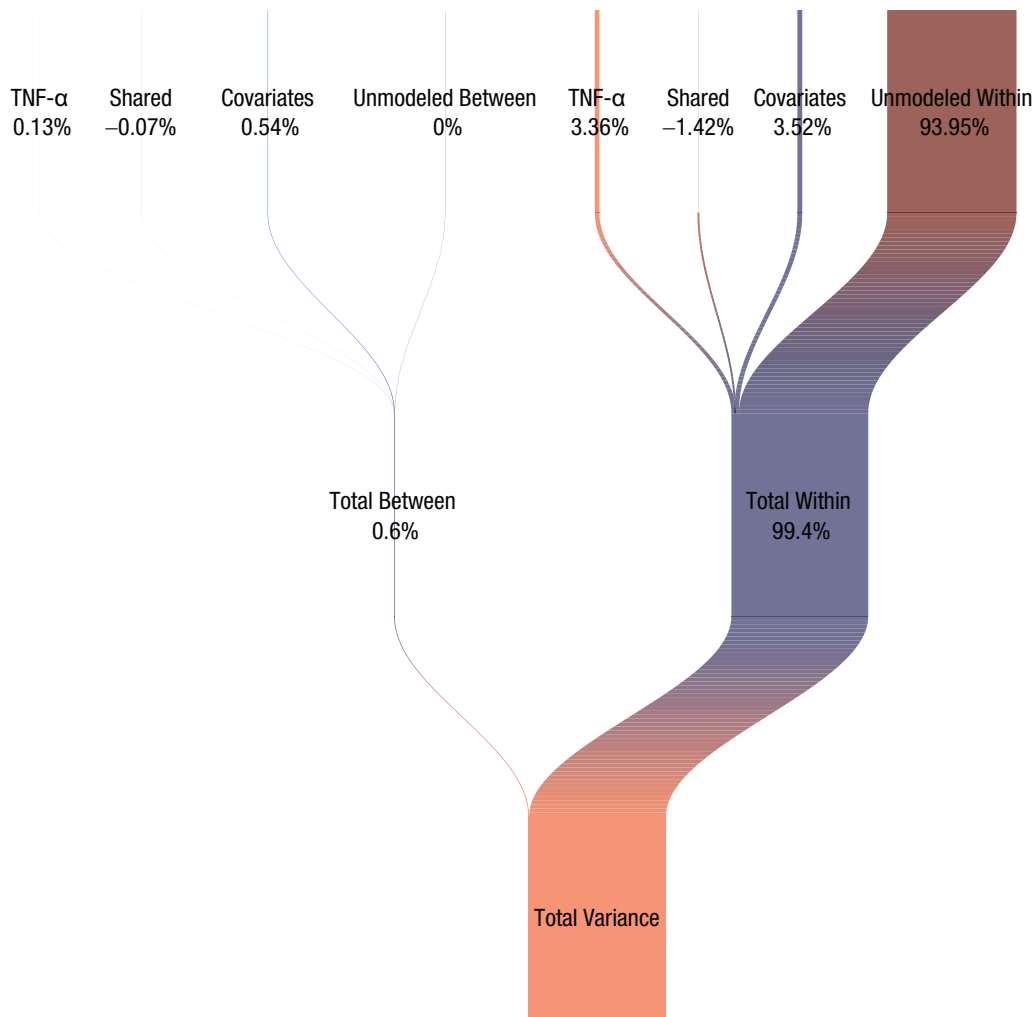


Fig. 1. Tumor necrosis factor α predicting variance in change in total depressive symptoms.

dysphoric symptoms (Fig. 2). Both results survived family-wise (grouped by inflammatory protein) Holm-Bonferroni corrections (adjusted p s = .045 and .048, respectively). No other within-persons effects of inflammatory biomarkers on symptom subtypes reached significance. Results with the between-persons variance components are provided in the Supplemental Material. See Figure 2 for a summary of significant exploratory results.

Depressive symptom subtypes predicting inflammatory biomarkers. Dysphoria had a small within-persons effect on changes in log IL-6 ($\beta = 0.192$, $SE = 0.059$, $p = .001$) and log IL-10 ($\beta = 0.178$, $SE = 0.057$, $p = .002$) and a moderate within-persons effect on log TNF- α ($\beta = 0.220$, $SE = 0.058$, $p = .0002$); increases in dysphoria predicted increases in these cytokines (Fig. 2). These significant findings were robust to familywise (grouped by symptom subtype) Holm-Bonferroni corrections (adjusted p s = .005, .006, .001, respectively). No other within-persons effects of symptom subtypes on inflammatory biomarkers reached

or approached significance. Results with the between-persons variance components are provided in the Supplemental Material (no significant results).

Discussion

There is substantial evidence of a relationship between inflammatory physiology and depressive symptoms; however, there is still much to be learned about the directionality and degree of causality between these variables. This study extends previous literature on the associations between inflammatory physiology and depressive symptoms in adolescents by concurrently testing the extent to which average levels of and changes in inflammatory biomarkers predict changes in depressive symptoms and vice versa. In addition, it provides some support for bidirectional associations between inflammatory biomarkers and dysphoric symptoms. In these analyses, we found a within-persons effect of TNF- α on the development of total depressive

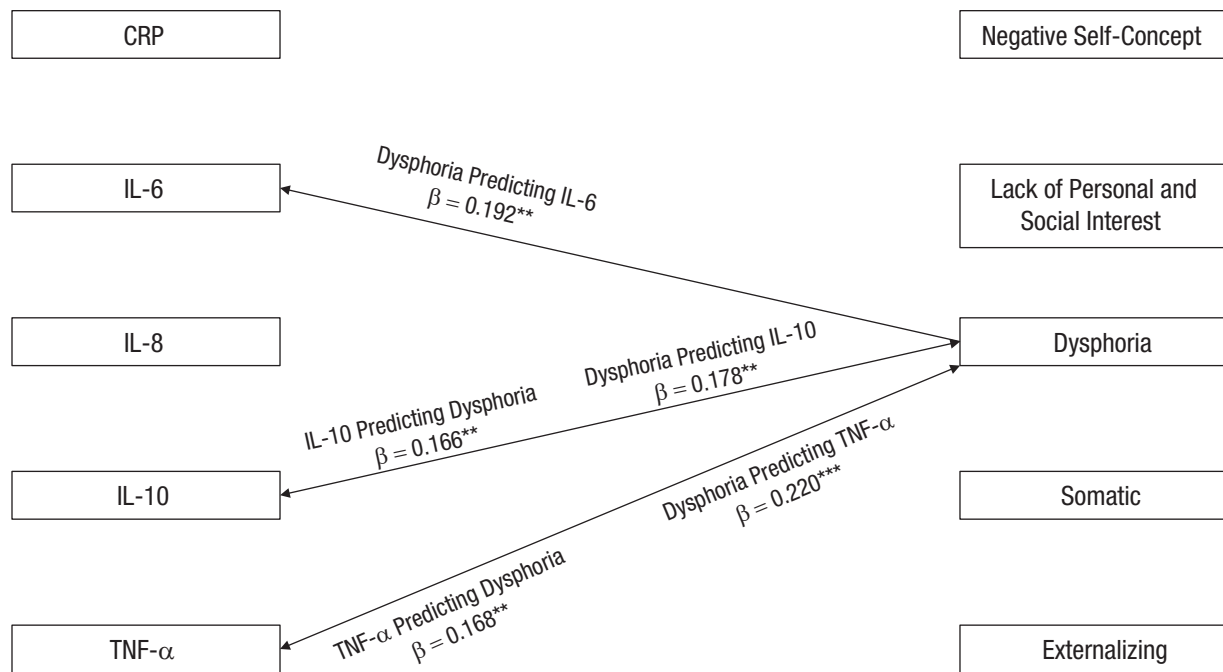


Fig. 2. Summary of significant exploratory results. CRP = C-reactive protein, IL = interleukin, TNF- α = tumor necrosis factor α . Asterisks represent significant associations (* $p < .05$, ** $p < .01$, *** $p < .001$).

symptoms in adolescents. Note that the significant within-persons association of TNF- α with change in depressive symptoms is suggestive of a potential causal relationship. Furthermore, the presence of a significant within-persons association of this cytokine with total depressive symptoms but lack of a within-persons association of total depressive symptoms with any biomarkers provides support for viewing inflammation as a risk factor rather than just as a downstream consequence of depression. However, results from our exploratory analyses suggest there might be important differences in the strength and direction of these associations by symptom domains.

Exploratory analyses were conducted using depressive symptom subscales, in line with theory that different depressive symptoms have different risk factors and that inflammatory physiology may be more closely related to some depressive phenotypes than others (Dooley et al., 2018; Felger et al., 2018; Fried, Nesse, Zivin, Guille, & Sen, 2014; Krishnadas & Harrison, 2016). The results indicated that biomarkers were differentially predictive of different subscales of symptoms, providing further insight into the development of an inflammatory phenotype of depression and potential sources of heterogeneity among existing studies that use clinical diagnoses or total depressive symptoms without consideration of the types of symptoms endorsed by participants. Specifically, increases in TNF- α and IL-10

predicted increases in dysphoric symptoms, and increases in dysphoric symptoms predicted increases in TNF- α , IL-10, and IL-6. Note that there were significant, bidirectional within-persons effects of TNF- α and IL-10 with dysphoric symptoms, which supports a bidirectional and potentially causal relationship (Falkenström et al., 2017). The results also are in keeping with the conclusions of Dooley et al. (2018), who concluded that changes in inflammation might induce greater affective reactivity. In addition, this result is congruent with Kuhlman and colleagues (2018), who also focused on within-persons effects of inflammation on depression symptoms, as was the null findings predicting somatic symptoms. Although the analysis provided preliminary evidence for specificity, 50 models were run in total for the exploratory analyses, which resulted in an increased chance of Type I error. However, it is worth noting that all significant results were robust to Holm-Bonferroni corrections.

The observation that only the within-persons effect of TNF- α predicted increases in total depression symptoms potentially could indicate that it is associated with a less specific set of symptoms than IL-6 or IL-10, which were associated only with dysphoria. Alternatively, differences in the association between an inflammatory protein and behavioral outcomes could be due to differences in the synthesis and release of specific biomarkers. For example, it has been hypothesized that

TNF- α might be an important inflammatory protein in the pathogenesis of depression because of its role in maintaining proinflammatory states and the ability to dampen synaptic plasticity (for a review on the role of TNF- α in depression, see Brymer, Romay-Tallon, Allen, Caruncho, & Kalynchuk, 2019). However, until this specific pattern of results is replicated, it is more parsimonious to interpret that this result was driven by TNF- α 's association with dysphoria symptoms given that this was the only depression subscale that TNF- α was associated with. Either way, these results suggest that TNF- α should be strongly considered when selecting inflammatory biomarkers for depression studies given that it is currently studied much less frequently than CRP or IL-6.

Given the fact that the significant effects in our models were all within-persons effects, some heterogeneity in the extant literature might be due to reliance on parameters that solely represent between-persons effects or conflate between- and within-persons effects. Furthermore, considering the results using symptom subscales, another source of variation in extant studies using depression diagnoses or total depressive symptoms might be the distribution of symptoms endorsed in the sample. Indeed, in addition to more significant associations, the effect sizes for significant associations with dysphoria were larger than the significant effect size between TNF- α and total depression symptoms. For example, given these results, significant associations between TNF- α , IL-6, or IL-10 and depression diagnoses/total depression symptoms would be most likely in samples with high rates of endorsement of dysphoric symptoms. In addition to providing evidence that inflammatory activity could be a precipitating cause of depressive symptoms and vice versa, the selective linkages with specific symptom subtypes may inform how best to characterize and diagnose inflammation-related depression in adolescents.

Finally, our evidence that inflammation was predictive of change in depressive symptoms in adolescents also concurs with the recent interest in anti-inflammatory drugs as a therapeutic modality for depression resistant to traditional treatment modalities. Although the majority of our effect sizes were modest, it is important to note that these effect sizes were for single proteins. Thus, broad-acting anti-inflammatory treatments might have a larger effect on symptom reduction. Specifically, our results suggest they may be useful for targeting specific symptoms, such as dysphoria and affective reactivity (Dooley et al., 2018). The likelihood of some reciprocal association also is consistent with the efficacy reported for several cognitive-behavioral interventions (e.g., mindfulness-based stress reduction) that have been found to reduce both inflammatory activity

and negative affect in practitioners (Malarkey, Jarjoura, & Klatt, 2013; Raison et al., 2013; Rosenkranz et al., 2013).

Contrary to the a priori hypotheses but consistent with several other studies (Copeland et al., 2012; Khandaker et al., 2014; Miller & Cole, 2012), CRP was not predictive of depressive symptoms in any model. This lack of association may partially reflect the young age of the participants because it is known that CRP levels typically rise in adulthood. In addition, the rise of CRP in middle-aged adults often is associated with obesity, which is also a risk factor for depression (Preiss, Brennan, & Clarke, 2013). Even in these adolescent participants, log CRP was correlated significantly with BMI at $r = .56$; thus, including BMI as a covariate in all models would have accounted for more variance in the models with CRP compared with models with other biomarkers. In addition, CRP remained fairly stable over time, which resulted in less variation to explain within-persons changes in depression symptoms.

Strengths and limitations

This study had several important strengths. First, it included a large, racially diverse, community sample of adolescents, a population still understudied in behavioral medicine research. Second, most adolescents typically are subject to fewer potential confounds of the association between inflammatory physiology and depression (e.g., medication status, cumulative life stress, cumulative illness) compared with an identical study with adults. Third, the delineation of symptom and biomarker predictor variables into between-persons and within-persons components in a lagged model design is a powerful and novel statistical approach to this area of research, which can be applied to other data sets interrogating temporal relationships between physiology and biobehavioral health. It allows for an examination of potential causal effects resulting from changes over time as opposed to differences between individuals in average levels of a predictor (Falkenström et al., 2017). Finally, the exploratory analyses using symptom subscales were informative for potential explanations for inconsistencies in the extant literature as well as for generating additional hypotheses about inflammatory phenotypes of depression.

However, several limitations also should be acknowledged. First, participants were at the upper end of the age range for which the CDI was validated. Second, this study used self-reported depressive symptoms rather than clinical interviews and thus did not include diagnosed depressive episodes. Although inflammatory activity is believed to be associated with discrete depressive symptoms, not just clinical depression diagnoses,

inclusion of analyses testing clinically relevant episodes would have improved the clinical relevance of this study. This concern was mitigated to some degree by the presence of at least mild levels of depressive symptoms in 21% of the sample. Fourth, although within-persons predictive associations may suggest potential causal relationships, there remains the possibility that unmeasured, time-varying confounding variables might be driving the effects (e.g., changes in exercise, life stress, and sleep). Fifth, although Moriarity and colleagues (2019) found that at least 13 months was ideal for finding associations between inflammatory biomarkers and change in depression symptoms, note that this previous study tested only between-persons effects. Thus, this time lag might not be ideal for testing the within-persons effects that were the focus of this article, potentially resulting in an underestimation of effects. Finally, it should be acknowledged that the majority of observed associations were modest. This concern is not surprising given typical effect sizes of biological variables on psychiatric symptoms and the use of models separating predictors into two different components. However, the translational relevance for clinical practice should be considered with respect to the magnitude of the observed relationships.¹

Conclusion

This study provides support for predictive and potentially causal relationships between some aspects of inflammatory physiology and depressive symptoms, specifically dysphoria, in adolescents. The findings have implications both for the etiology of depression and specific inflammatory profiles and for the classification of an inflammatory phenotype of depression. Furthermore, the prospective associations between inflammatory physiology and depressive symptoms in adolescents suggest that treatments with anti-inflammatory properties (pharmacological or otherwise) might be beneficial in treating symptoms of depression, specifically dysphoria.

Transparency

Action Editor: Christopher G. Beevers

Editor: Scott O. Lilienfeld

Author Contributions

D. P. Moriarity generated hypotheses, developed the analytic strategy, wrote analysis code, and ran and interpreted analyses. D. P. Moriarity drafted the manuscript. M. M. Kautz and C. L. Coe participated in database creation. M. M. Kautz and N. Mac Giollabhui participated in data analysis. L. M. Ellman participated in the design and cleaning of the inflammation data. J. Klugman provided statistical consultation for the project. C. L. Coe assayed blood samples. L. Y. Abramson and L. B. Alloy helped design the original

study, wrote the grant that supported the current study, and participated in the design and coordination of the current study. M. M. Kautz, N. Mac Giollabhui, L. M. Ellman, C. L. Coe, L. Y. Abramson, and L. B. Alloy provided feedback on the manuscript. All the authors approved the final version of the manuscript for submission.



Declaration of Conflicting Interests

The author(s) declared that there were no conflicts of interest with respect to the authorship or the publication of this article.

Funding

This research was supported by National Institute of Mental Health Grants MH079369 and MH101168 (to L. B. Alloy). D. P. Moriarity was supported by National Institute of Mental Health Research Service Award F31MH122116. M. M. Kautz was supported by National Science Foundation Graduate Research Fellowship 2018263024. N. Mac Giollabhui was supported by National Institute of Mental Health Research Service Award F31MH118808.

ORCID iDs

Daniel P. Moriarity  <https://orcid.org/0000-0001-8678-7307>
Naoise Mac Giollabhui  <https://orcid.org/0000-0003-4226-5704>

Supplemental Material

Additional supporting information can be found at <http://journals.sagepub.com/doi/suppl/10.1177/2167702620917458>

Note

1. There was negative shared variance between biomarkers/depressive symptoms and covariates in several models. Although this is nonintuitive, this is likely due to the coefficients of some of the biomarker/symptom predictors being larger in the described models, which included covariates that might account for variance in the outcome variable unrelated to the primary predictors, compared with the models containing only the biomarker/symptom predictors that were used to calculate proportions of variance accounted for by the r2MLM function (Rights & Sterba, 2019).

References

- Acock, A. C. (2014). *A gentle introduction to Stata* (4th ed.). College State, TX: Stata Press.
- Alanna, M., Zhao, L., Ahmed, Y., Stoyanova, N., Hooper, W. C., Gibbons, G., . . . Vaccarino, V. (2011). Association between depression and inflammation—differences by race and sex: The META-Health study. *Psychosomatic Medicine*, *73*, 462–468. doi:10.1097/PSY.0b013e318222379c
- Alloy, L. B., Black, S. K., Young, M. E., Goldstein, K. E., Shapero, B. G., Stange, J. P., . . . Abramson, L. Y. (2012). Cognitive vulnerabilities and depression versus other psychopathology symptoms and diagnoses in early adolescence. *Journal of Clinical Child and Adolescent Psychology*, *41*, 539–560. doi:10.1080/15374416.2012.703123
- Balázs, J., Miklösi, M., Keresztény, Á., Hoven, C. W., Carli, V., Wasserman, C., . . . Wasserman, D. (2013). Adolescent subthreshold-depression and anxiety: Psychopathology,

- functional impairment and increased suicide risk. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *54*, 670–677. doi:10.1111/jcpp.12016
- Bang, Y. R., Park, J. H., & Kim, S. H. (2015). Cut-off scores of the children's depression inventory for screening and rating severity in Korean adolescents. *Psychiatry Investigation*, *12*, 23–28.
- Bates, D., Maechler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, *67*, 1–48. doi:10.18637/jss.v067.i01
- Bell, J. A., Kivimäki, M., Bullmore, E. T., Steptoe, A., Bullmore, E., Vértés, P. E., . . . Carvalho, L. A. (2017). Repeated exposure to systemic inflammation and risk of new depressive symptoms among older adults. *Translational Psychiatry*, *7*(8), Article e1208. doi:10.1038/tp.2017.155
- Breen, E. C., Reynolds, S. M., Cox, C., Jacobson, L. P., Magpantay, L., Mulder, C. B., . . . Norris, P. J. (2011). Multisite comparison of high-sensitivity multiplex cytokine assays. *Clinical and Vaccine Immunology*, *18*, 1229–1242. doi:10.1128/CVI.05032-11
- Brymer, K. J., Romay-Tallon, R., Allen, J., Caruncho, H. J., & Kalynchuk, L. E. (2019). Exploring the potential antidepressant mechanisms of TNF α antagonists. *Frontiers in Neuroscience*, *13*, Article 98. doi:10.3389/fnins.2019.00098
- Calder, P. C. (2006). n-3 Polyunsaturated fatty acids, inflammation, and inflammatory diseases. *The American Journal of Clinical Nutrition*, *83*, 1505–1519. doi:10.1093/ajcn.116.5.1505
- 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*, 15–21. doi:10.1016/j.biopsych.2011.09.023
- Dabitaio, D., Margolick, J. B., Lopez, J., & Bream, J. H. (2011). Multiplex measurement of proinflammatory cytokines in human serum: Comparison of the Meso Scale Discovery electrochemiluminescence assay and the Cytometric Bead Array. *Journal of Immunological Methods*, *372*, 71–77. doi:10.1038/jid.2014.371
- Dantzer, R., & Kelley, K. W. (2007). Twenty years of research on cytokine-induced sickness behavior. *Brain Research*, *21*, 153–160. doi:10.1016/j.bbi.2006.09.006
- 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*, 46–57.
- de Ferranti, S. D., Gauvreau, K., Ludwih, D. S., Newburger, J. W., & Rifai, N. (2006). Inflammation and changes in metabolic syndrome abnormalities in US adolescents: Findings from the 1988-1994 and 1999-2000 National health and nutrition examination surveys. *Clinical Chemistry*, *52*, 1325–1330.
- Deverts, D. J., Cohen, S., Kalra, P., & Matthews, K. A. (2012). The prospective association of socioeconomic status with C-reactive protein levels in the CARDIA study. *Brain Behavior and Immunity*, *26*, 1128–1135. doi:10.1016/j.bbi.2012.07.017
- Dhabhar, F. S., Burke, H. M., Epel, E. S., Mellon, S. H., Rosser, R., Reus, V. I., & Wolkowitz, O. M. (2009). Low serum IL-10 concentrations and loss of regulatory association between IL-6 and IL-10 in adults with major depression. *Journal of Psychiatric Research*, *43*, 962–969. doi:10.1016/j.jpsychires.2009.05.010
- Dominguez-Rodriguez, A., Abreu-Gonzalez, P., & Kaski, J. C. (2009). Inflammatory systemic biomarkers in setting acute coronary syndromes—effects of the diurnal variation. *Current Drug Targets*, *10*, 1001–1008.
- Dooley, L. N., Kuhlman, K. R., Robles, T. F., Eisenberger, N. I., Craske, M. G., & Bower, J. E. (2018). The role of inflammation in core features of depression: Insights from paradigms using exogenously-induced inflammation. *Neuroscience and Biobehavioral Reviews*, *94*, 219–237. doi:10.1016/j.neubiorev.2018.09.006
- Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctôt, K. L. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry*, *67*, 446–457. doi:10.1016/j.biopsych.2009.09.033
- Duivis, H. E., Kupper, N., Vermunt, J. K., Penninx, B. W., Bosch, N. M., Riese, H., . . . de Jonge, P. (2015). Depression trajectories, inflammation, and lifestyle factors in adolescence: The Tracking Adolescents' Individual Lives Survey. *Health Psychology*, *34*, 1047–1057. doi:10.1037/hea0000210
- Eisenberger, N. I., Moieni, M., Inagaki, T. K., Muscatell, K. A., & Irwin, M. R. (2017). In sickness and in health: The co-regulation of inflammation and social behavior. *Neuropsychopharmacology*, *42*, 242–253. doi:10.1038/npp.2016.141
- Falkenström, F., Finkel, S., Sandell, R., Rubel, J. A., & Holmqvist, R. (2017). Dynamic models of individual change in psychotherapy process research. *Journal of Consulting and Clinical Psychology*, *85*, 537–549.
- Felger, J. C., Haroon, E., & Miller, A. H. (2018). What's CRP got to do with it? Tackling the complexities of the relationship between CRP and depression. *Brain Behavior and Immunity*, *73*, 163–164. doi:10.1016/j.bbi.2018.08.003
- Fried, E. I., Nesse, R. M., Zivin, K., Guille, C., & Sen, S. (2014). Depression is more than the sum score of its parts: Individual DSM symptoms have different risk factors. *Psychological Medicine*, *44*, 2067–2076. doi:10.1017/S0033291713002900
- Gilman, S. E., Kawachi, I., Fitzmaurice, G. M., & Buka, S. L. (2003). Socio-economic status, family disruption and residential stability in childhood: Relation to onset, recurrence and remission of major depression. *Psychological Medicine*, *33*, 1341–1355.
- Gimeno, D., Kivimäki, M., Brunner, E. J., Elovainio, M., De Vogli, R., Steptoe, A., . . . 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*, 413–423. doi:10.1017/S0033291708003723
- Goodwin, R. D., Fergusson, D. M., & Horwood, L. J. (2004). Asthma and depressive and anxiety disorders among young persons in the community. *Psychological Medicine*, *34*, 1465–1474. doi:10.1017/S0033291704002739
- Hankin, B. L., Abramson, L. Y., Moffitt, T. E., Silva, P. A., McGee, R., & Angell, K. E. (1998). Development of depression from preadolescence to young adulthood:

- Emerging gender differences in a 10-year longitudinal study. *Journal of Abnormal Psychology*, *107*, 128–140. doi:10.1037/0021-843X.107.1.128
- Hart, B. L. (1988). Biological basis of the behavior of sick animals. *Neuroscience & Biobehavioral Reviews*, *12*, 123–137. doi:10.1016/S0149-7634(88)80004-6
- Holm, S. (1979). A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics*, *6*, 65–70.
- 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*, 171–186. doi:10.1097/PSY.0b013e3181907c1b
- Huang, C., & Dong, N. (2014). Dimensionality of the Children's Depression Inventory: Meta-analysis of pattern matrices. *Journal of Child and Family Studies*, *23*, 1182–1192. doi:10.1007/s10826-013-9779-1
- Janeway, C. A., Jr. (2013). Pillars article: Approaching the asymptote? Evolution and revolution in immunology. *Journal of Immunology*, *191*(9), 4475–4487. (Reprinted from *Cold Spring Harbor Symposia on Quantitative Biology*, *54*, 1–13, 1989)
- 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*, 1121–1128. doi:10.1001/jamapsychiatry.2014.1332
- Klein, D., Dougherty, L. R., & Olino, T. M. (2005). Toward guidelines for evidence-based assessment of depression in children and adolescents. *Journal of Clinical Child & Adolescent Psychology*, *34*, 412, 432. doi:10.1207/s15374424jccp3403
- Kovacs, M. (1985). The Children's Depression Inventory (CDI). *Psychopharmacology Bulletin*, *21*, 995–998.
- Krishnadas, R., & Harrison, N. A. (2016). Depression phenotype, inflammation, and the brain: Implications for future research. *Psychosomatic Medicine*, *78*, 384–388. doi:10.1097/PSY.0000000000000339
- Kuhlman, K. R., Robles, T. F., Dooley, L. N., Boyle, C. C., Haydon, M. D., & Bower, J. E. (2018). Within-subject associations between inflammation and features of depression: Using the flu vaccine as a mild inflammatory stimulus. *Brain Behavior and Immunity*, *69*, 540–547. doi:10.1016/j.bbi.2018.02.001
- Kuznetsova, A., Brockhoff, P., & Christensen, R. H. B. (2017). lmerTest package: Tests in linear mixed effects models. *Journal of Statistical Software*, *82*(13), 1–26. doi:10.18637/jss.v082.i13.
- Mac Giollabhui, N., Swistun, D., Murray, S., Moriarity, D., Kautz, M., Ellman, L., . . . Alloy, L. (2020). Executive dysfunction in depression in adolescence: The role of inflammation and higher body mass. *Psychological Medicine*, *50*, 683–691.
- Malarkey, W. B., Jarjoura, D., & Klatt, M. (2013). Workplace based mindfulness practice and inflammation: A randomized trial. *Brain, Behavior, and Immunity*, *27*, 145–154. doi:10.1016/j.bbi.2012.10.009
- Meyer, T., Stanske, B., Kochen, M. M., Cordes, A., Yuksel, I., Wachter, R., . . . Herrmann-Lingen, C. (2011). Serum levels of interleukin-6 and interleukin-10 in relation to depression scores in patients with cardiovascular risk factors. *Behavioral Medicine*, *37*, 105–112. doi:10.1080/08964289.2011.609192
- 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. doi:10.1016/j.biopsych.2008.11.029
- Miller, G. E., Cohen, S., & Ritchey, A. K. (2002). Chronic psychological stress and the regulation of pro-inflammatory cytokines: A glucocorticoid-resistance model. *Health Psychology*, *21*, 531–541. doi:10.1037//0278-6133.21.6.531
- Miller, G. E., & Cole, S. W. (2012). Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. *Biological Psychiatry*, *72*, 34–40. doi:10.1016/j.biopsych.2012.02.034.
- Mills, N. T., Scott, J. G., Wray, N. R., Cohen-Woods, S., & Baune, B. T. (2013). Research review: The role of cytokines in depression in adolescents: A systematic review. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *54*, 816–835. doi:10.1111/jcpp.12080
- Moriarity, D. P., Mac Giollabhui, N., Ellman, L. M., Klugman, J., Coe, C. L., Abramson, L. Y., & Alloy, L. B. (2019). Inflammatory proteins predict change in depressive symptoms in male and female adolescents. *Clinical Psychological Science*, *7*, 754–767. doi:10.1177/2167702619826586
- Ohayon, M. M., & Schatzberg, A. F. (2003). Using chronic pain to predict depressive morbidity in the general population. *Archives of General Psychiatry*, *60*, 39–47. doi:10.1001/archpsyc.60.1.39
- Pan, A., Keum, N., Okereke, O. I., Sun, Q., Kivimaki, M., Rubin, R. R., & Hu, F. B. (2012). Bidirectional association between depression and metabolic syndrome: A systematic review and meta-analysis of epidemiological studies. *Diabetes Care*, *35*, 1171–1180. doi:10.2337/dc11-2055
- Preiss, K., Brennan, L., & Clarke, D. (2013). A systematic review of variables associated with the relationship between obesity and depression. *Obesity Reviews*, *14*, 906–918. doi:10.1111/obr.12052
- Raison, C. L., Rutherford, R. E., Woolwine, B. J., Shuo, C., Schettler, P., Drake, D. F., . . . Miller, A. H. (2013). A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression. *JAMA Psychiatry*, *70*, 31–41. doi:10.1001/2013.jamapsychiatry.4
- R Core Team. (2018). *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing.
- Rights, J. D., & Sterba, S. K. (2019). Quantifying explained variance in multilevel models: An integrative framework for defining R-squared measures. *Psychology Methods*, *24*, 309–338.
- Rosenkranz, M. A., Davidson, R. J., MacCoon, D. G., Sheridan, J. F., Kalin, N. H., & Lutz, A. (2013). A comparison of mindfulness-based stress reduction and an active control in modulation of neurogenic inflammation. *Brain*,

- Behavior, and Immunity*, 27, 174–184. doi:10.1016/j.bbi.2012.10.013
- Skovlund, C., Morch, L., Kessing, L., & Lidegaard, O. (2016). Association of hormonal contraception with depression. *JAMA Psychiatry*, 73, 1154–1162. doi:10.1001/jamapsychiatry.2016.2387
- 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, 936–944. doi:10.1016/j.bbi.2009.04.011
- Team, R. C. (2013). *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing.
- van Lang, N. D. J., Ferdinand, R. F., & Verhulst, F. C. (2007). Predictors of future depression in early and late adolescence. *Journal of Affective Disorders*, 97, 137–144. doi:10.1016/j.jad.2006.06.007
- Wasserstein, R. L., & Lazar, N. A. (2016). The ASA Statement on p-Values: Context, process, and purpose. *The American Statistician*, 70(2), 129–133. doi:10.1080/00031305.2016.1154108
- Watkins, L. R., & Maier, S. F. (1999). Implications of immune-to-brain communication for sickness and pain. *Proceedings of the National Academy of Sciences, USA*, 96, 7710–7713. doi:10.1073/pnas.96.14.7710
- Weiner, J. (2015). riverplot: Sankey or ribbon Plots (Version 0.5) [Computer software]. Retrieved from <https://cran.r-project.org/package=riverplot>
- Whooley, M. A. (2006). Depression and cardiovascular disease healing the broken-hearted. *JAMA*, 295, 2874–2881.
- Zalli, A., Jovanova, O., Hoogendijk, W. J. G., Tiemeier, H., & Carvalho, L. A. (2016). Low-grade inflammation predicts persistence of depressive symptoms. *Psychopharmacology*, 233, 1669–1678. doi:10.1007/s00213-015-3919-9