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Increased Inflammation Predicts Nine-Year Change in Major Depressive Disorder Diagnostic Status

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Cytokine theory of depression proposes that increased baseline inflammatory activity may accumulate over time and lead to future major depressive disorder (MDD). However, most research conducted on this topic has been cross-sectional and examined between- (vs. within-) persons and symptom severity (vs. diagnosis). Therefore, we tested if elevated inflammatory activity at Time 1 (T1) would predict future within-person 9-year change in MDD diagnosis. Community-dwelling adults (n = 945) participated in the Midlife Development in the United States (MIDUS) study. T1 and Time 2 (T2) MDD status was assessed using the Composite International Diagnostic Interview–Short Form, and markers of inflammatory activity at T1 were measured (e.g., levels of serum interleukin-6 [IL-6], C-reactive protein [CRP], fibrinogen). Latent change score modeling was conducted. Higher T1 IL-6, CRP, and fibrinogen levels of inflammatory activity predicted T1–T2 development/relapse of MDD within persons. This effect occurred more strongly among women (vs. men; d = .149 vs. .042), younger (vs. older) adults (d = .137 vs. .119), persons with more (vs. less) chronic health issues (d = .133 vs. .065), low- (vs. middle- or high-) income earners (d = .161 vs. .050), and persons with more (vs. less) frequent childhood trauma (d = .156 vs. .017). Findings aligned with expanded cytokine theories, which posit that the impact of increased T1 inflammatory activity on future change in MDD status will be larger for subgroups vulnerable to increased stress exposure. Cognitive–behavioral or pharmacological approaches to reduce markers of inflammatory activity may prevent development/relapse of MDD.

General Scientific Summary

Increased C-reactive protein (CRP), fibrinogen, and interleukin-6 (IL-6) levels predicted 9-year major depressive disorder (MDD) diagnostic status change more strongly in younger than older adults, women but not men, those with low (vs. high) income, as well as persons with high (vs. low) childhood trauma frequency and number of chronic illnesses. Findings aligned with expanded cytokine theories (e.g., social signal transduction theory of depression), which posit that markers of inflammatory activity predict future change in MDD status especially for populations vulnerable to heightened, chronic, and long-term exposure to environmental stressors. Continued efforts to empirically test expanded cytokine theories of depression may improve delineation of patterns of health disparities and facilitate effective measures to prevent the onset or recurrence of MDD.

Keywords: major depressive disorder, inflammation, latent change, etiology

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Major depressive disorder (MDD) is a common psychiatric disorder observed in the general population characterized by symptoms such as depressed mood, sleep disturbance, fatigue, difficulty concentrating, low self-worth, and suicidality (Kessler & Wang, 2008). MDD can incur large costs to individuals and societies, as it has been linked consistently to reduced quality of life, relationship satisfaction, job performance, and personal monthly income (Beutel et al., 2010; Dismuke & Egede, 2010; Jacobson & Newman, 2016; Kessler et al., 2008), as well as persistent health problems. Myriad health issues include autoimmune, cardiovascular, endocrine, and neurocognitive disease (Bialek et al., 2019; Butnoriene et al., 2015; Zainal & Newman, 2021a, 2021b). Consequently, MDD creates a large economic burden to healthcare systems and governments globally (e.g., accounting for 62% of total annual health care costs in Europe; DiLuca & Olesen, 2014). Therefore, understanding risk factors for MDD is important.

One such risk factor may be increased inflammatory activity. The *cytokine theory of depression* (Miller et al., 2009, 2013) posits that excessive peripheral bloodstream levels of markers of inflammatory activity may be actively transported to the brain and persistently interact with neurotransmitter metabolism, hormonal function, and neuroplasticity. Increased cytokines have been shown to trigger the secretion and buildup of corticotropin-releasing hormones, adrenocorticotropic hormones, and cortisol in the hypothalamic-pituitary-adrenal (HPA) axis. This is a feature reliably observed in persons with elevated MDD symptoms across multiple time points (e.g., Milrad et al., 2018; Pariante & Miller, 2001). Also, the theory posits that chronic or excessive activation of cytokine networks in the central nervous system may lead to altered glutamatergic, serotonergic, or dopaminergic activation, apoptosis, and oxidative stress in pertinent cell forms (e.g., oligodendrocytes, astrocytes) over time (Haroon & Miller, 2017; Miller & Raison, 2016; Shelton et al., 2011; Treadway et al., 2019). Peripheral cytokines might also compromise immunity, growth, and development of nerve tissue (Kim et al., 2016; Rajkowska & Miguel-Hidalgo, 2007). Additionally, it is thought that increased inflammatory activity can predict future MDD via abnormalities of reciprocal actions between glia or neurotransmitters and brain regions that regulate mood or cognitive functioning (e.g., hippocampus, prefrontal cortex, ventral striatum, dorsolateral anterior cingulate cortex; Páv et al., 2008; Tilleux & Hermans, 2007). Collectively, cytokine theory posits that increased inflammatory activity can predict future MDD.

Myriad markers of inflammatory activity form part of our highly complex immune system. These include interferons (IFN), interleukin-6 (IL-6), IL-8, IL-1β, C-reactive protein (CRP), and tumor necrosis factor (Beurel et al., 2020). There are also many possible biomarkers implicated in the etiology/relapse of MDD. Included among them are excessive levels of baseline IL-6, CRP, and/or fibrinogen (Chu et al., 2019; de la Torre-Luque et al., 2019; Eswarappa et al., 2019; Fancourt & Steptoe, 2020; Gimeno et al., 2009; Hamer et al., 2009; Kang et al., 2016; Khandaker et al., 2014; Lamers et al., 2019; Smith et al., 2018; Valkanova et al., 2013; Wium-Andersen et al., 2013; Zalli et al., 2016). Thus, our study examined these three biomarkers.

The proinflammatory cytokine IL-6 strongly catalyzes the creation and secretion of related markers of inflammatory activity such as acute phase protein, C-reactive protein (CRP), and coagulation protein fibrinogen (Heinrich et al., 1990). Fibrinogen and CRP are acute phase proteins (Ridker, 2016) that the liver releases upon increase in IL-6 levels. IL-6 is secreted by activated T cells and macrophages as well as nonimmune cells (e.g., adipose, osteoblastic cells, smooth muscle) and monocytes (Rose-John, 2018). Excessive levels of IL-6 have been implicated in the etiology of MDD through chronic alterations to the HPA or neurotransmitter metabolism (Ting et al., 2020). CRP mainly functions to unite with phospholipid species of pathogens or injured cells to trigger the complement system. As tissue impairments could have diverse causes, increased high-sensitivity CRP indicates a general inflammatory response as opposed to being ascribed to a specific cause (Macleod & Avery, 1941). Excessive CRP may predict future MDD by activation of the enzyme indoleamine-2,3-dioxygenase (IDO) which could thereby raise production of quinolinic and kynurenic acids and reduce creation of serotonin (Capuron & Miller, 2011). In addition, fibrinogen performs a coagulation function as an antecedent of fibrin and contributes to platelet aggregation in response to tissue and vascular injury (Koenig, 2003). During chronic inflammation, the liver synthesizes excessive quantities of fibrinogen (Herrick et al., 1999). Fibrinogen thus might play a role in the development of MDD by adversely affecting cardiovascular systems (Duivis et al., 2011).

Abundant data buttress both the short-term and long-term effects posited by the cytokine theory of depression. Meta-analytic evidence combined across more than 30 cross-sectional studies found that greater depression severity was consistently and independently associated with increased bloodstream levels of IL-6, CRP, fibrinogen, or related biomarkers (e.g., TNF; Dowlati et al., 2010; Haapakoski et al., 2015; Hiles et al., 2012). However, such cross-sectional data does not establish the temporal precedence of increased markers of inflammatory activity as a risk factor (Höfler, 2005). Prospective studies are thus required to clarify if and how inflammatory activity precedes and predicts future MDD symptoms or diagnosis.

Thus far, 18 empirical studies have tested if baseline levels of IL-6, CRP, or fibrinogen were linked to future heightened depression or related constructs across many years. Excessive IL-6, CRP, or fibrinogen at baseline predicted elevated depression severity, persistence, or reduced well-being and physical activity 4 to 12 years later in community-dwelling British children, adolescents, young-to-middle-aged adults (Chu et al., 2019; de la Torre-Luque et al., 2019; Fancourt & Steptoe, 2020; Hamer et al., 2009; Khandaker et al., 2014; Zalli et al., 2016), and civil servants (Gimeno et al., 2009). Likewise, greater initial levels of IL-6 were related to MDD diagnostic status and chronicity across 1 to 10 years among nonstatin-medicated stroke patients in South Korea (Kang et al., 2016) and community-dwelling adults in the Netherlands (Lamers et al., 2019) and Spain (de la Torre-Luque et al., 2019). Correspondingly, higher CRP level predicted greater psychological distress, depression symptoms, and risk for hospitalization with depression 4 to 12 years later in young (18–40 years), middle-aged (41–64 years), and older adults (65 years and older) in Denmark (Wium-Andersen et al., 2013). Moreover, increased fibrinogen, CRP, and erythrocyte sedimentation rate were associated with higher 4-year depression and posttraumatic stress disorder symptoms in U.S. veterans (Eswarappa et al., 2019). In a similar vein, meta-analytic data pooled across seven prospective studies in older adults showed that increased IL-6 and CRP predicted higher future depression severity over 2 to 6 years (Smith et al., 2018). Overall, the data suggest that higher levels of IL-6, CRP, and fibrinogen may precede and predict long-term change in future MDD diagnostic status.

Building on cytokine theory, the *social signal transduction theory of depression* (Slavich & Irwin, 2014) and its extension, the *social safety theory* (Slavich, 2020b), propose that the inflammation–future MDD connection is stronger among subgroups with heightened biopsychosocial vulnerabilities (Majd et al., 2020). Supporting this idea, increased inflammatory activity has been linked to elevated depression among more women than men (Köhler-Forsberg et al., 2017), and such a pattern has been attributed to hormonal, cognitive style, social, and lifestyle variations (e.g., less physical activity) (Derry et al., 2015; Slavich & Sacher, 2019). Further, it is possible that the inflammation–future MDD relation would be stronger for persons with more chronic health conditions (Patten et al., 2018). Moreover, it is plausible that inflammation would have a larger association with future MDD in persons with more (vs. less) frequent exposure to childhood abuse or neglect (Hostinar et al., 2015; Nusslock & Miller, 2016). Relatedly, based on these theories (Morozink et al., 2010; Slavich, 2020b), it stands to reason that increased inflammatory activity would forecast future MDD for lower- (vs. middle- or higher-) income earners afflicted with more financial, social, and related life stressors.

Thus, building on the aforesaid data and based on the cytokine theory of depression, this study aimed to determine if an increased latent factor composed of IL-6, CRP, and fibrinogen levels would be associated with future within-person 9-year change in MDD status in community-dwelling adults. By using structural equation modeling (SEM) with latent change score (LCS) approaches, we were able to expand on prior longitudinal between-person studies in several ways. First, LCS methods adjust for between-person, cross-sectional effects. In addition, they control for regression to the mean and minimize measurement error (Zainal & Newman, 2019). Moreover, LCS permitted us to examine within-person change in MDD status across 9 years. Further, this study adds to literature by examining the moderators of the within-person relation between increased inflammation and future change in MDD status. Most prior research on this topic used ordinary least squares regression (Eswarappa et al., 2019; Gimeno et al., 2009; Hamer et al., 2009; Kang et al., 2016; Khandaker et al., 2014; Smith et al., 2018; Wium-Andersen et al., 2013; Zalli et al., 2016). Doing so only informs between-person relations and does not account for clustering of repeated measures within persons across time (Grimm et al., 2011; Huang, 2018). Specifically, we aimed to test expanded cytokine theories of depression (e.g., Majd et al., 2020; Slavich, 2020b) and predicted that Time 1 (T1) inflammatory activity would positively predict 9-year T1–T2 (Time 2) change in MDD status for the entire sample (nonmoderated main effect hypothesis (Hypothesis 1; H1). We also hypothesized that the inflammation–future change in MDD status relation would be stronger among the following subgroups with more biopsychosocial vulnerabilities: older versus younger adults (H2); women versus men (H3); persons facing higher (vs. lower) number of chronic health conditions (H4); persons exposed to more (vs. less) frequent childhood maltreatment (H5); and lower- (versus middle- or higher-) income earners (H6).

Method

Participants

This was a secondary analysis of the publicly available Midlife Development in the United States (MIDUS) dataset (Ryff, Almeida, et al., 2019; Ryff, Seeman, et al., 2019; Ryff & Davidson, 2019). Participants (n = 945) were community-dwelling adults aged 54.33 years on average (SD = 11.06, range = 34–83). Females comprised 52.78% of the sample, 20.42% attained a college education, and 95.37% identified as White relative to African American, Asian, Pacific Islander, or other ethnicities.

Measures

The present study focused on participants who voluntarily consented to complete the in-person MDD diagnostic interview and biomarker data collection at T1 conducted in 2004; as well as another follow-up psychiatric diagnostic interview at T2 in 2013. Whereas the MDD diagnostic interview was carried out at T1 and T2, the biomarker data collection was performed only at T1.

T1 and T2 MDD Diagnostic Interview

The *Diagnostic and Statistical Manual of Mental Disorders–Third Edition–Revised* (*DSM–III–R*) consistent Composite International Diagnostic Interview–Short Form (CIDI-SF; American Psychiatric Association, 1987; Kessler et al., 1998; Wittchen, 1994) was used to assess MDD at T1 and T2. The CIDI-SF MDD module asked whether participants experienced depressed mood or anhedonia in the past 12 months, and associated symptoms of fatigue, appetite changes, sleep difficulties, trouble concentrating, worthlessness, and/or suicidal ideation. The instrument has strong sensitivity (.939) and specificity (.896) for MDD. It has also shown high internal consistency and good retest reliability for its continuous scale, and high concordance with the *DSM-Fourth Edition* (*DSM–IV*) clinical interview as a diagnostic measure (Kessler et al., 1998; Kessler & Üstün, 2004; Wang et al., 2000).

T1 Inflammatory Activity

Following overnight fasting, respondents offered biomarkers based on an established protocol (Love et al., 2010). The biomarker samples were frozen at −60° to −80 °C using dry ice and shipped to the MIDUS Biocore Laboratory, where they were stored at −65 °C for monthly batch evaluations to ensure consistency across laboratories involved in the data collection (Ryff, Seeman, et al., 2019). IL-6 was measured from participants' blood serum using the enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN; Friedman & Herd, 2010). CRP was assessed using a particle-enhanced immunonepholometric instrument (Dade Behring Inc., Deerfield, IL; Friedman & Herd, 2010). Likewise, the BNII nephelometer (N Antiserum to Human Fibrinogen) at the same laboratory (Dade Behring Inc., Deerfield, IL) was used to measure fibrinogen (Hostinar et al., 2017). In addition, a partially automated and adapted Claus method was used to examine blood serum on a BNII nephelometer (Clauss, 1957). The researchers computed all inflammation level values in duplicate; markers of inflammatory activity that were >10 pg/ml were reanalyzed and rerun in diluted sera to conform to the normal distribution (Love et al., 2010). For all of these markers of inflammatory activity, the coefficients of variance within- and between-laboratories fell within normal limits (<12%).

Potential Moderators

Participants reported on the following variables: age (in years), gender (male vs female), annual income (reported based on wages,

pension, or supplemental security income), body mass index (BMI; kg/m^2), frequency of exposure to childhood abuse or neglect, and number of chronic health conditions. The specific health problems assessed in the metric of total number of chronic health condition were as follows: past-year diseases or problems related to AIDS/HIV, alcohol/drug, asthma, backache, bladder, bones, constipation, diabetes, dry/sore skin, face rash, foot, gall bladder, gum/mouth, hair loss, hand rash, hay fever, hernia, hypertension, itch, lung, lupus, piles/hemorrhoids, migraine, neurological disorders, pimples, skin, sleep, stomach, stroke, swallowing, sweating, thyroid, tuberculosis, ulcer, varicose veins, warts). Also, frequency of childhood trauma was assessed using the 25-item Childhood Trauma Questionnaire (Bernstein & Fink, 1998) for which participants endorsed items on a 5-point Likert scale ranging from 1 = *never true* to 5 = *very often true* (possible total score range = 25–125).

Data Analyses

SEM analyses were conducted using the *lavaan R* package (Rosseel, 2012) with *RStudio* software (Version 1.3.959). We used practical fit indices, confirmatory fit index (CFI; Bentler, 1990) and root mean square error of approximation (RMSEA; Steiger, 1980), to assess model fit. Next, to examine T1–T2 change in MDD status (i.e., autoregressive self-feedback parameter), establish temporal precedence, and partition between- and within-person effects, we used LCS models (McArdle, 2011, 2009). As LCS models move closer toward causal inference by combining latent growth and cross-lagged panel SEM (Grimm & Ram, 2018), they could determine if increased T1 inflammatory activity predicted within-person 9-year T1–T2 change in MDD diagnosis status. Therefore, LCS measured true, within-person change of a variable of interest over two successive time-points while attenuating measurement error (Zainal & Newman, 2021c). The course of MDD is a function of its initial status and latent change score between two successive time-points. Equation 1 examines within-person change in MDD status:

$$\Delta D_{[T1-T2]} = \alpha_D * D_S + \beta_S * D_{[T1]} \quad (1)$$

where $\Delta D_{[T1\text{-}T2]}$ signifies the latent change in MDD status from T1 to T2, α_D indicates the between-person constant change parameter linked to the latent slope of MDD status, D_S, and β_S indicate the within-person self-feedback loop of MDD status (or T1 MDD status, $D_{[T1]}$, predicting its future change). Equation 1 denotes the dual LCS model, such that the between-person *constant change* parameter (α_D) and within-person proportional effect (β_S) models course of change in MDD status between two successive time-points. Equation 2 expands on Equation 1 by adding a *within-person level-to-change coupling parameter* (δ_D):

$$\Delta D_{[T1-T2]} = \alpha_D * D_S + \beta_S * D_{[T1]} + \delta_C * C_{[T1]} \quad (2)$$

The δ_C indicates the *within-person coupling effect* of latent inflammatory activity composite predicting T1–T2 change in MDD status. We obtained a latent T1 inflammatory activity index based on serum levels of IL-6, CRP, and fibrinogen using CFA, as this approach enhances power and reduces measurement error (Tomarken & Waller, 2005). Further, we presented unstandardized regression coefficients (βs) and standard errors (*SE*s) herein.

Following recommendations (Graham, 2005; Jacobson & Newman, 2014; Maslowsky et al., 2015), we also conducted a series of moderator analyses (H2–H6). Specifically, we assessed the degree to which LCS parameter estimates were moderated by below-median versus at- or above-median values of continuous variables (age, annual income, number of chronic health conditions, childhood trauma frequency; Iacobucci et al., 2015) and a categorical variable (women vs. men; i.e., we dichotomized continuous variables to allow for testing of group differences in model equivalence). Group differences were evaluated by constraining the factor loadings and regression coefficients to be equal across groups, and by inspecting any statistically significant change in the χ^2 fit index ($\Delta\chi^2$) between the fully constrained model (restrict all factor loadings and regression coefficients to be equal) and the freely estimated model (restrict all factor loadings to be equal but freely estimate all regression coefficients; Graham, 2005; Jacobson & Newman, 2014). Although covarying variables is common practice, we decided to examine moderator effects instead because covarying prevents detecting potential moderator influences (Majd et al., 2020).

In total, 1.91% of the data was missing. We managed the missing data using full information maximum likelihood as it uses all available information (vs. listwise deletion) and because the data was missing at random (Little's MCAR test: $\chi^2(24) = 28.73$, $p = .230$). Effect sizes were computed with the formula: Cohen's $d = t/\sqrt{(2(1-r)/N)}$, where $r = \sqrt{(t^2/(t^2+df))}$. Note that t is the t-statistic of the parameter estimate, N is the sample size, and df is the degrees of the error term (Dunlap et al., 1996; Dunst et al., 2004).

Results

Confirmatory Factor Analysis of Latent Inflammatory Activity Composite

Following an exploratory factor analysis of the six inflammatory markers in the current dataset, CFA supported the fit of a one-factor model for three markers of inflammatory activity IL-6, CRP, and fibrinogen ($\chi^2(df = 1) = .090$, $p = .762$, CFI = 1.000, RMSEA = .000). Moreover, the standardized factor loadings were statistically significant (all $p < .001$) and high for IL-6 (.612), CRP (.823), and fibrinogen (.579). Further, the mean (or intercepts; IL-6: .679; CRP: .312; fibrinogen: 5.792) and residual variances (IL-6: .626; CRP: .323; fibrinogen: .665; latent inflammatory activity composite: 1.000) were all statistically significant (all $p < .001$).[1]

Testing Nonmoderated Main Effect Hypothesis (H1)

Based on the pattern of fit indices, the model showed good fit ($\chi^2(df = 6) = 15.78$, $p = .015$, CFI = .974, RMSEA = .042, 95% CI [.017, .068]). Within persons, increased T1 latent inflammatory activity was significantly associated with future 9-year change in MDD status (β = .065, *SE* = .027, $p = .016$, $d = .159$). This effect

[1] An expanded explanation on how the biomarkers (IL-6, CRP, and fibrinogen) were selected using a series of EFA (Lim & Jahng, 2019; Lubbe, 2019; Matsunaga, 2010; Revelle, 2020; Rosellini & Brown, 2021; Watkins, 2005) and CFA was included in the online supplementary materials on pages 5 to 6.

of baseline inflammatory activity predicting future latent change in MDD status was significant even after adjusting for the self-feedback loop (β = -.711, *SE* = .054, $p < .001$, *d* = -.872) and other parameters in the LCS model. Collectively, the results were consistent with H1.

Testing Moderator Hypotheses (H2–H6)

Age emerged as a moderator, such that increased T1 inflammatory activity predicted change in T1–T2 MDD status significantly more strongly among younger (vs. older) adults ($\Delta\chi^2(4) = 8.795$, $p = .046$). Simple slope analyses showed that increased T1 inflammatory activity significantly predicted 9-year change in MDD status among adults below the median age of 45 years (β = .085, *SE* = .041, $p = .039$, *d* = .137). However, no relation was found between T1 inflammatory activity and T1–T2 change in MDD status for persons at or above age 45 (β = .063, *SE* = .035, $p = .073$, *d* = .119). Therefore, H2, which posited stronger effects in older as opposed to younger adults, was not supported. Table 1 displays the regression weights and factor loadings.[2]

Gender also presented as a moderator. Increased T1 inflammatory activity predicted 9-year change in MDD status more strongly in females than males ($\Delta\chi^2(4) = 14.996$, $p < .001$). Simple slope analyses revealed that T1 inflammatory activity predicted 9-year future change in MDD status in females (β = .082, *SE* = .037, $p = .024$, *d* = .149). However, no relation between T1 inflammatory activity and 9-year change in MDD status was found in males (β = .023, *SE* = .037, $p = .636$, *d* = .042). Thus, findings were consistent with H3 (see Table 2).

T1 inflammatory activity level predicted future change in MDD status considerably more strongly among persons with more (vs. fewer) chronic health conditions ($\Delta\chi^2(4) = 9.119$, $p = .050$). Simple slopes analyses showed that increased T1 inflammatory activity predicted 9-year future change in MDD status for persons with three or more chronic health conditions (β = .074, *SE* = .036, $p = .044$, *d* = .133). Conversely, for those with two or less chronic health conditions, increased T1 inflammatory activity did not predict latent 9-year change in MDD status (β = .043, *SE* = .044, $p = .324$, *d* = .065). Thus, the results were congruent with H4. Table 3 presents the regression weights and factor loadings for H4.

Also, analyses demonstrated income to be a moderator; increased T1 inflammatory activity predicted future 9-year change in MDD status substantially more strongly among lower- (vs. higher-) income earners ($\Delta\chi^2(4) = 34.659$, $p < .001$). Simple slopes analyses showed that elevated increased T1 inflammatory activity significantly predicted future 9-year change in MDD status in persons with an annual income below the median level of $38,750 (β = .096, *SE* = .039, $p = .015$, *d* = .161). However, increased T1 inflammatory activity was not related to 9-year latent change in MDD status in those earning annual income at or above the median level (β = .025, *SE* = .033, $p = .452$, *d* = .050). Therefore, the findings aligned with H5 (see Table 4).

Further, increased T1 inflammatory activity predicted subsequent change in MDD status significantly more strongly among persons with at or above median (vs. lower) CTQ score of 33 ($\Delta\chi^2(4) = 39.180$, $p < .001$). Simple slopes analyses showed that increased T1 inflammatory activity significantly predicted future 9-year change in MDD status for persons with at or above the median childhood trauma frequency (CTQ score of 33; β = .095, *SE* = .042, $p = .024$, *d* = .156). However, increased T1 inflammatory activity did not predict change in MDD status among persons with CTQ score below 33 (β = .012, *SE* = .028, $p = .989$, *d* = .017). Thus, the results were consonant with H6 (refer to Table 5).

Discussion

The present study offers an advance on inflammation–depression relations by examining if an elevated latent factor consisting of IL-6, CRP, and fibrinogen levels predicted future 9-year change in MDD status using LCS approaches and moderator analyses. Consistent with the cytokine theory of depression, increased inflammation activity predicted within-person 9-year change in MDD status, over and above T1 MDD status, its autoregressive self-feedback parameter, and between-person variance. Notably, findings were partially consistent with expanded cytokine theories of depression (e.g., social safety theory; Slavich, 2020b); increased T1 inflammatory activity predicted future 9-year change in MDD status considerably more strongly in younger (vs. older) adults (*d* = .137 vs. .119), females (vs. males; *d* = .149 vs. .042), persons with more (vs. less) chronic health issues (*d* = .133 vs. .065), lower- (vs. higher-) income earners (*d* = .161 vs. .050), and those exposed to more (vs. less) childhood trauma frequency (*d* = .156 vs. .017). Overall, this pattern of results concurs with and extends a meta-analysis of 11 prospective studies which showed that excessive IL-6 and CRP serum levels predicted future heightened depression, with small yet substantial effect sizes in diverse populations (*d* = .092–.138) (Valkanova et al., 2013). Further, our effect sizes for significant findings (*d* = .123–.163) were about 1.5 to 2 times the effect size (*d* = .07) reported by Lamers et al. (2019), who tested the effect of increased IL-6 and CRP levels on MDD diagnosis in adults across 2 to 6 years. They were also higher than the small but significant effect (*d* = .08) observed in the meta-analysis of cross-sectional studies by Howren et al. (2009). Potential accounts for these effects are discussed as follows.

Importantly, the results support expanded cytokine frameworks of depression (e.g., social signal transduction theory of depression; Slavich, 2020a) that thoroughly consider biopsychosocial vulnerabilities as moderators. The effect of increased inflammatory activity predicting 9-year change in MDD status was larger in women and younger adults. The gender difference is consistent with recent findings that increased CRP predicted subsequent depression severity more strongly in older adult women than men (Hiles et al., 2015; Niles et al., 2018). This pattern may be explained by ruminative tendencies in women as well as sex hormonal changes and

[2] Based on a reviewer comment, we were curious whether this effect was driven by a healthy older population and therefore, grouped participants into 10-year age cohort categories (see Table S1 in the online supplementary materials) and examined mean chronic health conditions. This led us to conclude that this counter-intuitive age moderator effect was likely driven by a particularly healthy group of persons above 80 years of age ($n = 6$) whose mean number of chronic health conditions were substantially lower than most other age groups at T2. Upon removing these six participants, the age moderator findings were no longer significant. The revised moderator analysis indicated that age did not moderate the effect of inflammatory activity level on 9-year MDD status change ($\Delta\chi^2(4) = 6.200$, $p = .185$). Higher inflammatory activity level was significantly related to 9-year MDD status change in both younger adults (β = 0.073, *SE* = 0.027, $p = .008$, *d* = 0.136) and older adults (β = 0.073, *SE* = 0.027, $p = .008$, *d* = 0.136).

Table 1
Age Moderating T1 Inflammatory Activity Predicting T1–T2 Change in MDD Status

Parameter estimates and fit indices	Younger	Older
	β (*SE*)	β (*SE*)
Factor loadings		
T1 Latent inflammatory activity		
T1 Log IL-6 level	0.482	0.591
T1 Log CRP level	0.833*** (0.234)	0.813*** (0.278)
T1 Log fibrinogen level	0.659*** (0.037)	0.504*** (0.040)
ΔMDD status	0.482	0.838
Regression slopes		
T1 MDD status → T1-T2 ΔMDD status	−0.467*** (0.101)	−0.833*** (0.071)
T1 Inflammatory activity → T1-T2 ΔMDD status	0.085* (0.041)	0.063 (0.035)
Model fit indices		
χ^2	43.396	
df	12	
p	<.001	
CFI	.940	
RMSEA	.075	

Note. β = unstandardized regression weight or standardized factor loading; T1 = time 1; T2 = time 2; Δ = change across T1 and T2; CFI = confirmatory factor index; CRP = C-reactive protein; IL-6 = interleukin-6; *df* = degrees of freedom; MDD = major depressive disorder; RMSEA = root mean square error of approximation; *SE* = standard error.
* $p < .05$. *** $p < .001$.

menopause-related biological processes that can build up chronic systemic inflammation (Abu-Taha et al., 2009; Moieni et al., 2015; Slavich & Sacher, 2019; Zoccola et al., 2014). Alternatively, given higher prevalence and variability of depressive symptoms in women than men (Salk et al., 2017), the null effect of inflammatory activity on MDD status change among men herein might be due to reduced variability in MDD severity and inflammation levels (as shown in Table S2 in the online supplemental materials).

Regarding age, the stronger effect in younger (vs. older) adults is counterintuitive because older adults accrue higher levels of inflammation in the bloodstream and face greater risk of chronic illnesses (Chung et al., 2011). However, this finding appears to be due to the unusually healthy above 80 participants in the present study who showed relatively lower levels of number of chronic health conditions at T2 compared to most other age groups. Note that the age moderator analyses were no longer significant after removing these six older adults with outlying data from the analysis. In addition, the counterintuitive age moderator result might be due to the fact that age was significantly negatively correlated with childhood trauma frequency ($r = -.123$; as reflected in Table S3 in the online supplemental materials). Furthermore there was reduced variability of inflammation levels among older (vs. younger) adults (as reflected in Table S4 in the online supplemental materials). Future empirical work can test these ideas and determine the degree to which this pattern of findings is replicated.

Apart from demographic moderators, why was the effect of inflammatory activity on future 9-year change in MDD larger in persons with heightened frequency of childhood trauma exposure and number of chronic health conditions as well as persons with below-median income? Perhaps increased inflammatory activity over time raised hippocampal and amygdala dopaminergic activity that was instrumental in triggering fear conditioning, fear reactivity, and traumatic recall, particularly for those with more (vs. less) childhood trauma. This notion is consistent with the social signal transduction theory of depression (Slavich, 2020a) and abundant data (Gill et al., 2010; Yang & Jiang, 2020), and future studies could test such a hypothesis. Relatedly, based on theory, those with elevated chronic health conditions and increased inflammatory activity could be at risk for MDD due to illness-related constraints. Such constraints might reduce the capacity to engage in pleasure-enhancing valued activities or to execute skills that confer a sense of agency over life situations. On that note, evidence has shown that increased levels of IL-6, CRP, and fibrinogen could persistently induce a set of illness behaviors, such as deficits in motivation, suboptimal diet and nutrition, and poor sleep quality, similar to MDD (Dantzer et al., 2008). Multiwave studies could empirically test the conjecture that increased inflammatory activity and chronic health problems predict future MDD via suboptimal lifestyle choices. Also, consistent with the social signal transduction theory of depression, persons with below-median income and elevated inflammation displayed higher odds of developing future MDD plausibly due to persistent environmental stressors (e.g., limited access to quality health care and social services, substandard housing conditions). This idea aligns with ample evidence that chronic poverty exposure was related to dysregulated metabolism and immune response as well as wear and tear of physiological stress modulatory systems and mood regulation and executive functioning-linked brain regions across long periods (cf., review by Kim et al., 2018). It is also consistent with recent evidence that lower family income predicted higher pre–post social stressor task-induced increase in IL-6 (Quinn et al., 2020). Health disparity researchers can continue to replicate and empirically examine these ideas.

With respect to the nonmoderated main effect finding, why did increased IL-6, CRP, and fibrinogen predict within-person 9-year

Table 2
Gender Moderating T1 Inflammatory Activity Predicting T1–T2 Change in MDD Status

Parameter estimates and fit indices	Male	Female
	β (*SE*)	β (*SE*)
Factor loadings		
T1 Latent inflammatory activity		
T1 Log IL-6 level	0.585	0.644
T1 Log CRP level	0.812*** (0.298)	0.792*** (0.193)
T1 Log fibrinogen level	0.598*** (0.051)	0.567*** (0.029)
ΔMDD status	0.900	0.523
Regression slopes		
T1 MDD status → T1–T2 ΔMDD status	−0.896*** (0.062)	−0.513*** (0.097)
T1 Inflammatory activity → T1–T2 ΔMDD status	0.023 (0.037)	0.082* (0.037)
Model fit indices		
χ^2	49.518	
df	12	
p	< .001	
CFI	.923	
RMSEA	.082	

Note. β = unstandardized regression weight or standardized factor loading; T1 = time 1; T2 = time 2; Δ = change across T1 and T2; CFI = confirmatory factor index; CRP = C-reactive protein; IL-6 = interleukin-6; *df* = degrees of freedom; MDD = major depressive disorder; RMSEA = root mean square error of approximation; *SE* = standard error.
* $p < .05$. *** $p < .001$.

Table 3
Number of Chronic Health Conditions Moderating T1 Inflammatory Activity Predicting T1–T2 Change in MDD Status

Parameter estimates and fit indices	0 to 2 conditions	3 or more
	β (*SE*)	β (*SE*)
Factor loadings		
T1 Latent inflammatory activity		
T1 Log IL-6 level	0.584	0.610
T1 Log CRP level	0.867*** (0.347)	0.790*** (0.219)
T1 Log fibrinogen level	0.542*** (0.043)	0.598*** (0.038)
ΔMDD status	0.877	0.527
Regression slopes		
T1 MDD status → T1–T2 ΔMDD status	−0.882*** (0.068)	−0.567*** (0.085)
T1 Inflammatory activity → T1–T2 ΔMDD status	0.043 (0.044)	0.074* (0.036)
Model fit indices		
χ^2	54.363	
df	12	
p	< .001	
CFI	.908	
RMSEA	.087	

Note. β = unstandardized regression weight or standardized factor loading; T1 = time 1; T2 = time 2; Δ = change across T1 and T2; CFI = confirmatory factor index; CRP = C-reactive protein; IL-6 = interleukin-6; *df* = degrees of freedom; MDD = major depressive disorder; RMSEA = root mean square error of approximation; *SE* = standard error.
* $p < .05$. *** $p < .001$.

change in MDD status? Plausibly, based on cytokine theory, buildup of threat appraisal-induced peripheral markers of inflammatory activity may have been transported to the brain (Ramirez et al., 2017), and affected myeloid (Wohleb et al., 2015) and basal ganglia (Miller, 2009) cells in ways that heightened MDD symptoms (e.g., anhedonia, psychomotor slowing, social withdrawal) in the long term. For instance, these markers of inflammatory activity could stimulate transmission of activated immune cells (e.g., monocytes) to the brain parenchyma and vasculature and impacted brain function over time (Wohleb et al., 2013). Empirical data suggests that other mechanisms might include the upregulation of amygdala-related negativity bias or threat hypervigilance in the long run (Inagaki et al., 2012). Simultaneously, these markers of inflammatory activity could have down-regulated basal ganglia, nucleus accumbens, ventral striatum, or other reward responses-linked brain activity (Eisenberger et al., 2010, 2017; Inagaki et al., 2015). It might also weaken functional connectivity among those regions across protracted time scales (Felger et al., 2016). Because high threat and low reward have been shown to be risk factors for depression (Nielson et al., 2021; Paulus & Yu, 2012; Rackoff & Newman, 2020), increased inflammatory activity might lead to depression via these factors. Additionally, based on literature, these markers might have crossed through leaky areas of the blood–brain barrier (e.g., circumventricular organs, choroid plexus) and merged with saturable transport molecules on the blood–brain barrier (Quan & Banks, 2007). Also, markers of inflammatory activity could have attached to peripheral afferent nerve fibers (e.g., vagus nerve) that thereby stimulated upward catecholaminergic brain fibers, and/or were reconverted into primary cytokine signals (D'Mello et al., 2009). Upcoming neuroimaging and animal studies can continue to shed light on the strength of evidence for these propositions.

This study has a number of limitations. Relations between MDD and inflammation have been found to be bidirectional and intricate (Dowlati et al., 2010). However, given that markers of inflammatory activity were measured only at baseline, we could not investigate such bidirectionality. Further, inflammation is a complex process and only a few biomarkers were analyzed among a possible wide array of biomarkers to which the cytokine theory of depression could apply. Furthermore, the immune measurement approaches within the MIDUS dataset we used are dated and it is possible that additional recent methods would also lead to similar long-term effects. Additionally, the naturalistic prospective dataset of the current study precludes strong causal inferences. Moreover, the pattern of results may be explained by unmeasured third variables (e.g., genetics; Gustavson et al., 2019) that deserve attention. In addition, future studies should evaluate if the results would be replicated with the use of *DSM–5* compared to the *DSM–III–R*-consistent measures used herein. Relatedly, the self-report measure of childhood trauma frequency in adulthood might be subject to retrospective recall biases. Also, future research should recruit culturally and socioeconomically diverse samples to increase generalizability of study findings. Limitations notwithstanding, study strengths include the well-powered sample size, use of an advanced data analytic technique, and inclusion of moderation analyses to understand complex interactions.

If the pattern of findings is replicated, some clinical implications merit consideration. Reducing levels of IL-6, CRP, and fibrinogen may successfully prevent the development or recurrence of future MDD. This may be achieved through alterations in diet and nutrition (e.g., N-acetyl-d-cysteine, omega-3 supplementation) and lifestyle (e.g., mindfulness meditation, cognitive–behavioral strategies, yoga, exercise; Dutcher et al., 2021; Felger, 2019; Taylor et al., 2009;

Table 4
Income Moderating T1 Inflammatory Activity Predicting T1–T2 Change in MDD Status

Parameter estimates and fit indices	Low income	≥ Median income
	β (*SE*)	β (*SE*)
Factor loadings		
T1 Latent inflammatory activity		
T1 Log IL-6 level	1.000	0.577
T1 Log CRP level	0.638*** (0.235)	0.820*** (0.265)
T1 Log fibrinogen level	0.801*** (0.036)	0.546*** (0.043)
ΔMDD status	0.514	0.905
Regression slopes		
T1 MDD status → T1–T2 ΔMDD status	−0.502*** (0.098)	−0.901*** (0.060)
T1 Inflammatory activity → T1–T2 ΔMDD status	0.096* (0.039)	0.025 (0.033)
Model fit indices		
χ^2	23.466	
df	12	
p	.024	
CFI	.976	
RMSEA	.045	

Note. β = unstandardized regression weight or standardized factor loading; T1 = Time 1; T2 = Time 2; Δ = change across T1 and T2; CFI = confirmatory factor index; CRP = C-reactive protein; IL-6 = interleukin-6; *df* = degrees of freedom; MDD = major depressive disorder; RMSEA = root mean square error of approximation; *SE* = standard error.
* $p < .05$. *** $p < .001$.

Table 5
Childhood Trauma Frequency Moderating T1 Inflammatory Activity Predicting T1–T2 Change in MDD Status

Parameter estimates and fit indices	Low trauma	High trauma
	β (*SE*)	β (*SE*)
Factor loadings		
T1 Latent inflammatory activity		
T1 Log IL-6 level	0.589	0.625
T1 Log CRP level	0.843*** (0.300)	0.797*** (0.217)
T1 Log fibrinogen level	0.508*** (0.036)	0.645*** (0.043)
ΔMDD status	1.902	1.620
Regression slopes		
T1 MDD status → T1–T2 ΔMDD status	−1.921*** (0.198)	−1.275*** (0.146)
T1 Inflammatory activity → T1–T2 ΔMDD status	0.012 (0.047)	0.110* (0.047)
Model fit indices		
χ^2	21.112	
df	11	
p	.032	
CFI	.979	
RMSEA	.045	

Note. β = unstandardized regression weight or standardized factor loading; T1 = Time 1; T2 = Time 2; Δ = change across T1 and T2; CFI = confirmatory factor index; CRP = C-reactive protein; IL-6 = interleukin-6; *df* = degrees of freedom; MDD = major depressive disorder; RMSEA = root mean square error of approximation; *SE* = standard error.
* $p < .05$. *** $p < .001$.

Tolkien et al., 2019). Further, tailoring treatment based on inflammation profiles may be beneficial as elevated markers of inflammatory activity can impede optimal psychopharmacological treatment response (Carvalho et al., 2013). Furthermore, the antidepressant properties of anti-inflammatory drugs may work best for people with heightened depression (Raison et al., 2013). Clinical science can profit from future research using randomized controlled trials or other appropriate study designs to clarify these topics as part of efforts to develop personalized treatments.

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