Biopsychosocial Science and Medicine Publish Ahead of Print
DOI:10.1097/PSY.0000000000001494

The Mediating Role of Daily Affect Dynamics in Bidirectional and Longitudinal Associations between Depressive Symptoms and Inflammation

Sun Ah Lee, MA[1], Jennifer E. Graham-Engeland, PhD[1,2], Soomi Lee, PhD[4], David M. Almeida, PhD[1,3]

Affiliations

[1] Center for Healthy Aging, The Pennsylvania State University, University Park, PA, USA

[2] Department of Biobehavioral Health, The Pennsylvania State University, University Park, PA, USA

[3] Department of Human Development and Family Studies, The Pennsylvania State University, University Park, PA, USA

[4] Department of Child and Family Studies, Yonsei University, Seoul, South Korea

Contact information

Sun Ah Lee: sbl5704@psu.edu, ORCID https://orcid.org/0000-0002-4237-7012
Jennifer E. Graham-Engeland: jeg32@psu.edu, ORCID https://orcid.org/0000-0002-9940-2856
Soomi Lee, smlee95@yonsei.ac.kr, ORCID https://orcid.org/0000-0002-7623-3770
David M. Almeida: dma18@psu.edu, ORCID https://orcid.org/0000-0002-5233-8148

Article Editor: Suzanne C. Segerstrom

Total Number of Tables: 1; Figures: 2; Supplemental Digital files: 1

Corresponding Author

Sun Ah Lee, sbl5704@psu.edu, (US) 814-777-3498,
422 Biobehavioral Health Building, 296 Henderson Drive, University Park, PA, 16802

Conflicts of Interest and Source of Funding

Publicly available data from the MIDUS study were used for this research. Since 1995, the MIDUS study has been funded by John D. and Catherine T. MacArthur Foundation Research Network and National Institute on Aging (P01-AG020166 and U19-AG051426). MIDUS Biomarker data collection was further supported by the National Institutes of Health (NIH) National Center for Advancing Translational Sciences Clinical and Translational Science Award program as follows: UL1TR001409 (Georgetown), UL1TR001881 (UCLA), UL1RR025011 (UW). Author SAL was supported by the National Institute on Aging under Grant T32AG049676 to The Pennsylvania State University. Outside of the current work, SL was supported by NIH grant R01HL163226 (PI: Lee) and JEG was supported by NIH grant P01AG003949. The authors declare no conflict of interest.

Transparency and Openness Promotion Standards

This study is a secondary analysis of publicly available dataset. De-identified data from this study are available in a public archive. The MIDUS study procedure and data documentation are publicly available at https://www.icpsr.umich.edu/web/ICPSR/series/203. The current study was not preregistered.

Abstract

Objectives. Extensive research has established relationships between depression and inflammation, yet greater attention is needed to elucidate mechanisms through which these processes unfold across multiple levels of analysis and time scales. This cohort panel study evaluated the role of daily affect dynamics in bidirectional and longitudinal associations between depressive symptoms and inflammation.

Methods. Using data from the second and third waves of the Midlife in the United States (MIDUS) study, the sample included 563 adults (M_{age} = 52.4; 57% female; 84% White). During the Biomarker Project, depressive symptoms were assessed at a single time point using the CESD-20, and the inflammatory markers were collected including CRP and four cytokines (IL-6, IL-8, TNFα, IL-10). During the Daily Diary Project, daily affect and stress were measured over eight consecutive days. Two affect dynamics indicators were specified: affective variability and reactivity to daily stressors. Multilevel structural equation models simultaneously tested autoregressive and cross-lagged associations between depressive symptoms and inflammation at the person-level, and day-level mediated paths involving daily affect dynamics.

Results. Results revealed that affective variability and reactivity mediated the autoregressive paths of depressive symptoms across two waves. Positive affective variability mediated the pathway from heightened baseline depressive symptoms to higher CRP levels at follow-up. Negative affective reactivity to daily stressors mediated the pathway from higher baseline CRP to subsequent depressive symptoms.

Conclusions. Findings suggest daily affective processes as potential mechanisms linking depressive symptoms and inflammation, underscoring the significance of promoting affective stability and adaptive stress responses in everyday life.

Keywords: Depression, depressed mood, inflammation, affect dynamics, multilevel structural equation modeling, daily diary

Introduction

Depression and inflammation are closely interconnected, with immune activation increasingly recognized as a core biological process implicated in major depressive disorder (MDD)[1-3]. A substantial body of evidence indicates that individuals with MDD exhibit heightened inflammatory activity, including elevated circulating levels of proinflammatory cytokines produced by innate immune cells (e.g., interleukin-1 [IL-1], IL-6, and tumor necrosis factor-alpha [TNF-α]), acute-phase proteins (e.g., C-reactive protein [CRP]), and other markers of inflammatory signaling[4-6]. Consistent with these findings, depression commonly co-occurs with autoimmune and other chronic conditions characterized by immune dysregulation, including cardiovascular diseases, diabetes, and cancer, further underscoring the relevance of inflammatory pathways to depressive symptomatology.

Several longitudinal studies demonstrated that the diagnosis of MDD or higher levels of depressive symptoms were associated with subsequent elevated levels of inflammatory markers[7-9]. Conversely, studies have found mixed evidence on the inflammation-to-depression link: some reported that elevated inflammatory markers were associated with heightened risk of MDD or higher subsequent depressive symptoms[10-12], whereas others did not[7]. However, the complexities of the reciprocal influence of depression and inflammation across varying time scales have not been fully considered.

In addition to the shared physiological etiologies of depression and inflammation, several factors have been explored as underlying mechanisms, including physical activity[13], sleep quality[14], obesity[15], and psychological and biological (e.g., salivary cortisol) measures of the stress response[16-18]. An underexplored yet plausible psychological mechanism may be dynamic characteristics of daily affective processes (i.e., daily affect dynamics). Affect dynamics capture

the state component of affectivity, the actual mood or emotion experienced by an individual at a certain point in time, addressing the inherent time-dynamic nature of affective experiences[19,20]. Using repeated assessments of affect over a shorter timeframe (i.e., intensive longitudinal data; ILD), affect dynamics capture the temporally varying characteristics of one's affective processes in daily life[21].

Process-based models of health highlight that accumulated daily affective experiences may exert enduring effects on health by disrupting physiological systems[22,23]. Similarly, the scar hypothesis posits that depression leaves lasting effects on health[24,25]. To test this possibility, we focused on two key features of daily affect dynamics—variability and reactivity to daily stressors—as potential pathways linking depression and inflammation. Affective variability refers to the average fluctuation of affect across time, reflecting the amount of affect changes occurring irrespective of when the change occurs[26]. Affective reactivity pertains to emotional responses that are elicited by a particular external event, such as a valenced stimulus or a specific daily event[27,28]. We examined both positive and negative affective variability and reactivity, given recent efforts highlighting the role of positive affect dynamics in health[29-31].

Depressive Symptoms and Affect Dynamics

Heightened depressive symptoms or MDD have been linked to altered dynamic characteristics of affect, in addition to lower levels of positive affect and higher levels of negative affect in daily life[19,32]. Studies with both clinical and non-clinical samples have consistently reported that depressed individuals exhibit heightened affective variability[32-35] and heightened affective reactivity to daily negative events[33,36].

Recent evidence suggests that these dynamic markers of affect also serve as significant precursors of depression. Affective variability seems to play a role in prospective depression

trajectories among depressed populations. For example, higher affective variability was associated with future MDD recurrence[32], more pronounced changes in symptoms post- and pre-treatment[37], and deleterious trajectories (i.e., an initial increase and return to higher depressive symptom levels)[38]. A meta-analysis revealed that higher negative and positive affective variability were associated with depression in the general population[26]. Furthermore, studies found that heightened positive and negative affective reactivity to daily stressors was associated with a greater risk for MDD 7-10 years later[39,40]. Recognizing the reciprocal links between depressive symptoms and affect dynamics, the current study examines both directions, testing whether affect dynamics mediate the autoregressive paths of depressive symptoms across time points.

Inflammation and Affect Dynamics

The link between inflammation and affect dynamics has been investigated within the context of physical health. Studies found that higher affective variability was associated with adverse physical health outcomes, such as a higher composite physical ill health score[41], a diagnosis of angina[42], and increased risk of mortality[43]. Recent studies have also revealed that higher affective variability can be associated with heightened inflammatory markers[44] and lower antibody titers to an influenza vaccine[45]. It is possible that large and repeated affective fluctuations are associated with chronic activation of the autonomic system, leading to higher systemic inflammation[46]. In keeping with this possibility, more pronounced affective reactivity to daily events was linked to increased levels of inflammatory markers[31] and heightened immune cell gene expression[29], along with greater mortality[47,48] and higher risk of reporting a chronic condition[49].

One notable yet empirically underexplored research question is the role of inflammation in daily affective well-being. The cytokine theory of depression[2] and the biopsychosocial model of emotion regulation[50,51] offer a theoretical basis for understanding how inflammation influences affective processes in daily life. These theoretical models suggest that elevated inflammation may impact mood and emotional regulation by disrupting neural regions and functions critical for emotion processing and regulation. This may lead to difficulties in employing adaptive emotion regulation strategies, resulting in increased sensitivity and reactivity to daily challenges. However, empirical studies provide mixed evidence; some found heightened levels of inflammatory markers were associated with maladaptive emotion regulation strategies (i.e., less use of cognitive reappraisal and greater use of expressive suppression)[52-55], whereas others showed the reverse associations[56]. Examining the effects of inflammation on daily affect dynamics could enrich current literature by highlighting the fluctuating nature of affective processes in everyday life.

Age and Gender Differences

Age and gender can serve as important factors underlying the associations among depressive symptoms, inflammation, and daily affect dynamics. With age, systemic inflammation seems to naturally increase at least in industrialized countries, contributing to a state of chronic low-grade inflammation[57,58]. Aging is also associated with changes in brain structure and function, including alterations in neural connectivity and reward-related regions, which may influence central nervous system sensitivity to inflammatory signaling[5]. Together, age-related changes in immune and neural processes have been proposed as mechanisms through which depressive symptoms and affective experiences may manifest differently across the lifespan and show distinct associations with inflammation[59]. In addition, depressive symptoms and affect

dynamics may contribute to higher inflammatory activity through behavioral and physiological pathways, potentially creating a bidirectional process in which sustained inflammation further exacerbates depressive symptoms and contributes to downstream health[60-62].

Gender differences additionally warrant attention, given evidence that men and women may differ in their inflammatory responses and their susceptibility to depression. Women are more likely to experience depressive symptoms[63], can show greater sensitivity to interpersonal stressors[64], and in some contexts exhibit heightened proinflammatory responses[65]. However, empirical evidence linking depression and inflammation has been mixed, varying by sample characteristics, study design, and whether basal or stimulated inflammatory markers are examined[66-68]. Despite these patterns, relatively few studies have explicitly examined age or gender as moderators of affect–inflammation linkages. Accordingly, the present study explored potential age- and gender-related differences in these mediating processes to better characterize individual differences in biopsychosocial pathways.

The Present Study

The goal of the present study was to examine the bidirectional longitudinal relationship between depressive symptoms and inflammation and the mediating role of daily affect dynamics in this relationship. This study leverages multiple time-scale longitudinal data, which incorporates the longitudinal panel data with daily diary data, capturing fluctuations and shifts in human behavior, psychological states, or physiological processes that manifest over distinct temporal intervals[69]. Guided by biopsychosocial frameworks[50], we conceptualized depressive symptoms and inflammation as components of a dynamic reciprocal system in which psychological and physiological processes influence one another across time. Our novel contribution is in identifying which specific aspects of daily affect dynamics (affective

variability vs. reactivity to daily stressors) and valence domains (positive vs. negative affect) serve as mechanisms linking these associations longitudinally. This suggests intervention implications, highlighting daily affective fluctuation or stress response as modifiable targets for interrupting the relationship between depressive symptoms and inflammation.

We examined two primary research aims. First, we examined whether there was a bidirectional and longitudinal relationship between depressive symptoms and inflammation by using a cross-lagged panel model. Second, we tested the mediating effects of daily affective variability and affective reactivity to daily stressors on this relationship. By employing multilevel structural equation modeling (MSEM), two research questions were simultaneously modeled including the following four indirect effects:

(1) depressive symptoms at Time 1 → affect variability/reactivity at Time 1 → affect variability/reactivity at Time 2 → depressive symptoms at Time 2,

(2) depressive symptoms at Time 1 → affect variability/reactivity at Time 1 → affect variability/reactivity at Time 2 → inflammation at Time 2,

(3) inflammation at Time 1 → affect variability/reactivity at Time 1 → affect variability/reactivity at Time 2 → inflammation at Time 2, and

(4) inflammation at Time 1 → affect variability/reactivity at Time 1 → affect variability/reactivity at Time 2 → depressive symptoms at Time 2.

As an exploratory analysis, we evaluated individual differences in these mediating effects, focusing on potential age (<50 years vs. ≥ 50 years) and gender differences.

Method

Data and Participants

The current study used publicly available data from the Midlife in the United States (MIDUS) study (https://www.icpsr.umich.edu/web/ICPSR/series/203), a national study investigating factors associated with health and well-being changes across the adult life span[70]. All procedures were approved by the Institutional Review Boards of the University of Wisconsin-Madison (IRB Protocol number: 2016-1051) and Pennsylvania State University (IRB Protocol number: PRAMS00042558).

MIDUS initially recruited 7,108 English-speaking adults in 1995-1996 (MIDUS 1), aged 25-74 years and from the continental U.S. using random digit dialing (RDD). Participants completed a baseline phone interview, followed by self-administered questionnaires sent by mail, with a response rate of 89%. In 2004-2005, a second wave of data collection (MIDUS II) included 4,963 of the original participants (response rate = 81%), with a 75% mortality-adjusted retention rate. To enhance minority representation in MIDUS 2, an additional sample (stratified by age, gender, and socioeconomic status) of 592 adults, primarily Black or African American participants, was recruited from Milwaukee County, WI, in 2005-2006 (response rate = 67.2%). The third wave of survey data (MIDUS III) was collected on a longitudinal sample of 3,294 participants in 2013-2014 (response rate = 83%) and on a longitudinal follow-up of Milwaukee sample (n = 389; response rate = 84.1%). The mortality-adjusted retention rate between MIDUS 2 and MIDUS 3 was 77% and that between the two waves of the Milwaukee sample was 78%.

The present study used a cohort design by using data from the second and third waves of the MIDUS study, including parent surveys and two sub-projects, the Daily Diary Project (the National Study of Daily Experiences [NSDE])[71] and the Biomarker Project. From the MIDUS parent survey participants (including Milwaukee samples) who completed the baseline interview and SAQs, the NSDE randomly selected a subsample of 2,022 participants from MIDUS 2 and

1,236 participants from MIDUS 3. NSDE participants completed daily telephone interviews across eight consecutive days about their daily experiences, including positive and negative affect and stressful events. Similarly, the Biomarker Project recruited a subsample of 1,255 from MIDUS 2 and 863 from MIDUS 3 parent surveys. Data collection for the Biomarker Project was carried out during an overnight stay at one of the three General Clinical Research Centers (CRUs) located in Madison, WI, Washington DC, or Los Angeles, CA. This collection included a wide range of biomarkers reflecting the functioning of various body systems (e.g., the immune system, cardiovascular system, and metabolic processes) as well as self-reported data including medication use and self-administered questionnaires regarding psychosocial well-being.

The final analytic sample included 563 adults who participated in either waves of the Daily Diary and Biomarker Projects, had no missing data on sociodemographic and health-related covariates, and provided at least one data point on depressive symptoms and inflammation. Missing data were addressed within the Bayesian estimation framework, which has parallels to maximum-likelihood-based approaches. For the affective reactivity models, the study sample was reduced to 472 adults with 3,383 observations, after excluding missingness in daily stressors in NSDE 2 and 3.

Measures

Daily variables from NSDE

Daily affect. Participants reported positive and negative affect during daily telephone interviews[72-74]. Positive affect was assessed with 13 items (feelings of being in good spirits, cheerful, extremely happy, calm and peaceful, satisfied, full of life, connected to others, having a sense of belonging, enthusiastic, attentive, active, proud, and confident), and negative affect was assessed with 14 items (feeling restless or fidgety, nervous, worthless, deeply sad, exhausted by

effort, hopeless, lonely, afraid, jittery, irritable, ashamed, upset, angry, and frustrated). Participants rated each item on a five-point scale from 0 (*none of the time*) to 4 (*all of the time*). Daily positive and negative affect were calculated by averaging scores of items. At Time 1 (i.e., NSDE 2), between-person reliability for daily negative affect was 0.92, and within-person reliability was 0.81. For daily positive affect, between-person reliability was 0.97, and within-person reliability was 0.85. At Time 2 (i.e., NSDE 3), between-person reliability for daily negative affect was 0.94, and within-person reliability was 0.81. For daily positive affect, between-person reliability was 0.97, and within-person reliability was 0.86[75].

Daily stressors. Daily stressors were assessed using the Daily Inventory of Stressful Events[76]. This inventory included seven questions asking if seven specific types of stressors had occurred in the past 24 hours (i.e., arguments, avoided arguments, work overloads, home overloads, discrimination, network stressors, and other stressors). Days when any of the seven stressors had occurred were coded as 1 (*stressor day*), and days without any stressors were coded as 0 (*non-stressor day*).

Depressive symptoms and inflammation from the Biomarker Project

Depressive symptoms. Depressive symptoms were assessed using the 20-item Center for Epidemiologic Studies Depression (CES-D) scale[77] as part of the Biomarker Project. The CES-D includes four subscales: depressed affect (7 items), positive affect (4 items), somatic complaints (7 items), and interpersonal problems (2 items). Participants rated the frequency of symptoms experienced during the past week on a 4-point scale ranging from 0 (“rarely or none of the time”) to 3 (“most or all of the time”). Four items for positive affect subscales were reverse-scored to represent that higher overall scores indicated greater depressive symptoms. The total depressive symptom score was calculated by summing responses across the 20 items, yielding a possible

range of 0 to 60. The internal reliability (Cronbach's alpha) was 0.90 at Time 1 and 0.88 at Time 2 in the current sample. To adjust the skewness of the distribution, the summed scores were log-transformed.

Inflammatory markers. For the current study, we used CRP, a broad marker of systemic inflammation, and a set of inflammatory cytokines (i.e., IL-6, IL-8, IL-10, and TNFα). On the second day of overnight stay at the CRUs, participants provided fasting blood samples before breakfast. Blood samples were stored at -60 to -80°C at each collection location until shipped to the MIDUS Biocore lab. Serum CRP (assay range: 0.014 - 216 pg/mL; inter-assay CV: 4.72-5.16%; intra-assay CV: 22.2-4.1%) was assessed using a particle enhanced immunonephelometric assay (BNII nephelometer, Dade Behring Inc., Deerfield, IL) utilizing a particle-enhanced immunonephelometric assay. Serum IL-6 (assay range: 0.156-10 pg/mL; inter-assay CV: 12.31%; intra-assay CV: 3.25%) was assayed using a commercially available high-sensitivity enzyme-linked immunosorbent assay (ELISA; Quantikine, R&D Systems, Minneapolis, MN). Serum IL-8 (assay range: 1.13-375 pg/mL; inter-assay CV: 6-7%; intra-assay CV: 2.88%), IL-10 (assay range: 0.68-233 pg/mL; inter-assay CV: 11-14%; intra-assay CV: 5.78%), and TNFα (assay range: 0.69-248 pg/mL; inter-assay CV: 7%; intra-assay CV: 3.19%) were assayed using a V-plex Custom Human Cytokine Kit (Meso Scale Diagnostics, Rockville, MD).

Pro-inflammatory cytokines (e.g., IL-6, IL-8, TNFα) and anti-inflammatory cytokines (e.g., IL-10) were positively correlated, with higher levels of these markers indicating a greater inflammatory load. In accordance with conceptual differences between CRP and cytokines[78-80], CRP was examined separately from inflammatory cytokines. Aggregated cytokine scores were used for the analyses with these markers using established methods[81-82]. This modeling approach

captures overlapping but distinct components of systemic inflammation: CRP primarily reflects downstream acute-phase activity, whereas circulating cytokines index immune signaling and regulatory processes. All inflammatory markers were log-transformed to adjust the skewness of distributions, and then winsorized to 3 standard deviations to adjust for the potential impact of outliers (< 2% of total observations; range: 0-11 observations). Z-scored cytokine levels across four inflammatory markers were averaged to calculate a composite cytokine score.

To further examine the structure of the inflammatory markers, we conducted exploratory factor analyses (EFA; see Table S3, Supplemental Digital Content, http://links.lww.com/PSYMED/B188). When all markers were included, a two-factor solution emerged with IL-6 and CRP clustering together and the remaining cytokines loading on a separate factor. However, when CRP was excluded, the cytokines formed a single-factor solution, supporting their aggregation. Notably, IL-6 loaded with the other cytokines in cytokine-only models but clustered with CRP when CRP was included, indicating that the factor structure was sensitive to model specification. This pattern is consistent with the role of IL-6 in both stimulating acute-phase responses and promoting cytokine signaling. Given this instability and the distinct biological role of CRP as a downstream marker of systemic inflammation, we treated CRP separately and used a composite score of the remaining cytokines. We also conducted sensitivity analyses examining individual cytokine markers separately to ensure that the observed findings were not driven by aggregation across cytokine markers.

Covariates

In keeping with recommendations informed by prior literature[14,83], sociodemographic variables, including age, gender (1=women, 0=men), education level (1=college graduate, 0=less than college graduate), race (1=White, 0=non-White), and household income (1=5th quintile,

0=less than 5th quintile) at Time 1, were included as person-level covariates. When predicting inflammation at Time 2, additional health-related variables at Time 2 from the Biomarker Project were included as covariates, which were body mass index (BMI), current smoking status (1=yes, 0=no), number of chronic health conditions, regular physical activity (1=engaging in regular exercise or activity of any type for 20 minutes or more at least 3 times/week; 0=no regular exercise) and medication uses for blood pressure (1=yes, 0=no) and controlling cholesterol (1=yes, 0=no). For affective reactivity models, when estimating random slopes of affective reactivity, a day-level variable that indicates whether an interview day was weekdays (vs. weekend) was included as a covariate.

Analytic Plan

We first estimated cross-lagged panel models (CLPM) to examine the direct, bidirectional associations between depressive symptoms and inflammation. In these models, cross-lagged paths indicate the extent to which the change in one construct can be predicted from the individual's prior deviation from the group mean on the other construct, whereas the autoregressive paths account for the stability of each construct across waves[84,85]. In the current analyses, we tested whether depressive symptoms predicted subsequent changes in inflammation (and vice versa) while controlling for the stability of both depressive symptoms and inflammation over time.

Then we utilized multilevel structural equation modeling (MSEM) to examine the mediating role of affective variability and affective reactivity to daily stressors. MSEM incorporates the features of multilevel modeling and structural equation modeling, enabling a multivariate examination of variables across varying levels of data[86]. Two-level MSEM analyses were conducted to account for the hierarchical structure of the current data where days are nested

in individuals. The proposed mediation model (Figure 2.1) was evaluated using a 2-1-2 mediation model, where the predictor variable (X) is a between-person variable (Level 2), the mediator variable (M) is a within-person variable (Level 1), and the outcome variable (Y) is a between-person variable (Level 2)[86,87]. MSEM allows random effect parameters, such as within-person residual variance (or random variability) and random slope coefficients, to be modeled simultaneously as exogenous predictors or endogenous outcomes across levels of analyses[87,88].

Guided by previous literature, the final analytic model was constructed by combining a cross-lagged panel model of depression and inflammation at Level 2 with mediation paths involving daily affective variability and affective reactivity to daily stressors as Level-1 mediators. The between-person part of the models specified the direct effects, including the cross-lagged paths and auto-regressive paths of depression and inflammation at Time 1 and Time 2. At the within-person level, models estimated each individual's residual variance in daily affect across days as a measure of affective variability. Affective reactivity was captured by random slopes of daily affect regressed on the occurrence of daily stressors, representing the degree to which daily affect shifted on stressor days relative to non-stressor days[89]. Separate models for positive and negative affect, as well as for affective variability and reactivity, were estimated to examine their unique associations with depressive symptoms and inflammation, using CRP and the composite cytokine measure as two separate outcomes. For each of the models, four direct and four indirect effects or mediation paths were tested. Exploratory analyses evaluated the individual differences in these pathways based on age (<50 years vs. ≥ 50 years) and gender. All analyses were conducted in Mplus Version 8.8 using Bayesian Monte Carlo Markov Chain (MCMC) estimation with a maximum of 50,000 iterations and two chains[90]. In Bayesian MCMC estimation, the credibility of an estimate is reflected in the posterior distribution, where the

standard deviation of the posterior serves as the MCMC analog of a frequentist standard error, and the 95% credible interval corresponds to the 2.5 and 97.5 percentiles of the posterior. Because Bayesian estimation does not rely on null-hypothesis testing or p-values, parameters are evaluated by whether their 95% credible interval includes zero, suggesting insufficient posterior evidence to distinguish the effect from zero[88,91].

Several sensitivity analyses were conducted. First, to account for the time intervals between the Biomarker Project and Daily Diary Projects at the second wave, we re-estimated the models by (1) including time intervals (in months) as a covariate and (2) restricting the sample who completed the Biomarker Project prior to the Daily Diary Project. Second, we assessed the independence of PA and NA dynamics by adjusting for the corresponding dynamics of the opposite valence (e.g., PA variability model adjusting for NA variability, and vice versa). Finally, we conducted analyses using individual cytokine markers, rather than a cytokine composite score, to evaluate whether associations differed across specific cytokine markers.

Results

Descriptive Statistics

At baseline, the mean age of participants was 52.4 years (SD = 9.7, range: 34-81), 57% were female, and 55% were college graduates. The racial composition of the study sample was 83% White, 13% Black and/or African American, 4% Native American, Asian, or other race. At Time 2, participants had an average of 4.9 chronic conditions, 41% had a body mass index of 30 or higher, 7% were current smokers, and 75% engaged in regular exercise. Approximately 50% of the sample used medication for blood pressure, and 44% used cholesterol medication. More

detailed descriptives are available in Table S1, Supplemental Digital Content, http://links.lww.com/PSYMED/B188.

Table 1 presents the bivariate correlations among age, depressive symptoms, inflammatory markers, and daily affect dynamics. Older age was correlated with lower depressive symptoms, daily affect variability, and reactivity to daily stressors, and higher levels of IL-6 at both time points. Depressive symptoms were positively correlated with affective variability and reactivity and CRP. Higher levels of IL-6 were correlated with higher PA and NA reactivity and PA variability, and higher levels of CRP were correlated with higher PA and NA variability and reactivity to daily stressors. There were positive correlations between PA and NA variability and between PA and NA reactivity. Higher PA variability was positively correlated with NA reactivity, whereas higher NA variability was positively correlated with higher PA and NA reactivity. The results from the MSEM models are presented in Figures 1 and 2 and Table S2, Supplemental Digital Content, http://links.lww.com/PSYMED/B188.

Cross-lagged Panel Models

The CLPM results showed that both depressive symptoms (cytokine model: Est. = 0.539; 95% CrI [0.472, 0.604], CRP model: Est. = 0.539; 95% CrI [0.473, 0.606]) and inflammation (cytokines: Est. = 0.390; 95% CrI [0.311, 0.469], CRP: Est. = 0.454; 95% CrI [0.363, 0.545]) showed credible autoregressive paths. Specifically, higher depressive symptoms at Time 1 were associated with higher depressive symptoms at Time 2, and higher inflammatory markers at Time 1 were also associated with higher inflammatory markers at Time 2. However, there were no credible cross-lagged paths between depressive symptoms and inflammation across all the CLPM models.

MSEM Mediation Models

Affective Variability Models

For the between-person direct effects, consistent with the CLPM results, the autoregressive paths for both depressive symptoms and inflammation were credible, whereas no credible cross-lagged associations between depressive symptoms and inflammation were observed in any of the models.

For within-person indirect effects, positive affect variability had indirect effects in the longitudinal autoregressive paths of depressive symptoms in both cytokines and CRP models (Figure 1; indirect effects; cytokine model: Est. = 0.012; 95% CrI [0.004, 0.023], CRP model: Est. = 0.012; 95% CrI [0.004, 0.023]). Higher depressive symptoms at Time 1 were associated with higher PA variability at Time 1, which was linked to higher PA variability at Time 2; further, higher PA variability at Time 2 was linked with higher depressive symptoms at Time 2. PA variability had indirect effects in the longitudinal cross-lagged path of depressive symptoms and CRP (indirect effects: Est. = 0.011; 95% CrI [0.003, 0.023]). Higher depressive symptoms at Time 1 were associated with higher PA variability across Time 1 (Est. = 0.048; 95% CrI [0.031, 0.066]) and Time 2 (CRP model: Est. = 0.359; 95% CrI [0.240, 0.471]), which was linked to higher CRP levels at Time 2 (Est. = 0.663; 95% CrI [0.212, 1.118]). There were no credible indirect effects for the autoregressive association of inflammation and the cross-lagged association from inflammation to depressive symptoms.

In contrast, negative affect (NA) variability had significant indirect effects in the longitudinal autoregressive paths of depressive symptoms (indirect effects; cytokines model: Est. = 0.078; 95% CrI [0.052, 0.109], CRP model: Est. = 0.077; 95% CrI [0.051, 0.108]). Specifically, higher depressive symptoms at Time 1 were associated with higher NA variability at Time 1, which was linked to higher NA variability at Time 2 as well as higher depressive

symptoms at Time 2. No credible mediating pathways were observed for the autoregressive association of inflammation and the cross-lagged associations between depressive symptoms and inflammation.

Affective Reactivity Models

In line with affective variability models and CLPM models, there were credible longitudinal autoregressive paths for depressive symptoms and inflammation. However, there were no direct cross-lagged associations between depressive symptoms and inflammation across the two time points.

For indirect effects, PA reactivity had indirect effects in the longitudinal autoregressive paths of depressive symptoms (indirect effects; cytokine model: Est. = 0.122; 95% CrI [0.006, 0.563], CRP model: Est. = 0.107; 95% CrI [0.005, 0.429]). Specifically, higher depressive symptoms at Time 1 were associated with lower PA reactivity (indicating greater reduction in PA in response to daily stressors), at Time 1. Lower PA reactivity at Time 1 was then linked to lower PA reactivity at Time 2, and lower PA reactivity at Time 2 was associated with higher depressive symptoms at Time 2.

Similarly, NA reactivity had indirect effects in both the longitudinal autoregressive paths of depressive symptoms (Figure 2; indirect effects; cytokine model: Est. = 0.077; 95% CrI [0.037, 0.131], CRP model: Est. = 0.075; 95% CrI [0.036, 0.129]). Higher depressive symptoms at Time 1 were linked to higher NA reactivity (indicating a greater increase in NA in response to daily stressors), at Time 1. This heightened NA reactivity at Time 1 was associated with heightened NA reactivity at Time 2, which was also linked to higher depressive symptoms at Time 2. Moreover, NA reactivity had indirect effects in the cross-lagged association from CRP to depressive symptoms (indirect effect: Est. = 0.025; 95% CrI [0.001, 0.061]). Higher levels of

CRP at Time 1 were associated with elevated NA reactivity at Time 1 (Est. = 0.030; 95% CrI [0.001, 0.060]) and Time 2 (Est. = 0.486; 95% CrI [0.345, 0.647]); NA reactivity at Time 2 was also linked with higher depressive symptoms at Time 2 (Est. = 1.781; 95% CrI [0.938, 2.727]; Figure 2). No credible mediating effects were found for the longitudinal autoregressive paths of inflammation or for the cross-lagged associations from depressive symptoms to inflammation.

Exploratory Analyses

Exploratory analyses were conducted to evaluate age and gender differences in the associations among depressive symptoms, inflammation measures, and daily affect dynamics. Overall, the results indicated that the mediating role of daily affect dynamics in the associations between depressive symptoms and inflammation was primarily driven by the younger sample (age < 50). Among four affect dynamic indicators, most showed consistent mediating effects in the pathways from baseline to follow-up depressive symptoms in both age groups, except PA reactivity, which showed no credible effects. In contrast, the mediating effects of PA variability in the depressive symptoms-to-CRP link and NA reactivity in the CRP-to-depressive symptoms link were only credible in the younger age group. Additional indirect effects involving NA variability as a mediator in the CRP-to-depressive symptoms link were observed only among individuals younger than 50.

Gender differences were also observed in the mediating effects of daily affect dynamics. The mediating paths of PA variability in the depressive symptoms-to-CRP pathway and NA reactivity in the CRP-to-depressive symptoms pathway were credible only among women. For longitudinal autoregressive paths of depressive symptoms, PA dynamics showed no credible mediation in either gender, except for PA variability, which mediated this path only among men.

In contrast, the mediating effects of NA dynamics in the longitudinal autoregressive paths of depressive symptoms remained credible in both men and women.

Sensitivity Analyses

The results from sensitivity analyses are summarized in Tables S4 and S5, Supplemental Digital Content, http://links.lww.com/PSYMED/B188. To account for variability in the timing between blood collection and daily diary assessments, we first estimated models including the time interval (i.e., months between the daily diary and biomarker projects) as an additional covariate. The results were consistent with the main analyses, indicating that adjusting for the time interval between assessments did not alter the findings. Restricting the sample to participants who completed the depressive symptoms measure prior to the daily diary assessments (Variability models: n_{days} = 2,648, n_{person} = 331; Reactivity models: n_{days} = 1,986, n_{person} = 276) yielded largely similar results, with the exception that the mediating effect of PA reactivity in longitudinal depressive symptoms was no longer credible. To examine the independent effects of PA and NA dynamics, we conducted additional analyses including the corresponding PA/NA dynamics as a covariate. Results were largely unchanged; however, the mediating effect of PA variability on longitudinal depressive symptoms was no longer evident. Finally, to assess whether the composite cytokine score obscured heterogeneity across individual cytokine markers, we estimated models using each cytokine separately (i.e., IL-6, IL-8, IL-10, and TNF-α). The results were consistent with those from the cytokine composite models, with no evidence of mediating effects of daily affect dynamics linking depressive symptoms and cytokine markers.

Discussion

The current study examined the mediating role of daily affect dynamics in the longitudinal and reciprocal associations between depressive symptoms and inflammation. Using multiple time-scale data collected across 13 years, the study assessed whether daily positive and negative affective variability and affective reactivity to daily stressors mediated the relationships between depressive symptoms and inflammatory markers. In models adjusting for sociodemographic and health-related covariates, results suggest that all four affect dynamics indicators mediated the longitudinal autoregressive paths of depressive symptoms, whereas none mediated the longitudinal autoregressive paths of inflammatory markers. NA reactivity to daily stressors mediated the paths from CRP at Time 1 to depressive symptoms at Time 2. PA variability mediated the paths linking higher depressive symptoms at Time 1 to higher CRP at Time 2. These associations were more evident among the younger age group under age 50 and women, compared to the older age group and men.

Findings indicated that higher depressive symptoms at baseline were associated with higher PA and NA variability and reactivity, which in turn were associated with higher depressive symptoms at 13-year follow-up. This is in line with previous studies that observed elevated affective variability and affective reactivity among depressed individuals, measured by intensive assessments in naturalistic settings[33,34,36]. Previous studies have also shown that higher affective variability, inertia, and instability were predictive of maintaining higher depression severity[38]. Our findings extend this work by showing that disrupted daily affect dynamics are not only cross-sectional markers of depression, but also contribute to long-term depressive symptomologies, suggesting that sustained elevations in depressive symptoms may be

maintained through daily affect dynamics. These results underscore daily affect regulation as a key mechanism underlying long-term depressive symptoms.

Results of the present work further revealed that daily NA dynamics mediated the association between baseline inflammation and subsequent depressive symptoms. Specifically, higher baseline CRP was associated with heightened NA reactivity to daily stressors and, among younger individuals (age < 50), with greater NA variability, both of which predicted elevated depressive symptoms at follow-up. These findings support the cytokine theory of depression[2]; inflammatory signaling may contribute to everyday mood fluctuation by activating the HPA axis, altering neurotransmitter systems, reducing serotonin secretion, and impairing neurocircuitry involved in emotional processing, all of which may contribute to the development of depression[92]. As such, elevated inflammatory markers likely reflect underlying cytokine activity that disrupts emotion regulation processes. In line with empirical evidence linking maladaptive emotion regulation strategies to elevated inflammation[54], our findings extend this work to dynamic characteristics of affect, highlighting the role of CRP in predicting daily negative affective reactivity. One plausible explanation for this association between CRP and NA reactivity is the comorbidity of inflammation, physical symptoms, and negative affect, in which inflammation-related physical symptoms such as fatigue and pain contribute to heightened negative affect[93,94]. In other words, inflammation may increase physical discomfort in daily life, which may interfere with effective affective regulation and lead to greater reactivity to daily stressors. It is also plausible that underlying physical conditions may contribute to both heightened inflammation and disrupted affective regulation. Notably, NA reactivity emerged as a more consistent pathway linking inflammation to subsequent depressive symptoms, whereas NA variability appeared to be less relevant to the depression-inflammation pathway. NA reactivity

captures the degree to which individuals mount affective responses to daily stressors, reflecting individual differences in stress sensitivity. These processes are closely tied to underlying stress-response systems that are also implicated in inflammatory activity. In contrast, NA variability may reflect more general affective liability, but may be less indicative of how individuals respond to environmental challenges relevant to inflammation. This pattern suggests that associations between NA dynamics and inflammation may be context-dependent.

Furthermore, our findings highlight the role of positive affect dynamics as a key affective regulatory process linking depressive symptoms and inflammation. Whereas previous literature has primarily focused on NA dynamics[95], the present research identified PA dynamics as a pathway from depressive symptoms to inflammation. Specifically, higher depressive symptoms at baseline were associated with greater PA variability, which in turn predicted higher CRP at follow-up. This pattern of associations supports the scar hypothesis of depression, potentially through mechanisms such as altering self-image[25], engaging in maladaptive health behaviors[13,14], and increasing emotional and physiological susceptibility to stress[16,18]. The current study extends this line of work by suggesting that disrupted affect dynamics can function as a pathway linking depression to health. It is notable that PA reactivity did not emerge as a significant pathway, suggesting that reduced capacity to sustain stable positive emotional states, rather than context-dependent fluctuations in response to stressors, may be more closely linked to chronic physiological processes such as inflammation. PA variability reflects the capacity to experience fluctuation in rewarding or engaging states across days and captures aspects of regulatory instability in reward-related systems. Greater PA variability may index flexibility and access to positive experiences, which can buffer the impact of chronic low-grade inflammation on depressive symptoms. In contrast, PA reactivity to stressors is a relatively constrained process;

positive affect often shows smaller, less consistent within-person changes in response to daily stressors than negative affect. As such, PA reactivity may provide limited additional information beyond overall PA variability in distinguishing who is protected versus vulnerable in the context of inflammation. Sensitivity analyses further indicated that pathways involving PA dynamics were attenuated in some models, including those adjusting for NA dynamics, whereas associations involving NA dynamics remained robust when adjusting for PA dynamics. This pattern suggests that NA dynamics may represent a more stable and independent pathway linking inflammation and depressive symptoms, whereas associations involving PA dynamics may partially overlap with or be accounted for by NA processes. Together, these findings highlight distinct roles of positive and negative affect dynamics in daily life, with NA dynamics showing more consistent and robust associations. These findings suggest that intervention strategies may benefit from targeting PA and NA systems separately, depending on individuals' existing mental and physical conditions.

Exploratory analyses revealed that the mediating effects of daily affect dynamics in the depressive-symptoms-to-inflammation link were more pronounced among individuals under age 50 and among women. Among younger individuals (age < 50), elevated inflammation may be indicative of individual variations in deteriorating health or increased allostatic load and stress. In contrast, older individuals (age ≥ 50) often exhibit elevated inflammatory levels, perhaps due to existing disease or the accumulation of low-grade systemic inflammation associated with aging[57]; these phenomena might make it more difficult to observe additional variation in response to psychological processes. In addition, recent studies have pointed to gender/sex differences in the relationship between inflammation and depression[68]. For example, men with elevated depressive symptoms have been shown to mount higher inflammatory responses in

contrast with women[68,96]. Aligning with some previous work[14], our findings offer preliminary support for gender/sex differences in the role of daily affect dynamics in depressive symptoms and inflammation, particularly among women. Further work is needed to elucidate the mechanisms underlying such gender/sex differences.

Notably, mediated associations between depressive symptoms and inflammation were observed for CRP, but not for cytokines. Prior work suggests that links between affective experiences and inflammatory processes may depend on the temporal alignment of psychological and biological assessments[81]. Proinflammatory cytokines tend to respond rapidly to external stressors and exhibit substantial short-term variability, whereas CRP – an acute-phase protein downstream in the inflammatory cascade – integrates inflammatory signaling over longer periods and seems to be less sensitive to transient perturbations[78-80]. Consistent with this distinction, previous studies have shown that when affect and inflammatory markers are assessed in close temporal proximity, cytokines are more strongly associated with short-term affective dynamics, whereas CRP is more consistently linked to indices of daily affect dynamics when assessments are spaced further apart[44,81,97]. Given that the time lag between diary assessments and blood draws in the present study spanned months to years, the observed specificity to CRP is consistent with evidence supporting CRP as a more stable indicator of systemic inflammation in long-term observational research.

The current study did not find direct cross-lagged relationships between depressive symptoms and inflammatory markers. Previous cross-sectional studies reported robust correlations between depression and inflammation[98], with some mixed evidence[68,99,100]. Longitudinal evidence varies across studies, with findings differing based on the directionality of effects, whether baseline levels are adjusted, and characteristics of study samples such as age and

clinical depression status[7,10-12,14]. In the current study sample, we found cross-sectional correlations, but not longitudinal associations, possibly due to the long-time gap between assessments. However, our results found credible indirect effects of daily affect dynamics on this relationship, suggesting that the links between mental and physical health may unfold through dynamic, time-sensitive processes in daily life. These findings are in line with process-based models of health that underscore the cumulative effects of daily experiences on physiological systems[22,23,101]. Together, these results suggest that the intricate prospective relationships between depressive symptoms and inflammation require nuanced examination to uncover the underlying mechanisms across different temporal dynamics.

Limitations and Strengths

There are several limitations to consider in interpreting the current findings. First, the generalizability of the results is constrained by the limited racial, ethnic, and socioeconomic diversity of the MIDUS sample. Moreover, as the MIDUS sample is a community-based sample, the applicability of these results to clinical contexts remains uncertain, and the findings should be interpreted as reflecting associations with depressive symptoms rather than processes specific to MDD. It would be valuable for future research to replicate the current findings in more diverse and clinically representative study samples. Second, using a two-time-point mediation model limits the capacity to test complete mediation with distinct temporal and causal pathways. Recent methodological critiques of traditional CLPMs have pointed out that models with only two time points may not produce accurate estimates of within-person changes and limit causal interpretation[102]. The timing of daily diary and biomarker assessments also varied across individuals, further hindering the ability to determine temporal sequencing. Extended longitudinal designs across three or more time points and alternative analytic approaches, such as

random-intercept cross-lagged panel models, would enable future studies to better clarify the mediating mechanisms linking depression, inflammation, and daily affect dynamics. Furthermore, the current study only included two affect dynamic indicators based on 8-day diary design to balance data limitations and modeling feasibility. Future investigations could incorporate more intensive assessments over longer periods, combining high-frequency affect assessments with closely timed cytokine sampling, to examine additional affect dynamic indicators and clarify the temporal specificity of cytokine-affect linkages. In addition, although we adjusted for relevant covariates, inflammatory markers were assessed at a single time point during an overnight visit to the research center, which may be influenced by situational factors related to travel. Further, although soluble intercellular adhesion molecule (sICAM-1) and E-selectin were available in the dataset, these markers are often considered indicators of endothelial function and vascular activation[103]. Although they are relevant to inflammation, they do not index systemic inflammation in the same way as CRP and inflammatory cytokines and there is less work linking them to psychosocial processes. Accordingly, the present study focused on CRP and inflammatory cytokines. Future studies using more rigorous and controlled assessment conditions, along with a broader range of inflammatory markers, may help minimize contextual influences on inflammatory measures and clarify the distinct roles of different markers in psychosocial processes. Lastly, the analyses were limited to testing linear and unique effects of affect dynamic indicators on depressive symptoms and inflammation. Given the recent evidence on the non-linear relationships between affective variability/reactivity and health outcomes[44,104] and growing emphasis on considering multiple dynamic indicators[105,106], future work should consider modeling non-linear and joint effects to capture more nuanced patterns of these associations.

Despite these limitations, the current study has several strengths. First, this study expands the current literature by linking affect dynamics to longitudinal changes in health and well-being. Whereas previous research has primarily focused on individual differences in affect dynamics based on sociodemographic characteristics or pre-existing conditions, the current study demonstrates how these dynamic affective characteristics may serve as indicators or mechanisms underlying long-term changes in mental and physical health. Second, this study leveraged multiple time-scale data that includes longitudinal collection of daily diary data, self-reported surveys, and biomarker assessments. The richness of the data and integrative design allowed for a novel and comprehensive examination of the interplay between depression, inflammation, and daily affective experiences. Further, our MSEM approach provides a methodological strength by appropriately accounting for the nested data structure. By simultaneously estimating within- and between-person components of the models, this approach can produce more accurate and less biased estimates by accounting for measurement errors. Finally, this study simultaneously considered the bidirectional nature of the relationship between depressive symptoms and inflammation. Whereas prior research has often focused on unidirectional relationships, the present work incorporated cross-lagged panel modeling, enabling direct comparison of the significance of associations in both directions.

Conclusion

The current study leveraged multiple time-scale data to evaluate the mediating role of daily affect dynamics in the longitudinal and bidirectional relationship between depressive symptoms and inflammation. Findings showed that sustained elevations in depressive symptoms across two time points were mediated by daily affective variability and reactivity to stressors. Moreover, positive affective variability mediated the pathway from heightened baseline

depressive symptoms to higher CRP levels at follow-up, whereas negative affective reactivity to daily stressors mediated the pathway from higher baseline CRP to increased subsequent depressive symptoms. These results provide empirical support for daily affect dynamics as potential mechanisms underlying the reciprocal link between depression and inflammation. Findings from the study underscore the role of daily affective processes in the link between depressive symptoms and inflammation. Intervention strategies that promote affective stability and adaptive stress response in daily lives may help disrupt this reinforcing cycle.

References

1. Irwin MR, Miller AH. Depressive disorders and immunity: 20 years of progress and discovery. Brain Behav Immun. 2007;21(4):374-83. doi: 10.1016/j.bbi.2007.01.010.
2. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry. 2009;65(9):732-41. doi: 10.1016/j.biopsych.2008.11.029.
3. Yirmiya R. The inflammatory underpinning of depression: an historical perspective. Brain Behav Immun. 2024;122:433-443. doi: 10.1016/j.bbi.2024.08.048.
4. Blume J, Douglas SD, Evans DL. Immune suppression and immune activation in depression. Brain Behav Immun. 2011;25(2):221-9. doi: 10.1016/j.bbi.2010.10.008.
5. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 2006;27(1):24-31. doi: 10.1016/j.it.2005.11.006.
6. Zunszain PA, Hepgul N, Pariante CM. Inflammation and depression. In: Cowen P, Sharp T, Lau J, editors. Behavioral neurobiology of depression and its treatment. Springer; 2013. p. 135-151. doi: 10.1007/7854_2012_211.
7. Copeland WE, Shanahan L, Worthman C, Angold A, Costello EJ. Cumulative depression episodes predict later C-reactive protein levels: a prospective analysis. Biol Psychiatry. 2012;71(1):15-21. doi: 10.1016/j.biopsych.2011.09.023.
8. de la Torre-Luque A, Ayuso-Mateos JL, Sanchez-Carro Y, de la Fuente J, Lopez-Garcia P. Inflammatory and metabolic disturbances are associated with more severe trajectories of late-life depression. Psychoneuroendocrinology. 2019;110:104443. doi: 10.1016/j.psyneuen.2019.104443.
9. Deverts DJ, Cohen S, DiLillo VG, Lewis CE, Kiefe C, Whooley M, Matthews KA. Depressive symptoms, race, and circulating C-reactive protein: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Psychosom Med. 2010;72(8):734-41. doi: 10.1097/PSY.0b013e3181ec4b98.
10. Chu AL, Stochl J, Lewis G, Zammit S, Jones PB, Khandaker GM. Longitudinal association between inflammatory markers and specific symptoms of depression in a prospective birth cohort. Brain Behav Immun. 2019;76:74-81. doi: 10.1016/j.bbi.2018.11.007.
11. Zalli A, Jovanova O, Hoogendijk WJ, Tiemeier H, Carvalho LA. Low-grade inflammation predicts persistence of depressive symptoms. Psychopharmacology (Berl). 2016;233(9):1669-78. doi: 10.1007/s00213-015-3919-9.
12. Zainal NH, Newman MG. Increased inflammation predicts nine-year change in major depressive disorder diagnostic status. J Abnorm Psychol. 2021;130(8):829-840. doi: 10.1037/abn0000716.
13. Werneck AO, Christofaro DGD, Ritti-Dias RM, Cucato GG, Stubbs B, Oyeyemi AL, Conceição RDO, Santos RD, Bittencourt MS. Does physical activity influence the association between depressive symptoms and low-grade inflammation in adults? A study of 8,048 adults. Physiol Behav. 2020;223:112967. doi: 10.1016/j.physbeh.2020.112967.
14. Song S, DeMeo NN, Almeida DM, Majd M, Engeland CG, Graham-Engeland JE. The longitudinal connection between depressive symptoms and inflammation: mediation by sleep quality. PLoS One. 2022;17(5):e0269033. doi: 10.1371/journal.pone.0269033.

15. Zou B, Miao C, Chen J. Depression and perceived stress, but not anxiety, are associated with elevated inflammation in an obese adult population. Risk Manag Healthc Policy. 2020;13:1489-1497. doi: 10.2147/RMHP.S270359.
16. Kim IB, Lee JH, Park SC. The relationship between stress, inflammation, and depression. Biomedicines. 2022;10(8):1929. doi: 10.3390/biomedicines10081929.
17. Lee STH. Inflammation, depression, and anxiety disorder: a population-based study examining the association between interleukin-6 and the experiencing of depressive and anxiety symptoms. Psychiatry Res. 2020;285:112809. doi: 10.1016/j.psychres.2020.112809.
18. Leonard BE. Inflammation and depression: a causal or coincidental link to the pathophysiology? Acta Neuropsychiatr. 2018;30(1):1-16. doi: 10.1017/neu.2016.69.
19. Kuppens P, Allen NB, Sheeber LB. Emotional inertia and psychological maladjustment. Psychol Sci. 2010;21(7):984-91. doi: 10.1177/0956797610372634.
20. Lischetzke T, Angelova R, Eid M. Validating an indirect measure of clarity of feelings: evidence from laboratory and naturalistic settings. Psychol Assess. 2011;23(2):447-455. doi: 10.1037/a0022211.
21. Bolger N, Laurenceau J-P. Intensive longitudinal methods: an introduction to diary and experience sampling research. New York (NY): The Guilford Press; 2013.
22. Hayes SC, Hofmann SG, Ciarrochi J. A process-based approach to psychological diagnosis and treatment: the conceptual and treatment utility of an extended evolutionary meta model. Clin Psychol Rev. 2020;82:101908. doi: 10.1016/j.cpr.2020.101908.
23. McEwen BS. Stress, adaptation, and disease: allostasis and allostatic load. Ann N Y Acad Sci. 1998;840:33-44. doi: 10.1111/j.1749-6632.1998.tb09546.x.
24. Lewinsohn PM, Steinmetz JL, Larson DW, Franklin J. Depression-related cognitions: antecedent or consequence? J Abnorm Psychol. 1981;90(3):213-219. doi: 10.1037/0021-843X.90.3.213.
25. Rohde P, Lewinsohn PM, Seeley JR. Are people changed by the experience of having an episode of depression? A further test of the scar hypothesis. J Abnorm Psychol. 1990;99(3):264-271. doi: 10.1037/0021-843X.99.3.264.
26. Houben M, Van Den Noortgate W, Kuppens P. The relation between short-term emotion dynamics and psychological well-being: a meta-analysis. Psychol Bull. 2015;141(4):901-30. doi: 10.1037/a0038822.
27. Bolger N, Zuckerman A. A framework for studying personality in the stress process. J Pers Soc Psychol. 1995;69(5):890-902. doi: 10.1037/0022-3514.69.5.890.
28. Thompson RJ, Mata J, Jaeggi SM, Buschkuehl M, Jonides J, Gotlib IH. The everyday emotional experience of adults with major depressive disorder: examining emotional instability, inertia, and reactivity. J Abnorm Psychol. 2012;121(4):819-29. doi: 10.1037/a0027978.
29. Apsley AT, Lee SA, Bhat AC, Rush J, Almeida DM, Cole SW, Shalev I. Affective reactivity to daily stressors and immune cell gene expression in the MIDUS study. Brain Behav Immun. 2024;115:80-88. doi: 10.1016/j.bbi.2023.09.025.
30. Sin NL, Almeida DM. Daily positive experiences and health: biobehavioral pathways and resilience to daily stress. In: Ryff CD, Krueger RF, editors. Oxford handbook of integrative health science. New York (NY): Oxford University Press; 2018. doi: 10.1093/oxfordhb/9780190676384.013.10.

31. Sin NL, Graham-Engeland JE, Ong AD, Almeida DM. Affective reactivity to daily stressors is associated with elevated inflammation. Health Psychol. 2015;34(12):1154-65. doi: 10.1037/hea0000240.
32. Wichers M, Peeters F, Geschwind N, Jacobs N, Simons CJ, Derom C, Thiery E, Delespaul PH, van Os J. Unveiling patterns of affective responses in daily life may improve outcome prediction in depression: a momentary assessment study. J Affect Disord. 2010;124(1-2):191-5. doi: 10.1016/j.jad.2009.11.010.
33. Mukherjee D, Lee SA, Almeida D. Daily affective dynamics in major depressive disorder: the role of daily stressors and positive events. Affect Sci. 2023;4(4):757-769. doi: 10.1007/s42761-023-00209-x.
34. Peeters F, Berkhof J, Delespaul P, Rottenberg J, Nicolson NA. Diurnal mood variation in major depressive disorder. Emotion. 2006;6(3):383-91. doi: 10.1037/1528-3542.6.3.383.
35. van Roekel E, Bennik EC, Bastiaansen JA, Verhagen M, Ormel J, Engels RC, Oldehinkel AJ. Depressive symptoms and the experience of pleasure in daily life: an exploration of associations in early and late adolescence. J Abnorm Child Psychol. 2016;44(5):999-1009. doi: 10.1007/s10802-015-0090-z.
36. Bylsma LM, Taylor-Clift A, Rottenberg J. Emotional reactivity to daily events in major and minor depression. J Abnorm Psychol. 2011;120(1):155-67. doi: 10.1037/a0021662.
37. Bosley HG, Soyster PD, Fisher AJ. Affect dynamics as predictors of symptom severity and treatment response in mood and anxiety disorders: evidence for specificity. J Pers Oriented Res. 2019;5(2):101-113. doi: 10.17505/jpor.2019.09.
38. Panaite V, Rottenberg J, Bylsma LM. Daily affective dynamics predict depression symptom trajectories among adults with major and minor depression. Affect Sci. 2020;1(3):186-198. doi: 10.1007/s42761-020-00014-w.
39. Rackoff GN, Newman MG. Reduced positive affect on days with stress exposure predicts depression, anxiety disorders, and low trait positive affect 7 years later. J Abnorm Psychol. 2020;129(8):799-809. doi: 10.1037/abn0000639.
40. Stawski RS, Cichy KE, Witzel DD, Schuyler AC, Nichols MJ. Daily stress processes as potential intervention targets to reduce gender differences and improve mental health outcomes in mid- and later life. Prev Sci. 2023;24(5):876-886. doi: 10.1007/s11121-022-01444-7.
41. Hardy J, Segerstrom SC. Intra-individual variability and psychological flexibility: affect and health in a national US sample. J Res Pers. 2017;69:13-21. doi: 10.1016/j.jrp.2016.04.002.
42. Chan DK, Zhang X, Fung HH, Hagger MS. Affect, affective variability, and physical health: results from a population-based investigation in China. Int J Behav Med. 2016;23(4):438-46. doi: 10.1007/s12529-015-9510-2.
43. Ong AD, Steptoe A. Association of positive affect instability with all-cause mortality in older adults in England. JAMA Netw Open. 2020;3(7):e207725. doi: 10.1001/jamanetworkopen.2020.7725.
44. Jones DR, Smyth JM, Engeland CG, Sliwinski MJ, Russell MA, Sin NL, Almeida DM, Graham-Engeland JE. Affect variability and inflammatory markers in midlife adults. Health Psychol. 2020;39(8):655-666. doi: 10.1037/hea0000868.
45. Jenkins BN, Hunter JF, Cross MP, Acevedo AM, Pressman SD. When is affect variability bad for health? The association between affect variability and immune response to the influenza vaccination. J Psychosom Res. 2018;104:41-47. doi: 10.1016/j.jpsychores.2017.11.002.

46. Levenson RW. The autonomic nervous system and emotion. Emot Rev. 2014;6(2):100-112. doi: 10.1177/1754073913512003.
47. Chiang JJ, Turiano NA, Mroczek DK, Miller GE. Affective reactivity to daily stress and 20-year mortality risk in adults with chronic illness: findings from the National Study of Daily Experiences. Health Psychol. 2018;37(2):170-178. doi: 10.1037/hea0000567.
48. Mroczek DK, Stawski RS, Turiano NA, Chan W, Almeida DM, Neupert SD, Spiro A 3rd. Emotional reactivity and mortality: longitudinal findings from the VA Normative Aging Study. J Gerontol B Psychol Sci Soc Sci. 2015;70(3):398-406. doi: 10.1093/geronb/gbt107.
49. Piazza JR, Charles ST, Sliwinski MJ, Mogle J, Almeida DM. Affective reactivity to daily stressors and long-term risk of reporting a chronic physical health condition. Ann Behav Med. 2013;45(1):110-20. doi: 10.1007/s12160-012-9423-0.
50. Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977;196(4286):129-36. doi: 10.1126/science.847460.
51. Perry NB, Calkins SD. A biopsychosocial perspective on the development of emotion regulation across childhood. In: Cole PM, Hollenstein T, editors. *Emotion regulation.* New York (NY): Routledge; 2018. p. 3-30.
52. Appleton AA, Buka SL, Loucks EB, Gilman SE, Kubzansky LD. Divergent associations of adaptive and maladaptive emotion regulation strategies with inflammation. Health Psychol. 2013;32(7):748-56. doi: 10.1037/a0030068.
53. Graham-Engeland JE. Moving toward affective immunology: legacy and future directions. Compr Psychoneuroendocrinol. 2024;19:100241. doi: 10.1016/j.cpnec.2024.100241.
54. Lopez RB, Brown RL, Wu EL, Murdock KW, Denny BT, Heijnen C, Fagundes C. Emotion regulation and immune functioning during grief: testing the role of expressive suppression and cognitive reappraisal in inflammation among recently bereaved spouses. Psychosom Med. 2020;82(1):2-9. doi: 10.1097/PSY.0000000000000755.
55. Moriarity DP, Grehl MM, Walsh RFL, Roos LG, Slavich GM, Alloy LB. A systematic review of associations between emotion regulation characteristics and inflammation. Neurosci Biobehav Rev. 2023;150:105162. doi: 10.1016/j.neubiorev.2023.105162.
56. Ospina LH, Beck-Felts K, Ifrah C, Lister A, Messer S, Russo SJ, Gross JJ, Kimhy D. Inflammation and emotion regulation: findings from the MIDUS II study. Brain Behav Immun Health. 2022;26:100536. doi: 10.1016/j.bbih.2022.100536.
57. Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. Inflamm-aging: an evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000;908:244-54. doi: 10.1111/j.1749-6632.2000.tb06651.x.
58. McDade TW. Three common assumptions about inflammation, aging, and health that are probably wrong. Proc Natl Acad Sci U S A. 2023;120(51):e2317232120. doi: 10.1073/pnas.2317232120.
59. Straka K, Tran ML, Millwood S, Swanson J, Kuhlman KR. Aging as a context for the role of inflammation in depressive symptoms. Front Psychiatry. 2021;11:605347. doi: 10.3389/fpsyt.2020.605347.
60. Burke HM, Davis MC, Otte C, Mohr DC. Depression and cortisol responses to psychological stress: a meta-analysis. Psychoneuroendocrinology. 2005;30(9):846-56. doi: 10.1016/j.psyneuen.2005.02.010.
61. Roshanaei-Moghaddam B, Katon WJ, Russo J. The longitudinal effects of depression on physical activity. Gen Hosp Psychiatry. 2009;31(4):306-15. doi: 10.1016/j.genhosppsych.2009.04.002.

62. Steiger A, Pawlowski M. Depression and sleep. Int J Mol Sci. 2019;20(3):607. doi: 10.3390/ijms20030607.
63. Nolen-Hoeksema S. Gender differences in depression. Curr Dir Psychol Sci. 2001;10(5):173-176. doi: 10.1111/1467-8721.00142.
64. Cyranowski JM, Frank E, Young E, Shear MK. Adolescent onset of the gender difference in lifetime rates of major depression: a theoretical model. Arch Gen Psychiatry. 2000;57(1):21-7. doi: 10.1001/archpsyc.57.1.21.
65. O'Connor MF, Motivala SJ, Valladares EM, Olmstead R, Irwin MR. Sex differences in monocyte expression of IL-6: role of autonomic mechanisms. Am J Physiol Regul Integr Comp Physiol. 2007;293(1):R145-51. doi: 10.1152/ajpregu.00752.2006.
66. Derry HM, Padin AC, Kuo JL, Hughes S, Kiecolt-Glaser JK. Sex differences in depression: does inflammation play a role? Curr Psychiatry Rep. 2015;17(10):78. doi: 10.1007/s11920-015-0618-5.
67. Ford DE, Erlinger TP. Depression and C-reactive protein in US adults: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2004;164(9):1010-4. doi: 10.1001/archinte.164.9.1010.
68. Majd M, Graham-Engeland JE, Smyth JM, Sliwinski MJ, Lipton RB, Katz MJ, Engeland CG. Distinct inflammatory response patterns are evident among men and women with higher depressive symptoms. Physiol Behav. 2018;184:108-115. doi: 10.1016/j.physbeh.2017.11.009.
69. Nesselroade JR. Interindividual differences in intraindividual change. In: Collins LM, Horn JL, editors. Best methods for the analysis of change: recent advances, unanswered questions, future directions. Washington (DC): American Psychological Association; 1991. p. 92-105. doi: 10.1037/10099-006.
70. Radler BT. The Midlife in the United States (MIDUS) Series: A National Longitudinal Study of Health and Well-being. Open Health Data. 2014;2(1):e3. doi: 10.5334/ohd.ai.
71. Almeida DM, Charles ST, Piazza JR, Stawski RS, Cichy KE, Cerino ES, Rush J, Nicholson JS, Holmberg JC, Cramer N, Mogle J. The National Study of Daily Experiences: protocol for assessments of daily stress, well-being, health, and salivary biomarkers in a longitudinal cohort. JMIR Res Protoc. 2025;14:e76453. doi: 10.2196/76453.
72. Mroczek DK, Kolarz CM. The effect of age on positive and negative affect: a developmental perspective on happiness. J Pers Soc Psychol. 1998;75(5):1333-1349. doi:10.1037/0022-3514.75.5.1333.
73. Watson D, Clark LA, Carey G. Positive and negative affectivity and their relation to anxiety and depressive disorders. J Abnorm Psychol. 1988;97(3):346-353. doi:10.1037/0021-843X.97.3.346.
74. Charles ST, Rush J, Piazza JR, Cerino ES, Mogle J, Almeida DM. Growing old and being old: emotional well-being across adulthood. J Pers Soc Psychol. 2023;125(2):455-469. doi: 10.1037/pspp0000453.
75. Geldhof GJ, Preacher KJ, Zyphur MJ. Reliability estimation in a multilevel confirmatory factor analysis framework. Psychol Methods. 2014;19(1):72-91. doi: 10.1037/a0032138.
76. Almeida DM, Wethington E, Kessler RC. The daily inventory of stressful events: an interview-based approach for measuring daily stressors. Assessment. 2002;9(1):41-55. doi: 10.1177/1073191102091006.
77. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas. 1977;1(3):385-401. doi:10.1177/014662167700100306.

78. Marsland AL, Walsh C, Lockwood K, John-Henderson NA. The effects of acute psychological stress on circulating and stimulated inflammatory markers: a systematic review and meta-analysis. Brain Behav Immun. 2017;64:208-219. doi: 10.1016/j.bbi.2017.01.011.
79. Mortensen RF. C-reactive protein, inflammation, and innate immunity. Immunol Res. 2001;24(2):163-76. doi: 10.1385/IR:24:2:163.
80. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA. 2001;286(3):327-34. doi: 10.1001/jama.286.3.327.
81. Graham-Engeland JE, Sin NL, Smyth JM, Jones DR, Knight EL, Sliwinski MJ, Almeida DM, Katz MJ, Lipton RB, Engeland CG. Negative and positive affect as predictors of inflammation: timing matters. Brain Behav Immun. 2018;74:222-230. doi: 10.1016/j.bbi.2018.09.011.
82. Knight EL, Majd M, Graham-Engeland JE, Smyth JM, Sliwinski MJ, Engeland CG. Depressive symptoms and other negative psychological states relate to ex vivo inflammatory responses differently for men and women: cross-sectional and longitudinal evidence. Physiol Behav. 2022;244:113656. doi: 10.1016/j.physbeh.2021.113656.
83. O'Connor MF, Bower JE, Cho HJ, Creswell JD, Dimitrov S, Hamby ME, Hoyt MA, Martin JL, Robles TF, Sloan EK, Thomas KS, Irwin MR. To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. Brain Behav Immun. 2009;23(7):887-97. doi: 10.1016/j.bbi.2009.04.005.
84. Kenny DA. Cross-lagged and synchronous common factors in panel data. In: Goldberger AS, Duncan OD, editors. Structural equation models in the social sciences. New York (NY): Seminar Press; 1973. p. 153-167.
85. Kenny DA, Zautra A. The trait-state-error model for multiwave data. J Consult Clin Psychol. 1995;63(1):52-59. doi: 10.1037/0022-006X.63.1.52.
86. Preacher KJ, Zhang Z, Zyphur MJ. Alternative methods for assessing mediation in multilevel data: the advantages of multilevel SEM. Struct Equ Modeling. 2011;18(2):161-182. doi: 10.1080/10705511.2011.557329.
87. Preacher KJ, Zyphur MJ, Zhang Z. A general multilevel SEM framework for assessing multilevel mediation. Psychol Methods. 2010;15(3):209-33. doi: 10.1037/a0020141.
88. Asparouhov T, Hamaker EL, Muthén B. Dynamic structural equation models. Struct Equ Modeling. 2018;25(3):359-388. doi: 10.1080/10705511.2017.1406803.
89. Almeida DM, Rush J, Mogle J, Piazza JR, Cerino E, Charles ST. Longitudinal change in daily stress across 20 years of adulthood: results from the national study of daily experiences. Dev Psychol. 2023;59(3):515-523. doi: 10.1037/dev0001469.
90. Muthén LK, Muthén BO. Mplus user's guide. 8th ed. Los Angeles (CA): Muthén & Muthén; 1998-2017.
91. McNeish D, Hamaker EL. A primer on two-level dynamic structural equation models for intensive longitudinal data in Mplus. Psychol Methods. 2020;25(5):610-635. doi: 10.1037/met0000250.
92. Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol Ther. 2011;130(2):226-38. doi: 10.1016/j.pharmthera.2011.01.014.
93. Janssen SA. Negative affect and sensitization to pain. Scand J Psychol. 2002;43(2):131-7. doi: 10.1111/1467-9450.00278.

94. Rost S, Van Ryckeghem DML, Koval P, Sütterlin S, Vögele C, Crombez G. Affective instability in patients with chronic pain: a diary approach. Pain. 2016;157(8):1783-1790. doi: 10.1097/j.pain.0000000000000582.
95. Reed RG, Mauss IB, Ram N, Segerstrom SC. Daily stressors, emotion dynamics, and inflammation in the MIDUS cohort. Int J Behav Med. 2022;29(4):494-505. doi: 10.1007/s12529-021-10035-9.
96. Knight EL, Majd M, Graham-Engeland JE, Smyth JM, Sliwinski MJ, Engeland CG. Gender differences in the link between depressive symptoms and ex vivo inflammatory responses are associated with markers of endotoxemia. Brain Behav Immun Health. 2020;2:100013. doi: 10.1016/j.bbih.2019.100013.
97. Jones DR, Ruiz JM, Schreier HMC, Allison MA, Uchino BN, Russell MA, Taylor DJ, Smith TW, Smyth JM. Mean affect and affect variability may interact to predict inflammation. Brain Behav Immun. 2023;109:168-174. doi: 10.1016/j.bbi.2023.01.008.
98. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med. 2009;71(2):171-86. doi: 10.1097/PSY.0b013e3181907c1b.
99. Cyranowski JM, Marsland AL, Bromberger JT, Whiteside TL, Chang Y, Matthews KA. Depressive symptoms and production of proinflammatory cytokines by peripheral blood mononuclear cells stimulated in vitro. Brain Behav Immun. 2007;21(2):229-37. doi: 10.1016/j.bbi.2006.07.005.
100. Steptoe A, Kunz-Ebrecht SR, Owen N. Lack of association between depressive symptoms and markers of immune and vascular inflammation in middle-aged men and women. Psychol Med. 2003;33(4):667-74. doi: 10.1017/s0033291702007250.
101. Epel ES, Crosswell AD, Mayer SE, Prather AA, Slavich GM, Puterman E, Mendes WB. More than a feeling: a unified view of stress measurement for population science. Front Neuroendocrinol. 2018;49:146-169. doi: 10.1016/j.yfrne.2018.03.001.
102. Hamaker EL, Kuiper RM, Grasman RP. A critique of the cross-lagged panel model. Psychol Methods. 2015;20(1):102-16. doi: 10.1037/a0038889.
103. Münzel T, Sinning C, Post F, Warnholtz A, Schulz E. Pathophysiology, diagnosis and prognostic implications of endothelial dysfunction. *Ann Med.* 2008;40(3):180-196. doi: 10.1080/07853890701854702.
104. Rush J, Ong AD, Piazza JR, Charles ST, Almeida DM. Too little, too much, and "just right": exploring the "goldilocks zone" of daily stress reactivity. Emotion. 2024;24(5):1249-1258. doi: 10.1037/emo0001333.
105. Dejonckheere E, Mestdagh M, Houben M, Rutten I, Sels L, Kuppens P, Tuerlinckx F. Complex affect dynamics add limited information to the prediction of psychological well-being. Nat Hum Behav. 2019;3(5):478-491. doi: 10.1038/s41562-019-0555-0.
106. Lee SA, Mukherjee D, Lanza ST, Almeida DM. Longitudinal profiles of affect dynamics in middle and later life: a latent transition analysis. Psychol Aging. 2025. doi: 10.1037/pag0000938.

Figure 1

Multilevel Mediation of Positive Affective Variability in Depressive Symptoms and CRP

Note. Bold lines indicate credible paths, and dashed lines represent non-credible paths. The analysis was adjusted for age, gender, education level, race, and household income at Time 1. When inflammation was the outcome, models were additionally adjusted for BMI, smoking status, chronic health conditions, regular physical activity, and use of medication for blood pressure and controlling cholesterol.

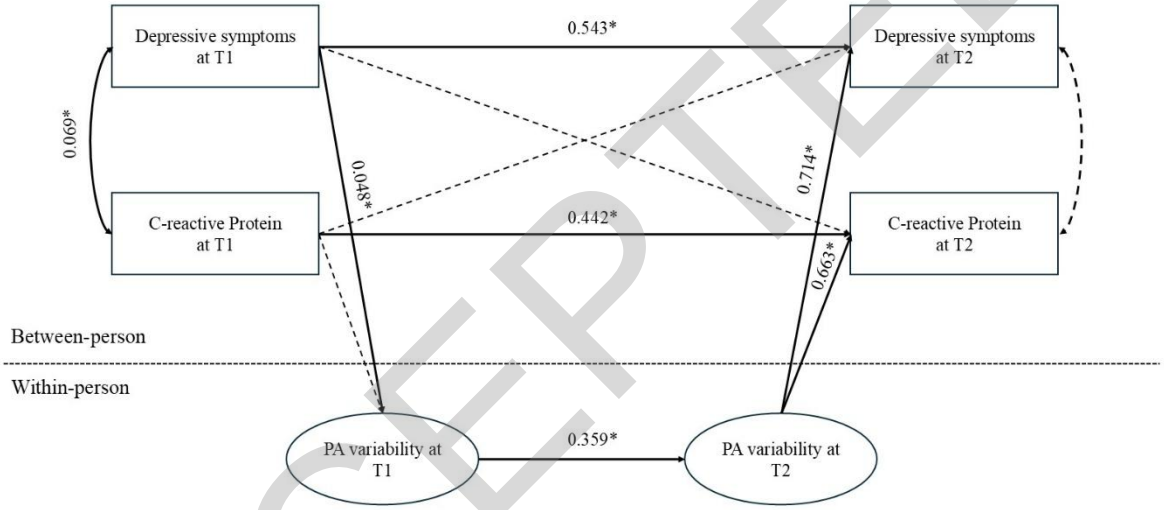

Figure 2

Multilevel Mediation of Negative Affective Reactivity to Daily Stressors in Depressive Symptoms and CRP

Note. Bold lines indicate credible paths, and dashed lines represent non-credible paths. The analysis was adjusted for age, gender, education level, race, and household income at Time 1. When inflammation was the outcome, models were additionally adjusted for BMI, smoking status, chronic health conditions, regular physical activity, and use of medication for blood pressure and controlling cholesterol.

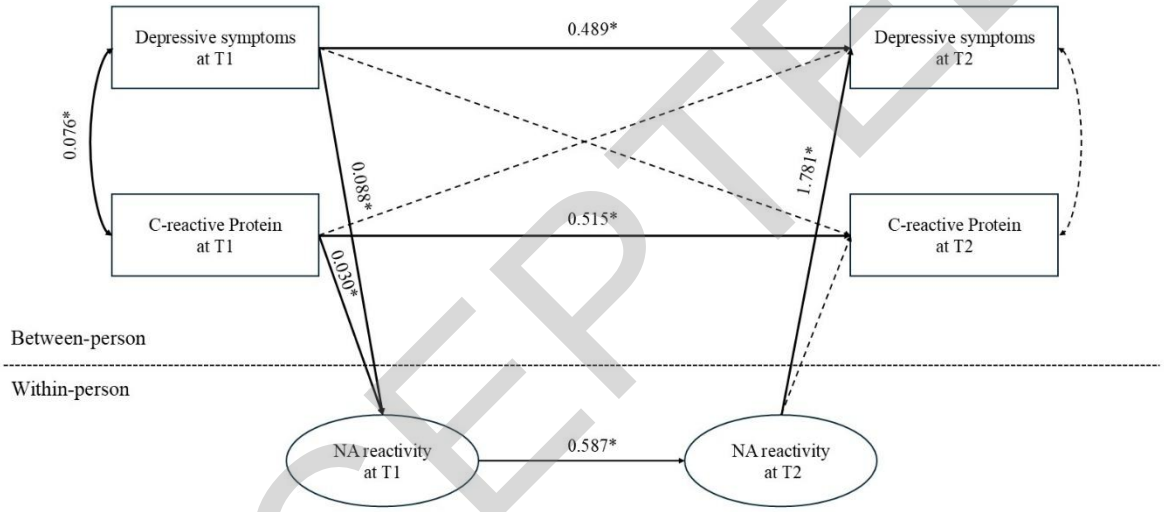

Table 1

Descriptive Statistics and Correlations among Main Study Variables ($N = 563$, $N_{days} = 4{,}504$)

Variable	*M* (*SD*)	range	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. T1 age	52.38 (9.74)	34-81	1.000													
2. T1 depressive symptoms	7.91 (8.01)	0-49	-0.182***	1.000												
3. T1 cytokines	4.70 (4.64)	1.76-97.25	0.226***	-0.026	1.000											
4. T1 CRP	2.92 (4.87)	0.07-59.3	-0.001	0.113**	0.357***	1.000										
5. T1 PA variability	0.33 (0.20)	0-1.36	-0.177***	0.244***	-0.021	0.065	1.000									
6. T1 NA variability	0.18 (0.16)	0-1.20	-0.190***	0.350***	-0.077†	0.065	0.406***	1.000								

7. T1 PA reactivity	-0.13 (0.05)	-0.33-0.03	-0.114*	0.320***	-0.035	0.000	0.031	0.188***	1.000						
8. T1 NA reactivity	0.18 (0.14)	0.05-1.05	-0.182***	0.428***	-0.036	0.098*	0.258***	0.798***	0.276***	1.000					
9. T2 depressive symptoms	8.72 (7.73)	0-57	-0.024	0.591***	0.009†	0.074†	0.232***	0.332***	0.193***	0.392***	1.000				
10. T2 cytokines	5.35 (3.24)	1.48-43.58	0.255***	0.030	0.463***	0.193***	0.027	-0.007	-0.013	-0.003	0.065	1.000			
11. T2 CRP	3.84 (5.51)	0.09-33.6	0.004	0.141**	0.202***	0.528***	0.111*	0.092*	-0.009	0.059	0.145**	0.366***	1.000		
12. T2 PA variability	0.32 (0.20)	0-1.34	-0.082†	0.205***	0.088†	0.178***	0.249***	0.193***	0.044	0.139**	0.212***	0.094*	0.226***	1.000	
13. T2 NA variability	0.15 (0.14)	0-0.95	-0.148**	0.367***	0.010	0.123**	0.237***	0.460***	0.170***	0.407***	0.372***	0.044	0.170***	0.513***	1.000

14. T2 PA reactivity	-0.13 (0.01)	-0.17--0.06	-0.116*	0.281**	0.028	0.089†	0.103*	0.196*	0.289**	0.261**	0.276**	0.036	0.098*	0.016	0.201**	1.000
15. T2 NA reactivity	0.14 (0.08)	-0.02-0.60	-0.180**	0.392**	0.057	0.121*	0.192**	0.431**	0.204**	0.513**	0.384**	0.029	0.131*	0.323**	0.712**	0.201**

Note. T1 = Time 1; T2 = Time 2; Affective reactivity was calculated based on 3,383 daily observations from 472 participants; Descriptive statistics are based on raw values; Correlations are based on transformed variables used in the analyses.

†$p < .10$, *$p < .05$, **$p < .01$, ***$p < .001$