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Mean affect and affect variability may interact to predict inflammation

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Abstract

Introduction: Individuals with greater affect variability (i.e., moment-to-moment fluctuations possibly reflecting emotional dysregulation) are at risk for greater systemic inflammation, which is associated with cardiovascular disease. Some evidence suggests that affect variability is linked with poorer health indicators only among those with higher average levels of affect, particularly for positive affect (PA), and that associations may be non-linear. The present study sought to examine whether links between both PA and negative affect (NA) variability and inflammation are moderated by average level of affect.

Methods: Participants (*N*=300, 50% female, ages 21–70, 60% non-Hispanic White, 19% Hispanic, 15% non-Hispanic Black) completed a lab assessment and provided a blood sample

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to measure systemic inflammation (i.e., TNF-α, IL-6, CRP). Affect was collected via a two-day ecological momentary assessment protocol where reports were collected about every 45-min during waking hours. Momentary affect ratings were averaged across both days (i.e., iM), separately for PA and NA, for each participant. Affect variability was calculated as the person-specific SD (i.e., iSD) of affect reports, separately for PA and NA. Linear and quadratic interactions were tested. Models included covariates for sex, race, and body mass index.

Results: There were significant interactions between NA iM and NA iSD predicting TNF-α (b=6.54; p<.05) and between PA iM and PA iSD predicting IL-6 (b=0.45; p<.05). Specifically, the association between these affect variability indicators and inflammatory markers were suggestive of a positive association among those with higher average affect but a negative association among those with lower average affect. There was no evidence of non-linear associations between affect and inflammation.

Discussion: Incorporating interactive effects between affect variability and average affect may be an important consideration in understanding affective-inflammatory associations.

1. Introduction

Average or global levels of affect (i.e., feeling states that are consciously accessible and which can include moods and emotions; see Russell & Barrett, 1999) are implicated in long-term health outcomes. Both positive affect (PA; affect states that are largely viewed as pleasant in valence) and negative affect (NA; affect states that are largely viewed as unpleasant in valence) have been associated with inflammation (Brouwers et al., 2013; Miyamoto et al., 2013). In this regard, higher average PA has generally been associated with lower systemic inflammation and potentially lower chronic disease risk, whereas higher average NA has generally been associated with higher systemic inflammation and potentially a higher risk. Systemic inflammation is a biological process that may lead to poorer long-term health outcomes (Franceschi & Campisi, 2014; Gouin et al., 2011; Steptoe et al., 2009).

Affect variability, or how much one's PA or NA states tend to fluctuate over time, is recognized as an increasingly important area of inquiry as higher affect variability has been linked with poorer health outcomes, including worse physical and mental health (Chan et al., 2016; Hardy & Segerstrom, 2017; Houben et al., 2015). Affect fluctuations that are large and repeated may be associated with chronic activation of the autonomic system (Levenson, 2014), resulting in higher systemic inflammation (Marvar & Harrison, 2012). Thus, it is plausible that repeated affect fluctuations have a substantive influence on health.

Although previous work linking affect variability to systemic inflammation is limited, there is some indication that associations between affect variability and inflammation may be especially strong among those with higher average affect (Jones et al., 2020). Moreover, previous work indicates that associations are better represented by quadratic associations (i.e., demonstrating U-shaped or J-shaped patterns; see Jones et al., 2020) indicating that, for those with higher average affect, both very high and very low affect variability may be associated with greater inflammation. Given the paucity of studies examining affect variability and inflammation, the purpose of the analysis presented below was to provide a

conceptual replication of previous work examining associations between affect variability and inflammation in another sample (Jones et al., 2020). This is important because relatively novel study findings may fail to conceptually replicate, leading to erroneous conclusions and pushing the field in unhelpful directions. To conduct our conceptual replication, we use data from the North Texas Heart study, which has several advantages in that it roughly maps on to national averages in terms of race and ethnicity (Bureau, 2021) and assesses multiple inflammatory markers (C-reactive protein, interleukin-6, and tumor-necrosis factor α) that may confer risk for the development of cardiovascular disease (Pearson et al., 2003). Additionally, in the present study affect is assessed approximately every 45 minutes, which is temporally aligned with research suggesting that most affective epochs resolve within an hour necessitating at least hourly measures to best capture variability (Lazarus et al., 2021).

1.1 Affect Variability and Inflammation

Generally, links between average or global affect and inflammation are expected to vary by valence with NA being positively and PA negatively associated with inflammation. In contrast, higher affect variability is theorized to be linked with poorer health outcomes (e.g., greater inflammation) regardless of affect valence (Chan et al., 2016; Hardy & Segerstrom, 2017; Houben et al., 2015). This is because higher affect variability is thought to reflect an inability to maintain ideal affective states (high PA and low NA) in the face of environmental demands, or perhaps a tendency to over-respond to environmental stimuli (Chan et al., 2016; Gruber et al., 2013; Wichers et al., 2015). It is possible, however, that there may be significant interactions between average levels of affect with measures of variability. According to the Fragile PA theory (Ong & Ram, 2016), although higher average PA tends to be associated with beneficial health outcomes, when combined with high PA variability, higher average PA may actually be linked with poorer health outcomes. NA that is high and stable (i.e., consistently high NA) may link more strongly with poorer health outcomes, but it is also possible that higher NA variability maintains a distinct association with health outcomes and does not interact with average levels of NA. More specifically, it may be that regardless of what their typical NA intensity is, a stress-response cascade may be triggered among those who tend to have heightened NA fluctuations to their environment, resulting in poorer health and wellbeing outcomes. Results from two studies provide limited evidence that associations may be partially dependent on average affect levels, particularly for PA. Jenkins and colleagues (2018) found that higher PA variability was linked with lower antibody titers to an influenza vaccine (indicating less immunity after vaccination) – but only among those with higher average PA. NA variability was more consistently linked with lower antibody titers across levels of NA intensity. In another study, both PA and NA variability were linked with higher systemic inflammation only among those with higher average affect (Jones et al., 2020).

As previously noted, some studies have found non-linear effects, indicating that for those with higher average PA or NA, both very high and very low affect variability may be associated with poorer health outcomes (Human et al., 2015; Jones et al., 2020). Previous work has interpreted these effects to indicate that a ‘moderate’ amount of variability in affective responding is likely adaptive for health in that it may indicate an individual is able to flexibly respond to their environments without being over or under-reactive to them

(Human et al., 2015; Jones et al., 2020). Here again, we conceptually replicate findings from Jones and colleagues to examine if there are significant non-linear associations between affect variability and inflammation.

In the study described below, we tested the hypothesis that there would be a significant interaction between an individual's average affect and their affect variability for different measures of inflammation. For Hypothesis 1, we expected that for those with higher average PA, higher PA variability would be associated with higher inflammation. For Hypothesis 2, we expected that for those with higher average PA, both very high and very low PA variability would be associated with greater inflammation (i.e., a quadratic association). Given the uncertainty around directionality for NA variability, we conducted analyses on an exploratory basis.

2. Methods

Data from the North Texas Heart Study (NTHS; Ruiz et al., 2017) were utilized for the present analysis. Ethical review boards at the University of North Texas approved the NTHS study protocol. The NTHS utilized a longitudinal measurement burst study design to examine the influence of social vigilance on subclinical atherosclerosis.

Three hundred community adults living near Denton, TX were recruited for the NTHS. Participants were recruited in stratified samples by age and within gender. Non-Hispanic Black/African American and Hispanic/Latin-x individuals were over-sampled to ensure representation among these racial/ethnic groups. The study protocol included clinical assessments of biomarkers known to have implications for cardiovascular disease, objective measures of atherosclerosis, and psychosocial and behavioral factors implicated in cardiovascular disease. Participants also engaged in two days of ecological momentary assessments (EMA) and ambulatory assessment of additional biomarkers related to cardiovascular disease.

2.1 Study Procedure

After providing consent, participants underwent a brief physical exam and answered questions regarding personal and health behaviors, current medications, and current medical conditions. If participants displayed signs of acute illness/infection, they were rescheduled. Those who were not ill underwent a fasting blood draw for the measurement of inflammatory markers (stored in 10 mL "red top" serum collection tubes that contained no additives via standard, sterile venipuncture procedures). Blood samples were centrifuged (1500g × g at 4 degrees C for 15 min) on site by the phlebotomist and separated, then immediately stored at −80°C until shipment. Serum samples were shipped overnight on dry ice for analysis to the Pennsylvania State University.

Next, participants were fitted with an ambulatory blood pressure monitor (ABPM: Oscar II; Suntech, Inc.) and given a smartphone for the 2-day/1-night ecological momentary assessment (EMA) portion of the study. ABPMs were programmed to assess blood pressure at semi-random times within 45-min intervals; this served as the prompt for participants

to fill out the EMA on the study smartphone. Thus, participants provided EMA responses approximately every 45-minutes during waking hours for two consecutive days.

2.2 Measures

2.2.1 Inflammatory Markers: Tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP).—

Three circulating inflammatory markers were derived from serum samples, which were assayed in duplicate using ELISA assay kits [TNF-α and IL-6 from Invitrogen, CRP (high sensitivity) from BioCheck – see Supplementary Table 1 for detection limits and inter- and intra-assay coefficients of variation]. Correlation coefficients were determined by linearity of dilution and were all $r \geq 0.99$. IL-6 was skewed (IL-6 skew = 3.97). Because 22 individuals had a 0 for IL-6 (and 0 scores cannot be logged), we first conducted a linear transformation by adding 1 and then natural log-transformed to correct for skewness (n_log IL-6 skew = −0.55).

Thirteen participants had CRP levels of 10 mg/L or higher. Because removal of those with "high CRP" (i.e., greater than 10) is still debated in the literature (Mac Giollabhui et al., 2020), we conducted analyses on CRP by 1) retaining those with high CRP and correcting for skewness by taking the natural log (raw CRP skew including "high CRP participants" = 2.81; n_log CRP skew including "high CRP participants" = −0.18), and 2) removing those participants with CRP greater than 10 (raw CRP skew without "high CRP participants" = 1.14).

2.2.2 Positive and Negative Affect.—

PA and NA were each measured with six items, broadly designed to comprise a circumplex model of affect with a mix of activated and non-activated items (Feldman Barrett & Russell, 1998). PA items included lively, energetic, cheerful, happy, relaxed, and calm. NA items included hostile, angry, nervous, tense, sad, and depressed. Participants were asked to indicate how they were feeling when the AMBP cuff inflated on a scale from 1 (not at all) to 7 (extremely). Momentary PA and NA were averaged to create average person-mean PA and NA for analyses. To approximate reliability for the PA iM and NA iM, we used the between-person reliability (R_{1F}) from Cranford et al. (2006). Reliability for PA and NA using this formula was excellent (PA = 0.99, NA = 0.99).

2.2.3 Positive and Negative Affect Variability.—

PA variability and NA variability were created by calculating the individual's standard deviation (iSD). We choose the iSD rather than other variability indicators (e.g., MSSD) as previous work has indicated that more complex measures of variability do not add novel information beyond the iSD (Dejonckheere et al., 2019). We calculated the iSD separately for both days of the study and then averaged across the two days to avoid incorporating the long overnight lag – which may not reflect the same processes as momentary fluctuations during the day. As a minimum requirement, there had to be three PA and NA responses for each day to calculate iSD. PA and NA iSD were squared (iSD^2) to test for quadratic associations. To approximate reliability for the PA iSD and NA iSD, we used the reliability for change (R_C) from Cranford et al. (2006). Reliability for PA and NA using this formula was acceptable (PA = 0.79, NA = 0.77).

2.2.4 Covariates.—Age, sex, race, and BMI were incorporated as covariates, given previous work demonstrating their importance for inflammatory outcomes (O'Connor et al., 2009). Race/ethnicity and sex were dummy coded (race/ethnicity: 0=white, 1=racial/ethnic minority; sex: 0=female, 1=male).

2.3 Analytic Plan

A priori power analyses for cardiovascular outcomes in the NTHS were conducted for the overall study (Ruiz et al., 2017). Briefly, power analyses indicated that there was sufficient power (0.83) to detect small effects (r=.20) with 210 participants. Data manipulation and analyses were performed in SAS (9.2). Analyses for Hypothesis 1 examined linear interactions between average affect intensity and affect variability (PA iM interacting with PA iSD, NA iM interacting with NA iSD) predicting TNF-α, IL-6, and CRP. PA and NA indicators were tested in separate models. Affect iM, affect iSD, and their interaction were regressed onto inflammatory markers using PROC GLM. Hypothesis 2 tested quadratic interactions between average affect intensity and affect variability (PA iM interacting with PA iSD^2, NA iM interacting with NA iSD^2) predicting TNF-α, IL-6, and CRP. Partial eta squared (η_p^2) was used as the indicator of effect size; $\eta_p^2 = 0.01$, $\eta_p^2 = 0.06$, and $\eta_p^2 = 0.14$ indicate small, medium, and large effects, respectively. Missing data were not imputed. Bonferroni corrections were applied for 9 comparisons; thus, a significant p-value would be p=.006.

3. Results

3.1 Preliminary Analyses

Participants were 50% female, 60% non-Hispanic Whites, 19% Hispanic/Latinx, and 15% non-Hispanic Blacks. The average age was 42.44 (*SD*=12.76, range= 21–70). Most participants were married or cohabiting (60%), homeowners (63%), employed (79%), and had a college degree (61%). Income was diverse: 19% of people reported yearly household incomes of less than $30,000, 33% reporting incomes between $30,000-$74,999, and 48% reporting incomes $75,000 or higher.

Participants responded to an average of 38.18 (*SD*=9.64) EMAs over the two-day period. We do not have data on how many EMAs were sent per person and actual adherence rates depend on wake times, which likely vary both within and between individuals. Given an 8-hour sleep cycle, however, participants should have responded to approximately 21 EMAs per day. Based on this approximation, response adherence was 91%.

All affect indicators and age were grand-mean centered. Means and SD (or frequencies) for all variables are in Supplementary Table 2. Bivariate associations (correlations or t-tests/chi-square tests) were used to examine preliminary associations among affect and inflammation variables, as well as demographic indicators. Results are available in Supplementary Table 3.

Although we calculated CRP in two ways (including those with CRP > 10 and excluding those with CRP > 10), there were no differences in terms of directionality or significance in any analysis between the two indicators of CRP. Thus, we report results including those with CRP > 10; results excluding those with CRP > 10 are available in Supplementary Table

4. Because our interest was in understanding interactions, we focus on those associations in text. Results for linear main effects are provided in Supplementary Table 5 and quadratic main effects are provided in Supplementary Table 6. Importantly, there was a small linear effect of NA iSD on CRP (b=0.66, SE=0.28, p<.05, η_p^2=0.0136), such that higher NA iSD was associated with greater CRP. This effect was not qualified by any interactions. When applying the statistical correction for multiple comparisons, this association was no longer significant and is not further discussed.

3.2 Hypothesis 1: Linear Interactions between Average Affect and Affect Variability

Results for all linear interactions between average affect and affect variability predicting inflammatory markers are reported in Table 1. There was a small-to-moderate interaction between NA iM and NA iSD predicting TNF-α (see Figure 1). Simple slopes were not significant at 1SD, but were significant at 2SD. Results suggested that there was a negative association between NA iSD and TNF-α for those who had low (−2SD) NA iM (b=−7.77, SE=3.49, p=.027). In contrast, there was a positive association between NA iSD and TNF-α for those who had high (+2SD) NA iM (b=5.58, SE=2.27, p=.014). There was also a small but significant interaction between PA iM and PA iSD predicting IL-6 (see Figure 1). Simple slopes were not significant at 1SD or 2SD.

3.3 Hypothesis 2: Quadratic Interactions between Average Affect and Affect Variability

Results for all quadratic interactions between average affect and affect variability predicting inflammatory markers are in Table 1. There were no significant quadratic associations between average affect and affect variability.

4. Discussion

Previous work has suggested that higher affect variability is associated with poorer health outcomes (Chan et al., 2016; Hardy & Segerstrom, 2017; Houben et al., 2015) and higher systemic inflammation may be one potential mechanism linking affect variability with long-term health outcomes (Jones et al., 2020). Given theoretical assertions that associations between affect variability and health status indicators may be moderated by mean levels of affect (Ong & Ram, 2016), the present study examined whether associations between affect variability and three inflammatory biomarkers that have implications for the development of several diseases (TNF-α, IL-6, and CRP) were higher among those with higher average affect.

4.1 Moderation by Average Affect

Based on theoretical assertions from the Fragile PA Theory (Ong & Ram, 2016), we expected that for those who generally experience higher PA, higher PA variability would be associated with greater systemic inflammation. The study results partially support this hypothesis. Specifically, average PA moderated associations between PA variability and IL-6, but reliable associations with TNF-α and CRP were not observed. As predicted, those with higher average PA and high PA variability demonstrated higher IL-6 (see Figure 1). Interestingly, those with lower average PA and low PA variability also demonstrated higher IL-6. This may suggest that in addition to having high but unstable PA, having too little

PA is a risk factor for higher IL-6. We examined associations between average NA and NA variability on an exploratory basis. Average NA moderated associations between NA variability and TNF-α, such that among those with higher average NA, higher NA variability was associated with higher TNF-α. It seems that at higher levels of average NA variability is positively associated with TNF-α, but that generally people with higher average NA have lower TNF-α.

The goal of the present study was to conduct a conceptual replication and extension of Jones et al., (2020). Our findings when examining linear interactions between average PA and PA variability were broadly similar to prior findings. Specifically, they found a significant linear interaction between average PA and PA variability on a composite measure of several cytokines (including IL-6 and TNF-α), and null associations with CRP. Our interactions showed the same pattern of association for IL-6 (and for null associations with CRP), although not for TNF-α. This difference in findings with TNF-α may be due to their use of a composite measure – perhaps IL-6 and other inflammatory cytokines in their composite measure were the main drivers in the significant relationship with their interaction term.

Our results for the interaction between average NA and NA variability were somewhat different. In contrast to the results of the present study, Jones and colleagues reported no significant linear interactions for NA and NA variability, but did report significant non-linear interactions (in the present study, there were no significant non-linear interactions). However, when comparing the direction of effects, results were again similar between the two studies. That is, in both studies among those with lower average NA, higher variability was associated with lower inflammation, whereas among those with higher average NA, higher variability was associated with higher inflammation. Consistent with interpretations in other work (Houben et al., 2015) and with the Fragile PA theory, it seems likely that individuals who have higher average affect and have higher affect variability may have lower regulatory control that influences both overall mean levels of emotion and responses to events in their environment, which in turn takes a subsequent toll on their physical health.

It is interesting that in the present study, affect variability indicators were only robustly associated with IL-6 and TNF-α, but not with CRP. IL-6 and TNF-α are highly responsive to environmental stress, showing strong responses in less than an hour (Marsland et al., 2017). In contrast, CRP is an acute phase protein secreted by the liver, and rises in response to elevations in other inflammatory markers. CRP is therefore a more downstream process in the acute phase response compared to IL-6 and TNF- α and is more stable across days (Pradhan et al., 2001). Thus, although speculative, perhaps because the present study measures of affect variability and inflammatory markers were assessed within days of one another, we do not see associations with CRP (which responds over longer timescales, e.g., weeks rather than days). Consistent with this possibility, in Jones and colleagues (2020) assessment periods were weeks apart and their results did suggest that both PA and NA variability were associated with CRP, although associations were non-linear.

In the present study, main effects of average PA and NA were not significantly associated with inflammatory outcomes. Previous work has demonstrated inconsistent associations between average levels of affect and inflammation (Graham-Engeland et al., 2018) and

work examining associations between affect variability and immune markers indicate that linkages tend to be moderated by average levels of affect (Jenkins et al., 2018; Jones et al., 2020). Thus, incorporating both average levels of affect and indications of affect variability may provide not only a more comprehensive understanding of typically occurring affective states, but may also be necessary to understand the nuanced associations between affect and inflammatory outcomes. Altogether, the findings from the present study suggest that among those who generally report higher average affect, higher affect variability is sometimes associated with inflammation in deleterious ways, but that much more work needs to be done to disentangle inconsistent findings. We note that our results were not as consistent as we had expected: most associations were not statistically significant, indicating that linkages between affect variability and inflammatory outcomes are tenuous.

4.2 Limitations

There are several limitations to the present study. First, results from the present study are cross-sectional and, therefore, we cannot exclude reverse causality. For example, previous work has suggested acute increases in inflammatory markers predict poorer affect (low PA or high NA; Kullmann et al., 2013; Wright et al., 2005), and it seems likely that chronic inflammation may also predict greater affect variability. Some longitudinal studies, however, have suggested that affect is a predictor of inflammatory markers and that – perhaps outside of acute increases in inflammation (e.g., related to illness), inflammation does not influence average levels of affect (Niles et al., 2018). To our knowledge, studies have not examined whether inflammation predicts variability in affect states. Future longitudinal studies are needed to establish the temporal ordering of these associations, including the possibility of reciprocal feedback over time.

A second set of limitations concerns the measurement of inflammation. The present study incorporated only three inflammatory markers, each of which is typically considered primarily a pro-inflammatory indicator (although IL-6 has some anti-inflammatory properties as well). Affect and affect variability may demonstrate different associations with anti-inflammatory markers, which help down-regulate pro-inflammatory indicators, or other types of immune markers (e.g., natural killer cells). Future studies should examine multiple types of inflammatory markers and indicators of immune function (e.g., vaccine responses) to obtain a more comprehensive picture of linkages between affect and inflammatory processes. Additionally, data on exogenous influences on inflammation (e.g., medication use) were not available.

Finally, participants only provided two days of ambulatory assessment data. This is a limited timeframe from which to examine affect and affect variability. Although participants reported a very large number of affect states across these two days, which is beneficial, it is possible that these days were not representative of their typical affective experiences. However, our measures do seem to be indicative of relatively stable individual differences, according to the reliability estimates (see Methods section). Moreover, we did not examine antecedents to affect states or variability, which may partly account for the variability between affect indicators and inflammation. That is, it could be that everyday events, such

as stress, cause fluctuations in both affect and in inflammation. Limited previous work, however, does not support this assertion (Reed et al., 2022).

4.3 Conclusion

Previous work has indicated that affect variability is linked with poorer health and wellbeing outcomes. The present study adds to this research by suggesting that higher affect variability may be linked with higher levels of inflammation, particularly among those with higher average affect. Future research should examine other affect dynamics (e.g., event reactivity and recovery) in everyday life to examine whether these demonstrate more robust associations with inflammatory markers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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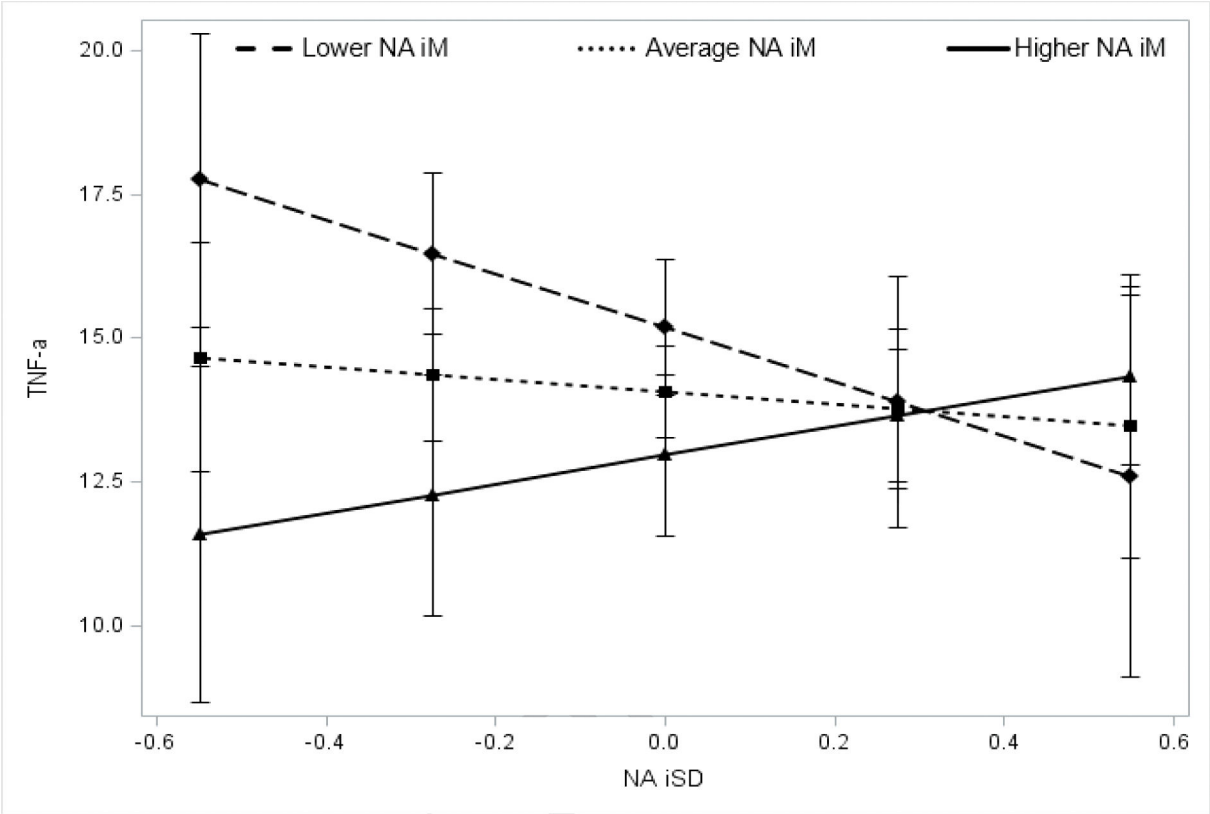
Highlights

- Average levels of affect are not linked with inflammatory markers
- Average negative affect moderates the association of negative affect variability and TNF-α
- Average positive affect moderates the association of positive affect variability and IL-6
- Those with high and unstable positive and negative affect may have higher inflammation



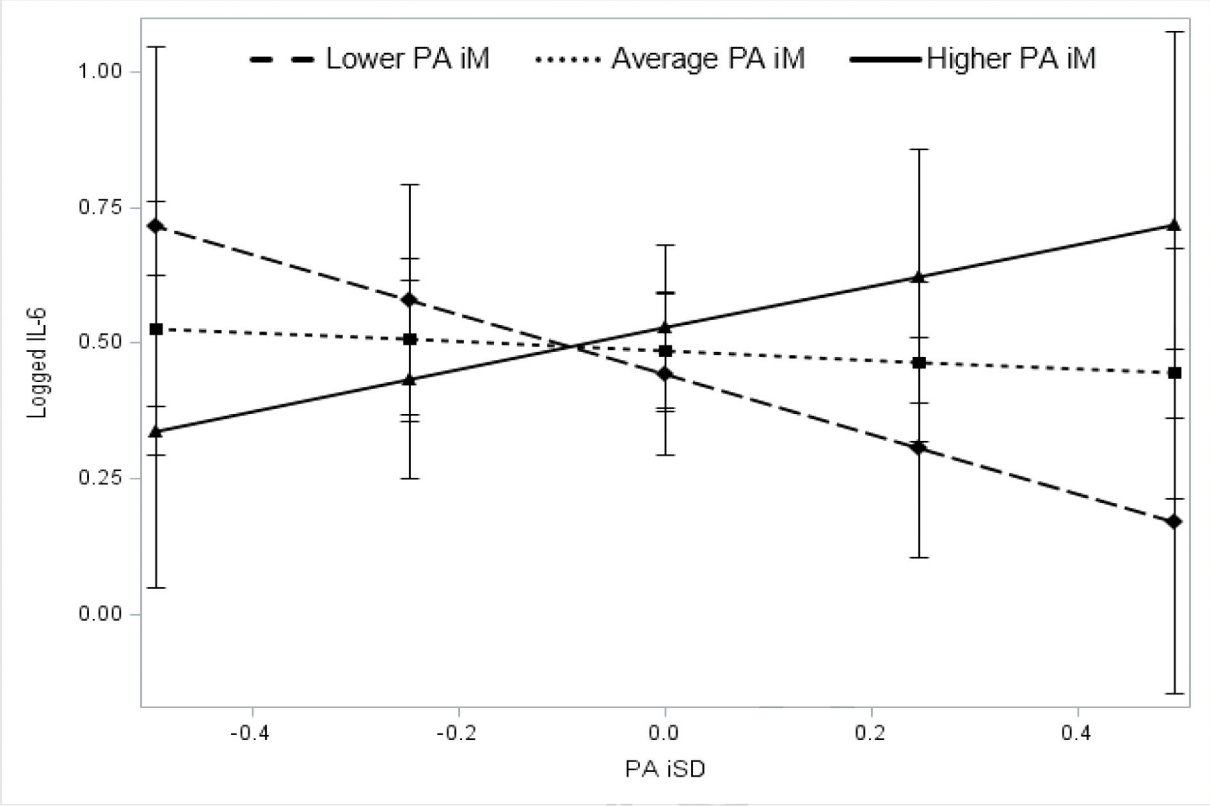


Figure 1.

Associations between affect variability and inflammation as moderated by average affect.

Note. PA= positive affect, NA= negative affect, iSD= individual standard deviation, TNF-α= tumor necrosis factor alpha, IL-6= interleukin 6. NA iM SD was graphed at + and − 0.61; PA iM SD was graphed at + and − 0.92.

Table 1.

Two-way interactive effects between affect variability, quadratic affect variability, and average levels of affect predicting inflammatory outcomes with BMI, race, sex, and age incorporated as covariates.

TNF-a							
Affect	**Estimate**	**SE**	**η_p^2**	**Affect**	**Estimate**	**SE**	**η_p^2**
PA iM × PA iSD	−0.82	1.4	0.0010	NA iM × NA iSD	6.34**	1.92	0.0346
PA iM × PA iSD^2	3.33	3.5	0.0027	NA iM × NA iSD^2	0.67	3.20	0.0000
IL-6							
Affect	**Estimate**	**SE**	**η_p^2**	**AfTect**	**Estimate**	**SE**	**η_p^2**
PA iM × PA iSD	0.48†	0.2	0.0178	NA iM × NA iSD	0.34	0.28	0.0030
PA iM × PA iSD^2	0.16	.31	0.0004	NA iM × NA iSD^2	−0.63	0.76	0.0024
Logged CRP							
Affect	**Estimate**	**SE**	**η_p^2**	**AfTect**	**Estimate**	**SE**	**η_p^2**
PA iM × PA iSD	0.07	0.2	0.0002	NA iM × NA iSD	−0.17	0.33	0.0006
PA iM × PA iSD^2	−0.41	03.6	0.0011	NA iM × NA iSD^2	0.33	0.90	0.0004

Note. Each interaction was tested in a separate model. With Bonferroni correction

† p<0.05

* p<.001

** p<0.001.

PA= positive affect, NA= negative affect, iM= individual mean, iSD= individual standard deviation, CRP= C-reactive protein, TNF-α= tumor necrosis factor alpha, IL- 6= interleukin 6.