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Daily Stressors, Emotion Dynamics, and Inflammation in the MIDUS Cohort

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Abstract

Background The current study (1) examined links between daily stressors and inflammation and (2) tested whether negative emotion dynamics (emotional variability) is one pathway through which stressors are linked to inflammation.

Method A cross-sectional sample of 986 adults (aged 35–86 years, 57% female) from MIDUS reported daily stressor frequency and severity and negative emotions on 8 consecutive nights. Negative emotion variability (intraindividual standard deviation), controlling for overall mean level (intraindividual mean), was the focus of the current study. Interleukin-6 (IL-6) and C-reactive protein (CRP) were assayed from blood drawn at a clinic visit. Regression models adjusted for demographics, health factors, and the time between assessments.

Results More severe daily stressors were associated with higher CRP, but this effect was accounted for by covariates. More frequent daily stressors were associated with lower IL-6 and CRP. In follow-up analyses, significant interactions between stressor severity and frequency suggested that participants with lower stressor severity and higher stressor frequency had the lowest levels of IL-6 and CRP, whereas those with higher stressor severity had the highest levels of IL-6 and CRP, regardless of frequency. Daily stressor frequency and severity were positively associated with negative emotion variability, but variability was not linearly associated with inflammation and did not operate as a mediator.

Conclusion Among midlife and older adults, daily stressor frequency and severity may interact and synergistically associate with inflammatory markers, potentially due to these adults being advantaged in other ways related to lower inflammation, or in a pattern aligning with hormetic stress, where frequent but manageable stressors may yield physiological benefits, or both. Negative emotion variability does not operate as a mediator. Additional work is needed to reliably measure and test other emotion dynamic metrics that may contribute to inflammation.

Keywords Daily stress · Negative affect · Inflammation · Affect variability · Inertia

Introduction

Daily stressors have been linked to concurrent and long-term health consequences, including mortality [1–4], which may be explained in part by systemic inflammation. Circulating levels of inflammatory proteins, including interleukin-6 (IL-6) and C-reactive protein (CRP), predict the development and progression of age-related chronic disease and increase risk for mortality [5, 6]. Models of stress and health suggest that stressors trigger negative emotional states that, through their effects on sympathetic nervous and neuroendocrine systems, may alter immune processes [7]. Meta-analyses, however, generally have not found overall levels of negative emotion states to be associated with immune outcomes [8, 9]. One reason might be that emotional responses to stress are inherently dynamic processes that manifest across time and situations. The current study investigated links between daily stressor frequency and severity on the one hand and inflammation on the other, as well as how day-to-day emotion dynamics may contribute to those links.

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Exposure to more frequent daily stressors is linked to higher circulating IL-6 and CRP levels and upregulation of proinflammatory gene expression [10–13], and exposure to more severe daily stressors is linked to higher stimulated IL-6 production [14]. However, whereas previous studies focused on a single dimension of daily stressors (e.g., frequency), or treated stressors as equal regardless of severity, the current study distinguished these stressor attributes to examine their individual and joint effects on inflammation. Examining stressor frequency and severity individually in the same study is useful to determine whether mere exposure versus severity of stressors yield similar patterns and magnitude effects on inflammation. Additionally, the interaction of stressor frequency and severity can highlight combinations of stressor dimensions that may yield the most detrimental immune effects; specifically, stressors that are both frequent and severe may indicate a form of chronic stress (see [15] for a related conceptualization) that repeatedly activates physiological systems, resulting in cumulative burden and allostatic load over time [16].

The link between daily stressors and inflammation may be explained by day-to-day emotion dynamics. Akin to other time-series data, fluctuations in daily emotions can be decomposed into the overall level, variability, and autocorrelation. The *overall level* or intraindividual mean (iM) is the mean across an individual's emotion observations. In the current study, *emotional variability* is defined as the extent to which a person's emotion scores deviate from their own mean, or the intraindividual standard deviation (iSD) of emotion across days [17]. Higher variability reflects emotions that deviate more from the individual's iM. *Emotional inertia* is the autocorrelation of emotion across days. More inert emotions are more likely to persist or linger from one moment to the next and may be more resistant to regulation efforts (slower return to homeostatic levels after perturbation) [18]. (The mean squared successive difference has been used in other studies as a measure of emotion variability; however, it is a function of both the iSD and autocorrelation [19] and is therefore less clearly interpretable.) Together, these three components (mean, variability, and autocorrelation) capture important aspects of emotion dynamics. As in most principal-component-type analyses, the first component (mean) accounts for the most variance and often has more predictive value than the second and third components [20, 21]. Nevertheless, the second and third components may be important health predictors; in the present study, we focus on variability and inertia controlling for their overlap with the mean level.

Naturally occurring stressors may influence emotion dynamics that, in turn, influence physical health. Previous daily diary studies have examined emotional reactivity or recovery to daily stressors (changes in emotion levels on or after days when one or more stressors occur) and their health correlates [22, 23]. However, these studies typically controlled for rather than directly tested stressor frequency and treated stressor days as equal regardless of the stressor(s) severity. Experimentally induced stress and higher levels of global perceived stress were associated with more variable and more inert negative emotions and behaviors [18, 24]. In turn, emotional variability and inertia contribute to psychological health (e.g., [18, 25, 26]), but less is known about their role in physical health. From a functionalist view, negative emotions promote states of action readiness; in preparation, the sympathetic and neuroendocrine systems are activated in coordinated ways [27] to support adaptive actions. General emotions that are *highly variable* in the context of stress may be associated with biological systems that become activated and then attempt to recover, potentially without sufficient time for restoration. Highly variable emotions may also lead to a mismatch between what is predicted based on past emotions (e.g., low negative emotion and little to no activation of biological systems) versus what actually happens (e.g., high negative emotion), leading to prediction errors [28] and, over time, a dysregulated immune response. Additionally, emotions that are *more inert* and do not return to equilibrium may be associated with biological systems that remain active and, after repeated occurrences, promote heightened inflammation [16]. Empirically, higher emotion variability is linearly associated with physical ill health and with poorer antibody response to vaccine and nonlinearly associated with higher inflammation [29–31].

Together, these empirical studies as well as theoretical work linking daily stressors to health suggest that exposure and emotional responses to daily stressors reflect individual differences that may contribute to poorer health over time if the exposure or responses are frequent enough or strong enough [32]. Specifically, people exposed to more frequent and severe daily stressors (which may lead to or represent a form of chronic stress [15, 33]) who, in turn, show more variable and inert emotion dynamic tendencies, may evidence physiological dysregulation that accumulates over time and leads to higher levels of inflammation and poorer health. This proposed model is important to test because first, much of the stress-immune health literature does not explicitly incorporate emotion, much less emotion dynamics, despite emotion processes being a theorized mechanism linking stress and health [7, 34]. Second, although previous empirical evidence supports individual links in the proposed conceptual model, such as between stress and emotion dynamics [18, 24] and emotion dynamics and immune health [30, 31], this piecemeal approach limits our understanding of the "big picture" and fails to test the entire model connecting daily stressors, emotion dynamics, and inflammation using the same data. Therefore, we propose and test a mediation model to provide a more accurate and nuanced view of one emotion pathway through which stress may influence immune health.

The current study examined the between-person associations among dimensions of daily stressors (frequency, severity) and inflammation and explored the mediating role of emotion dynamics (variability, inertia). We used data from the sample Midlife in the United States (MIDUS). Strengths include focus on a moderately diverse, aging sample with emerging health concerns and inclusion of biomarkers. Additionally, daily stressors and negative emotions were measured using daily diaries, which avoid longer-term retrospection, are more ecologically valid, and provide the ability to capture a process as it unfolds over time. We hypothesized that:

1. People who experienced more frequent and more severe daily stressors had higher inflammation, as measured by IL-6 and CRP. We followed up by testing whether stressor severity moderated the effect of stressor frequency on inflammation; more severe stressors could exacerbate the positive association between stressor frequency and inflammation.
2. Concurrent emotion dynamics mediated the association between daily stressors and inflammation, such that higher frequency and severity of daily stressors were associated with more variable and more inert[1] negative emotions, which, in turn, were associated with higher inflammation.

Additional exploratory emotion dynamics models tested discrete negative emotion states, whether mean levels of negative emotion interacted with variability to predict inflammation, and nonlinear associations between variability and inflammation.

Methods

Participants and Procedures

Participants came from the second wave of Midlife in the United States (MIDUS II), a national survey designed to examine the roles of behavioral, psychological, and social factors in aging and health. Data were drawn from two MIDUS subprojects (collected 2004–2009): the National Study of Daily Experiences (NSDE) and the Biomarker Project. Of the 1,011 participants who participated in both the NSDE and Biomarker Projects, for the current analyses, we excluded participants who were missing IL-6 ($n=1$), CRP ($n=3$), or both ($n=9$), or who had only 1 day of diary data ($n=12$). Participants ($N=986$) included in this analysis were on average 57.97 years old (SD = 11.55, range: 35–86) and 57% female; 81% were White, 15% were African American, 1.2% were Native American, 0.2% were Asian, and 2.3% were other (0.2% missing). The average total household income was $70,923 (SD = 56,978, range: $0–$300,000), and 73% of the sample had at least some college education. The sample included 96 sibling pairs; in sensitivity analyses, we removed one sibling from each family (see the "Data Analysis" section). Additional participant details are reported in supplementary materials.

For the NSDE, participants reported their daily stressors and negative emotions during a brief semi-structured telephone interview on eight consecutive evenings (95% completed 6 or more diaries; M = 7.51, SD = 0.99, range: 2–8). For the Biomarker Project, participants traveled to a Clinical Research Center (UCLA, University of Wisconsin, or Georgetown) to complete a medical history interview and provide blood. NSDE and biomarker collections were separated by a median of 6 months, with 38% completing the daily diary protocol first and 62% completing the biomarker protocol first. IL-6 and CRP are moderately stable over months to years (e.g., the ICCs for IL-6 and CRP were 0.57 and 0.55 across 2 years) [35], as are emotion dynamics (e.g., negative emotion variability $r_{stability}$ was 0.74 across a 4-month span) [36]. In sensitivity analyses, we assessed whether the noted associations were moderated by the time interval between daily diary and biomarker assessment (see the "Data Analysis" section). All procedures were approved by Institutional Review Boards at the participating institutions, and all participants provided informed consent.

Measures

Daily Stress

The Daily Inventory of Stressful Events [37] assessed whether participants experienced up to seven different stressors in the past 24 h, including the following: had an argument, avoided an argument, had a stressor at work or school, had a stressor at home, faced discrimination, had a network stressor (a stressor that occurred to a close friend or family member), other miscellaneous stressor (e.g., traffic), and obtained ratings of the severity of each (0 = not at all, 4 = very stressful). For each individual, *stressor frequency* was calculated as the sum total number of stressors reported across all days divided by the number of completed interview days (i.e., no. of stressors per day) and *stressor severity* was calculated as the average ratings of all stressors experienced on each day, averaged across days.

[1] We present the inertia hypotheses in accordance with our a priori plan of analysis; however, the inertia scores had prohibitively low reliability in the present study, so no results are reported for these hypotheses. See the "Methods" section for details.

Daily Negative Emotion

Negative emotion was assessed using items from the Non-Specific Psychological Distress Scale [38] and the Positive and Negative Affect Schedule (PANAS) [39]. The Non-Specific Psychological Distress Scale was developed for use in MIDUS I and supplemented with items from the PANAS in MIDUS II. In the current study, all items administered in MIDUS II were used. We combined items across scales to (1) expand the distress-related items to include additional negative emotion items from the PANAS and (2) follow the same negative emotion composite approach used by other daily diary MIDUS investigations to allow for comparisons across studies (e.g., [3, 4, 22, 23]). Participants rated how often (0 = not at all, 4 = all the time) they experienced 14 different emotion states during the previous 24 h: restless or fidgety, nervous, worthless, so sad that nothing could cheer them up, that everything was an effort, hopeless, lonely, afraid, jittery, irritable, ashamed, upset, angry, and frustrated. Ratings were averaged across the 14 discrete emotion states to obtain 2 to 8 daily negative emotion scores (Cronbach's $\alpha = 0.91$) that were then used to calculate person-level scores for *overall negative emotion* (iM), *variability* of negative emotion (iSD), and *inertia* of negative emotion (autocorrelation). Emotion dynamics calculated from only 2 days of daily diary data may be inferior; however, the results remained unchanged when we excluded the 5 participants with 2 days of data, so they are included in the analyses. Following the analytical derivations in Du and Wang [40], reliability of the variability measure was adequate at 0.70–0.76. However, as in prior studies using other diary data [21, 40], the reliability of the inertia measure was very poor at 0.03–0.05, and thus not used in any further analyses. When negative emotion variability was used as the outcome variable in a mediation analysis, it was log transformed and standardized to improve normality and obtain regression parameters in effect size units. Last, discrete negative emotion states may be of particular interest to readers, so a description of these analyses and results are presented in supplementary materials, Tables S1-S4.

Inflammatory Markers

Fasting venous serum samples were collected and stored at − 65° C until time of assay. IL-6 (pg/mL) was assayed at the MIDUS Biocore Lab (University of Wisconsin, Madison, WI) using the Quantikine high-sensitivity ELISA (R&D Systems, Minneapolis, MN). The assay range was 0.156–10 pg/mL. Intra-assay CV was 3.25% and inter-assay CV was 12.31%. CRP (mg/L) was assayed at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT) using the BNII nephelometer utilizing a particle enhanced immunonepholometric assay. The assay range was 0.175–1100 mg/L. Intra-assay CVs ranged from 2.3 to 4.4% and inter-assay CVs ranged from 2.1 to 5.7%. Both measures were positively skewed and thus natural log-transformed for analyses.

Covariates

Covariates accounted for extraneous variance in the inflammatory markers [41]. These included *age* (taken at the biomarker clinic visit), *sex* (self-reported as male or female), *body mass index* (BMI from height and weight measurements taken at the clinic visit), *medical comorbidities* (the number of diseases associated with more inflammation—i.e., cardiovascular disease, TIA or stroke, hypertension, arthritis, diabetes, and cancer—as reported during the clinic visit using a checklist of 20 physician-diagnosed chronic conditions), and *time interval* (the number of months between the daily diary and blood draw).

Data Analysis

The main hypotheses were examined using a series of standard regression models, implemented in R (version 4.0.0) using the base lm function and the lm.beta package (version 1.5.1). Log IL-6 and log CRP were each regressed (separately) on the measures of stressor frequency and stressor severity. The mediation hypothesis that individuals' stressor experiences lead to differences in inflammation through variability in negative emotion was tested using the mediation package with 5000 bootstraps and 95% bias-corrected confidence intervals [42]. Note that in the present analyses, the term mediator is used in the statistical sense because the current investigation does not meet all conditions for true mediation given the lack of temporal ordering of the predictors, mediator, and outcomes. All models were run with and without covariates; continuous variables were grand-mean centered, and alpha level was set at 0.05 for all inferential tests. Multicollinearity was not a problem (variance inflation factor values ranged between 1 and 2.73).

Robustness of results was checked using three sets of sensitivity analyses (Supplementary Tables S5-S8). First, we checked whether the time interval between the daily diary and blood collection moderated the strength of associations between daily experiences and inflammation [43]. Second, we checked whether the non-independence of siblings was consequential by rerunning the analyses after random removal of one sibling from the 96 sibling pairs. Third, we checked the influence of higher CRP values, which may indicate acute infection [44], by excluding 37 people with values greater than 10 mg/L.

Results

Table 1 shows descriptive statistics and bivariate correlations among main study variables. Participants reported between 0 and 2.7 stressors per day, with an average of less than one stressor per day. Stressors ranged from being "not at all" to "very" stressful and were rated as "somewhat" stressful on average. Moderate bivariate correlations indicated that the stressor and negative emotion measures were not redundant (r = 0.32–0.45), and that consistent with prior studies (e.g., [45]), individuals with higher mean negative emotion also had higher negative emotion variability ($r = 0.74$, $p < 0.001$). Younger age and female sex were related to more frequent daily stressors ($r = -0.20$–0.10, $ps < 0.002$), higher stressor severity ($r = -0.18$–0.23, $ps < 0.001$), and higher negative emotion variability ($r = -0.16$–0.10, $ps < 0.004$). As expected, more chronic conditions and higher BMI were associated with higher IL-6 ($r = 0.31$–0.35, $p < 0.001$) and CRP ($r = 0.23$–0.43, $p < 0.001$); in addition, older age was associated with higher IL-6 ($r = 0.22$, $p < 0.001$), and female sex was associated with higher CRP ($r = 0.18$, $p < 0.001$). Broadly summarized, all measures were associated in expected ways.

Daily Stressors and Inflammation

The first hypothesis was that higher daily stressor frequency and severity would each be associated with higher inflammation. Table 1 depicts unadjusted models' effect sizes and Table 2 depicts results from adjusted models. Unexpectedly, higher *stressor frequency* was associated with lower IL-6 in unadjusted ($p = 0.003$) and adjusted models ($p = 0.025$) and was associated with lower CRP in the adjusted ($p = 0.041$) but not the unadjusted model ($p = 0.22$). Per additional stressor, IL-6 and CRP decreased by 0.90 pg/mL and 0.86 mg/L respectively, which would be sufficient to put a person with the median IL-6 (2.07 pg/mL) and CRP levels (1.35 mg/L) into the lowest-risk quartiles for mortality [6]. As expected, higher *stressor severity* was associated with higher CRP (unadjusted model: $p = 0.005$) such that a 1-unit increase in stressor severity was associated with a 1.18 mg/L increase in CRP, which would be sufficient to put a person with the median CRP level (1.35 mg/L) near the highest-risk quartile for mortality [6]. However, this effect diminished and was no longer statistically significant in the adjusted model ($p = 0.18$). Contrary to the hypothesis, stressor severity was not associated with IL-6 ($p = 0.83$).

All associations remained unchanged in *adjusted* sensitivity models with one exception: daily stressor frequency

Table 1 Descriptive statistics and bivariate correlations for primary study variables

	1	2	3	4	5	6	7	8	9	10	11
1. Daily stressor frequency	—										
2. Daily stressor severity	**0.15**	—									
3. Mean negative emotion (iM)	**0.45**	**0.32**	—								
4. Negative emotion variability (iSD)	**0.36**	**0.33**	**0.74**	—							
5. Log IL-6	**−0.09**	−0.02	−0.02	−0.00	—						
6. Log CRP	−0.04	**0.09**	0.01	0.04	**0.50**	—					
7. Age	**−0.20**	**−0.18**	**−0.19**	**−0.16**	**0.22**	0.04	—				
8. Female	**0.10**	**0.23**	0.08	**0.10**	0.05	**0.18**	−0.06	—			
9. BMI	0.01	0.03	0.01	0.03	**0.35**	**0.43**	−0.03	0.00	—		
10. No. chronic conditions	−0.05	−0.02	0.02	0.04	**0.31**	**0.23**	**0.44**	0.01	**0.23**	—	
11. Time interval[a]	−0.01	−0.06	−0.06	−0.08	0.07	**−0.09**	0.05	0.00	−0.06	−0.06	—
M or % (SD)	0.56 (0.45)	1.75 (0.66)	0.21 (0.28)	0.18 (0.17)	0.77 (0.73)	0.37 (1.18)	57.97 (11.55)	57%	29.65 (6.48)	1.11 (1.12)	0.68 (17.44)
Range	0–2.71	0–3	0–2.55	0–1.23	−1.83–3.14	−3.94–4.12	35–86		14.99–64.06	0–6	−46–56

Given the sample size ($N = 986$), correlations ≥|.09| are significant at $p < .01$ (in bold). [a]The time interval in months was calculated as (date of blood draw–date of daily diary); negative values refer to blood drawn before the daily diary, and positive values refer to blood drawn after the daily diary

Table 2 Daily stressor frequency and severity predicting inflammation in adjusted models (*c* path)

	Log IL-6				Log CRP				Log IL-6				Log CRP			
Predictors	β	*B*	*SE*	*p-value*	β	*B*	*SE*	*p-value*	β	*B*	*SE*	*p-value*	β	*B*	*SE*	*p-value*
Intercept	−0.08	0.72	0.03	**< 0.001**	−0.21	0.13	0.05	**0.011**	−0.08	0.71	0.03	**< 0.001**	−0.20	0.14	0.05	**0.008**
Stressor frequency	−0.07	−0.11	0.05	**0.025**	−0.06	−0.15	0.08	**0.041**								
Stressor severity									−0.01	−0.01	0.03	0.827	0.04	0.07	0.05	0.181
Age	0.15	0.01	0.00	**< 0.001**	−0.01	−0.00	0.00	0.676	0.17	0.01	0.00	**< 0.001**	0.02	0.00	0.00	0.614
Sex (1 = male, 2 = female)	0.13	0.10	0.04	**0.020**	0.37	0.43	0.07	**< 0.001**	0.15	0.11	0.05	**0.018**	0.35	0.41	0.07	**< 0.001**
BMI	0.32	0.04	0.00	**< 0.001**	0.39	0.07	0.01	**< 0.001**	0.34	0.04	0.00	**< 0.001**	0.42	0.07	0.01	**< 0.001**
Chronic conditions	0.17	0.11	0.02	**< 0.001**	0.14	0.15	0.03	**< 0.001**	0.16	0.10	0.02	**< 0.001**	0.12	0.13	0.03	**< 0.001**
Time interval[a]	0.09	0.00	0.00	**0.001**	−0.06	−0.00	0.00	**0.050**	0.08	0.00	0.00	**0.007**	−0.05	−0.00	0.00	0.063
R^2/R^2 adjusted	0.214/0.209				0.238/0.233				0.218/0.213				0.254/0.250			

Standardized (β) and unstandardized (*B*) coefficients are shown. [a]The time interval was calculated as (date of blood draw–date of diary)

was not significantly associated with CRP when one sibling from each family was excluded ($p = 0.079$; likely due to less power—the estimate decreased by 0.01 and the standard error remained the same) and when people with higher CRP values were excluded ($p = 0.23$). The time interval between assessments did not moderate any associations between stressor dimensions and inflammation ($ps > 0.31$).

The Mediating Role of Negative Emotion Variability

To examine the intervening role of negative emotion variability on the association between daily stressors and inflammation, standardized log negative emotion variability was first regressed on daily stressor frequency and severity (*a* paths). Higher daily stressor frequency and severity each associated with higher negative emotion variability such that a 1-unit increase in stressor frequency was associated with 0.32 SDs increase in log variability, or 1.38 SDs increase in raw variability ($B = 0.32$, SE = 0.059, β = 0.14, $p < 0.001$), and a 1-unit increase in stressor severity was associated with 0.23 SDs increase in log variability, or 1.26 SDs increase in raw variability ($B = 0.23$, SE = 0.039, β = 0.16, $p < 0.001$). Next, however, negative emotion variability was not associated with IL-6 ($B = 0.067$, SE = 0.19, β = 0.015, $p = 0.72$) or CRP ($B = 0.26$, SE = 0.30, β = 0.036, $p = 0.39$; *b* paths). When daily stressor dimensions and negative emotion variability were entered together in adjusted models (*c′* path, Table 3), the effect of stressor frequency increased in size and remained statistically significant for IL-6 ($p = 0.011$) and CRP ($p = 0.045$), and the effect of stressor severity remained non-significant, as did negative emotion variability. All indirect paths were not statistically significant (results not shown), primarily as a result of very low associations between negative emotion variability and inflammation. The pattern of results was the same across the sensitivity checks, and the time interval between assessments did not moderate any associations between negative emotion variability and inflammation ($ps > 0.28$).

Stressor Severity Moderates Influence of Stressor Frequency on Inflammation

The effect of stressor frequency on IL-6 and CRP depended on stressor severity in both unadjusted (IL-6: $B = 0.22$, SE = 0.10, β = 0.078, $t = 2.18$, $p = 0.029$; CRP: $B = 0.47$, SE = 0.16, β = 0.10, $t = 2.93$, $p = 0.004$) and adjusted models (IL-6: $B = 0.19$, SE = 0.090, β = 0.068, $t = 2.18$, $p = 0.030$; CRP: $B = 0.38$, SE = 0.14, β = 0.085, $t = 2.76$, $p = 0.006$). Interactions were probed at one standard deviation (SD) units above and below the grand means of stressor frequency and severity (Fig. 1). At low stressor severity, more frequent daily stressors were associated with lower IL-6

Table 3 Daily stressor frequency and severity and negative emotion variability predicting inflammation in adjusted models (*c'* path)

	Log IL-6				Log CRP				Log IL-6				Log CRP			
Predictors	β	*B*	*SE*	*p*-value	β	*B*	*SE*	*p*-value	β	*B*	*SE*	*p*-value	β	*B*	*SE*	*p*-value
Intercept	−0.07	0.72	0.03	**< 0.001**	−0.20	0.13	0.05	**0.011**	−0.08	0.71	0.03	**< 0.001**	−0.20	0.14	0.05	**0.008**
Stressor frequency	−0.08	−0.13	0.05	**0.011**	−0.06	−0.17	0.08	**0.045**								
Stressor severity									−0.01	−0.01	0.04	0.687	0.05	0.08	0.06	0.151
Negative emotion variability (iSD)	0.02	0.09	0.19	0.622	0.04	0.29	0.30	0.332	0.03	0.12	0.19	0.536	0.03	0.20	0.30	0.511
Mean negative emotion (iM)	0.02	0.06	0.12	0.619	−0.02	−0.09	0.18	0.638	−0.01	−0.02	0.11	0.886	−0.05	−0.20	0.18	0.262
Age	0.15	0.01	0.00	**< 0.001**	−0.01	−0.00	0.00	0.736	0.17	0.01	0.00	**< 0.001**	0.01	0.00	0.00	0.718
Sex (1 = male, 2 = female)	0.13	0.10	0.04	**0.024**	0.36	0.43	0.07	**< 0.001**	0.14	0.11	0.05	**0.018**	0.35	0.41	0.07	**< 0.001**
BMI	0.32	0.04	0.00	**< 0.001**	0.39	0.07	0.01	**< 0.001**	0.34	0.04	0.00	**< 0.001**	0.42	0.07	0.01	**< 0.001**
Chronic conditions	0.16	0.11	0.02	**< 0.001**	0.14	0.14	0.03	**< 0.001**	0.16	0.10	0.02	**< 0.001**	0.13	0.13	0.03	**< 0.001**
Time interval[a]	0.09	0.00	0.00	**0.001**	−0.05	−0.00	0.00	0.059	0.08	0.00	0.00	**0.006**	−0.05	−0.00	0.00	0.065
R^2/R^2 adjusted	0.215/0.209				0.239/0.232				0.219/0.212				0.256/0.249			

Standardized (β) and unstandardized (*B*) coefficients are shown. [a]The time interval was calculated as (date of blood draw–date of diary)

(simple slope: B = −0.38, SE = 0.12, β = −0.22, *t* = −3.11, *p* = 0.002) and lower CRP (simple slope: B = −0.68, SE = 0.19, β = −0.25, *t* = −3.50, *p* = 0.0005), whereas at high stressor severity, participants had similarly high levels of IL-6 and CRP at both low and high stressor frequency (IL-6 simple slope: B = −0.090, SE = 0.062, β = −0.053, *t* = −1.47, *p* = 0.14; CRP: B = −0.062, SE = 0.098, β = −0.023, *t* = −0.63, *p* = 0.53). Interactions remained statistically significant when excluding one sibling from each family (IL-6: B = 0.21, SE = 0.093, β = 0.075, *t* = 2.23, *p* = 0.026; CRP: B = 0.43, SE = 0.14, β = 0.098, *t* = 3.02, *p* = 0.003) and when excluding participants with high CRP values (B = 0.37, SE = 0.13, β = 0.088, *t* = 2.74, *p* = 0.006).

To further probe this result, mediated moderation was tested using the lavaan package to determine whether the interaction between stressor frequency and severity on inflammation was mediated by negative emotion variability. However, the indirect effect from adjusted models was not statistically significant for IL-6 (0.000, SE = 0.010, 95% CI = −0.020 to 0.024) or CRP (−0.011, SE = 0.016, 95% CI = −0.046 to 0.020).

Variability and Inflammation Exploratory Analyses: Moderation and Nonlinear Associations

Exploratory analyses tested whether the mean level of negative emotion moderated the association between variability and inflammation and whether variability exhibited a quadratic association (iSD^2) with inflammation. These analyses were based on previous work demonstrating (1) that the health effects of emotional variability may depend on mean levels of emotion [30, 31], and (2) that while normal emotional responses to stress produce some variability in negative emotion, only the most extreme levels of variability may be maladaptive for health [31, 46]. Mean negative emotion did not moderate the associations between variability and IL-6 (*p* = 0.17) or CRP (*p* = 0.33) in adjusted models. The nonlinear model exposed a quadratic association between variability (iSD^2) and IL-6 (*B* = 0.94, SE = 0.41, β = 0.097, *t* = 2.32, *p* = 0.021), but not CRP (*p* = 0.95) in adjusted models. The quadratic effect of negative emotion variability on IL-6 describes a convex pattern (Fig. 2) whereby lower variability is associated with higher IL-6, but moderate and high variability is associated with lower IL-6. Although the fully quadratic function is U-shaped, we limit our interpretation to the dense region of the data (−1SD to +1SD, 81% of data).

Discussion

The ups and downs of everyday life, including daily stressors and fluctuating emotions, are relevant for health (e.g., [1]). The current study examined associations between

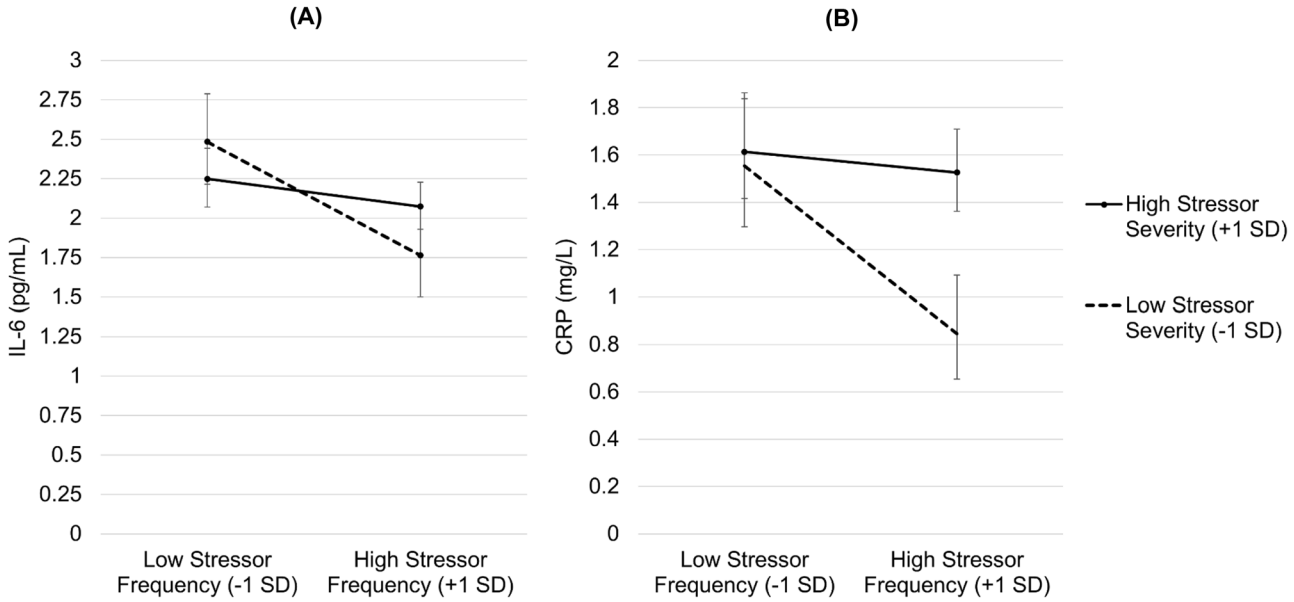

Fig. 1 Simple slopes depicting the unstandardized model estimates with their 95% confidence intervals for interleukin-6 (IL-6) and C-reactive protein (CRP)

daily stressor dimensions and inflammation and tested a theoretical model whereby negative emotion dynamics, specifically emotional variability, is a pathway through which daily stressors are associated with inflammation. In this sample of middle-age and older adults, daily stressor frequency and severity were significantly associated with inflammation and negative emotion variability, but variability was not associated with inflammation and did not operate as a mediator.

The main effect findings for stressor dimensions (frequency, severity) on inflammation partially supported hypotheses. As expected, more severe daily stressors were associated with higher CRP, but this effect was primarily accounted for by covariates. Unexpectedly, experiencing more frequent daily stressors was associated with lower levels of IL-6 and CRP. This finding was not hypothesized, but the results held for both IL-6 and CRP. However, the CRP effect did not hold in sensitivity analyses when

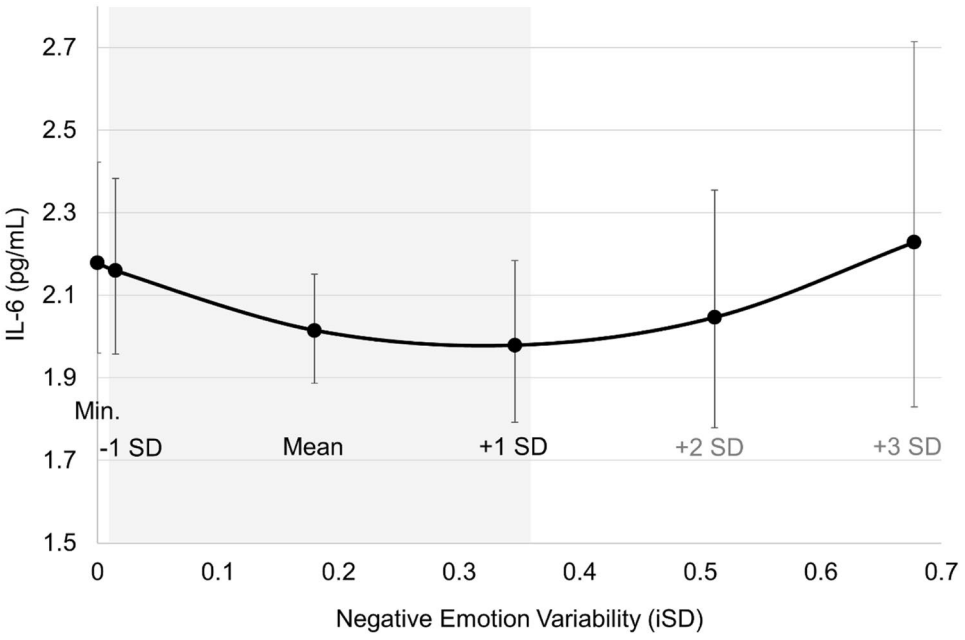

Fig. 2 The quadratic association between negative emotion variability and interleukin-6 (IL-6). Unstandardized variability estimates with their 95% confidence intervals are depicted. Most data (81%) are in the gray-shaded region (− 1SD to + 1SD)

participants with the highest CRP values (> 10 mg/L)—indicating possible acute infection [44]—were excluded, suggesting these participants may be reporting very few stressors, potentially due to sickness behavior and lower engagement with other people and activities, and therefore driving this effect. In addition, there was sufficient variability in stressor frequency (only 7% reported experiencing zero total stressors across the sampling period, whereas 93% reported between 1 and 19 total stressors), which increases confidence in this effect.

However, the individual effects of stressor dimensions were qualified by an interaction; specifically, stressors that were more frequent but low in severity were associated with significantly lower levels of IL-6 and CRP, whereas more severe stressors were associated with high levels of IL-6 and CRP regardless of frequency. One explanation for this finding in line with a previous MIDUS study [47] is that individuals who experience more frequent but less severe stressors may be advantaged in ways that are related to immune-health benefits, such as by being more socially integrated, working for pay, or having higher socioeconomic status. To test this interpretation, we examined post hoc whether controlling for these potential health buffers, including *social integration* (three items scored on a 7-point Likert-type scale from 1 = strongly agree to 7 = disagree strongly: "I don't feel I belong to anything I'd call a community," "I feel close to other people in my community," and "My community is a source of comfort," with higher scores reflecting a greater sense of social integration; Cronbach's $\alpha = 0.77$; $M = 14.96$, SD = 4.13, range: 3–21), *currently working for pay* (0 = no, 1 = yes; 47% working for pay), *education* (0 = high school or less, 1 = some college or more; 73% some college or more), and *household total income* ($M = 70{,}922$, SD = 56,977, range: 0–300,000 USD), affected the results. In regression models that tested the interaction between stressor frequency and severity on inflammation and included the planned covariates as well as the above health buffers, the effect for IL-6 decreased ($B = 0.16$, SE = 0.092, $\beta = 0.057$, $t = 1.76$, $p = 0.079$) but the results remained similar for CRP ($B = 0.36$, SE = 0.14, $\beta = 0.080$, $t = 2.53$, $p = 0.012$). Therefore, this interpretation may in part explain the IL-6 but not CRP findings. A different, not mutually exclusive, explanation untested by the present cross-sectional analyses is that this combination of stressor dimensions could help to highlight the effects of "hormetic stress," or stress that is limited and manageable and may result in physiological benefits [48]. More frequent but low severity stressors may activate the stress response and alter metabolic demands in short-term adaptive ways that strengthen cellular responses to stress. Moderate exercise is one such stressor, but mild psychological stressors may also act as hormetins. In addition, there may be differential effects across the lifespan, with hormesis present in midlife, but more detrimental effects of daily stressors early in life and in older age. This finding, which was not hypothesized, requires further investigation.

Global negative emotion variability did not mediate associations between daily stressors and inflammation. However, in supplemental analyses of more specific negative emotion states (composites of depressive symptoms, nervousness, and anger-related), variability in depressive symptoms yielded a statistically significant indirect effect at the Bonferroni-corrected level. Higher daily stressor frequency was associated with higher variability in depressive symptoms, which, in turn, was associated with higher IL-6. This finding requires replication but aligns with previous reports that higher variability in depressive symptoms predicts future stroke risk and cognitive decline [49, 50]; inflammatory processes have fundamental roles in both of these outcomes. The immune system may be more sensitive to certain negative emotions rather than more broad classifications, and future health research may detect more robust associations by reliably measuring emotion dynamics in specific emotions or emotion states.

How to reliably capture emotion dynamics warrants critical consideration. In the current study, the reliability of negative emotion variability scores was adequate. However, the negative emotion inertia scores had prohibitively low reliability, likely due to too few occasions with too large an interval between consecutive emotion measurements. Simulations indicate that even a large number of assessments (500) and high scale reliability (0.9) produced an average autocorrelation reliability of less than 0.4; the average autocorrelation reliability was larger than 0.80 only when the scale reliability was perfect (1.0) and there were more than 150 assessments [40]. Therefore, future studies that investigate health-relevant effects of emotion dynamics, particularly emotional inertia, may benefit from ecological momentary assessment with emotions measured with an adequate number of items for reliability estimates, assessed more frequently with a higher temporal resolution, and enriched with event-contingent measurement to improve signal-to-noise ratios ([51] and see [26] for recommendations). Continuing to estimate and report the reliabilities of emotion dynamics measures will be important to improving measurement in this area.

In the present study, negative emotion variability was not linearly associated with IL-6 or CRP. This is not consistent with previous reports that higher negative emotion variability predicts poorer immune function in younger adults (although this effect did not hold when including the mean level [30]) and physical ill health in the MIDUS sample [29]. The discrepancy may be due to measurement differences in the samples (younger vs. midlife and older adults), in the emotion variables (intensity vs. frequency), or in the outcome variables (a composite of self-reported physical ill health vs. inflammatory markers). The lack of significant

findings could also be due to small effect sizes. However, a recent study reported no significant linear association between negative emotion variability and inflammation, but there was evidence of moderation by mean emotion levels and nonlinear associations [31]. We did not find evidence of moderation by mean levels but did observe a similar pattern between variability (iSD^2) and inflammation (IL-6 in the present study, CRP in [31]). In both studies, low variability was associated with higher inflammation whereas moderate variability was associated with lower inflammation. Therefore, some emotional variability may be health-protective, but low variability may indicate a hyper-responsive, or conversely non-responsive, system that is less optimal for immune health.

Interpretation of the current findings is constrained by several limitations of the study design and methodology. Above all, these data are cross-sectional. Therefore, the reported results describe statistical mediation only and the temporal ordering of variables prevents definitive statements about directionality and potential mechanisms. However, the study provides relevant theoretical contribution, and an initial test of the model is an important starting point for future work with longitudinal data. Moreover, the absence of cross-sectional mediation does not necessarily mean the absence of longitudinal, time-ordered mediation [52]. There were no inflammatory biomarkers collected at baseline (MIDUS I), and MIDUS III biomarker data have not yet been released as of writing. Furthermore, the time interval between daily diary and biomarker collection varied. We controlled for this time interval in all analyses and further tested it as a moderator in sensitivity analyses, but no associations differed as a function of the time interval. Longitudinal data with multiple waves of daily experiences and inflammation data would strengthen confidence in the current findings and further clarify whether daily stressors and emotion dynamics relate to changes in inflammation over time, and their estimates of stability. In addition to emotion dynamics, *stressor dynamics* may also be of interest in future studies (e.g., the health effects of experiencing more variable and more inert stressors). The current study focused on negative emotions because they are an established predictor of poorer health [53] and are theorized to mediate the link between stress and stress-related biomarkers [7]; however, positive emotion dynamics may also influence immunity [30, 31]. In addition, although we tested in post hoc analyses plausible variables that may affect the current associations, unmeasured confounding may exist [54]. Last, although the sample was large, moderately diverse, with biomarker data and high compliance in daily diaries, adults were relatively educated and on average middle-aged. The findings may not generalize beyond these sample characteristics. Future investigations in even more diverse and older adult samples (e.g., 65 + years old) are needed to understand how racial, ethnic, and aging-related individual differences may further influence how daily experiences impact inflammation and later health and disease.

Conclusion

Daily stressors are common in everyday life, and the frequency with which these stressors occur and their severity may synergistically associate with inflammation. More severe daily stressors were associated with higher inflammatory levels at both low and high stressor frequency, but more frequent stressors that were less severe were associated with lower levels of inflammation. This effect may be due in part to adults who experience frequent but less severe stressors being advantaged in ways that are related to lower inflammation, or, if replicated, may represent hormetic stress, or both. In addition, more frequent and severe daily stressors were associated with higher variability in negative emotion, but overall negative emotion variability did not mediate the association between daily stressors and inflammation. Investigations that conceptualize more specific negative emotion states and incorporate more frequent emotion measures to reliably assess emotion dynamics, including inertia, will be valuable in uncovering how daily stressors and emotions influence disease-relevant immune health.

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Declarations

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Conflict of Interest The authors declare no competing interests.

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