## Title

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# Anger Is Associated with Increased IL-6 Stress Reactivity in Women, But Only Among Those Low in Social Support

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## Abstract

**Background—**Social connections moderate the effects of high negative affect on health. Affective states (anger, fear, and anxiety) predict interleukin-6 (IL-6) reactivity to acute stress; in turn, this reactivity predicts risk of cardiovascular disease progression.

**Purpose—**Here, we examined whether perceived social support mitigates the relationship between negative affect and IL-6 stress reactivity.

**Method—**Forty-eight postmenopausal women completed a standardized mental lab stressor with four blood draws at baseline and 30, 50, and 90 min after the onset of the stressor and anger, anxiety, and fear were assessed 10 min after task completion. Participants self-rated levels of social support within a week prior to the stressor.

**Results—**Only anger was related to IL-6 stress reactivity—those experiencing high anger after the stressor had significant increases in IL-6. IL-6 reactivity was marginally associated with



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perceived support, but more strikingly, perceived support mitigated anger associations with IL-6 stress reactivity.

**Conclusion—**Supportive ties can dampen the relationship of anger to pro-inflammatory reactivity to acute stress. Implications to cardiovascular disease are discussed.

### Keywords

Social support; Anger; Stress reactivity; Interleukin-6

## Introduction

High-quality social ties have protective effects on physical health, equivalent in magnitude to that of many health behaviors, including physical activity and smoking status [1]. People who perceive more supportive social networks are less likely to develop and die from cardiovascular disease (CVD) [2–4]. The social support buffering hypothesis suggests that social support does not simply benefit people directly but can also moderate the negative impact of psychological stress and high negative affect on well-being, including, but not limited to, immune system functioning [3, 5, 6]. As the health benefits of support are now well established, growing emphasis is placed on understanding the physiological pathways and mechanisms through which perceived support benefits individuals in general and mitigates the deleterious effects of psychological stress and negative affect on health [6].

Increasingly, research attention has focused on inflammatory processes, given their key mediating roles in the development of CVD [7] and other diseases of aging [8]. The pro-inflammatory cytokine, interleukin-6 (IL-6), has been proven particularly good at predicting CVD morbidity and mortality in healthy and unhealthy individuals [9–13]. For example, among a sample of apparently healthy men, higher IL-6 levels significantly predicted increased risk of development of myocardial infarction over the next 6 years [13]. One study demonstrated that elderly adults in the highest quartile of IL-6 levels had a twofold increased risk of CVD-related and all-cause mortality 4–5 years later compared to those in the lowest quartile of the cytokine [14]. Another study showed that only IL-6 was related to mortality over a 9-year period, whereas other cytokines, such as IL-8, IL-10, IL-12, and TNF-alpha, were unrelated to mortality [9]. Elevated circulating IL-6 levels are similarly related to the development of frailty, disability, and common diseases of aging, such as inflammatory autoimmune diseases, type 2 diabetes mellitus, and some cancers [8, 15].

Furthermore, IL-6 promotes the production of other regulatory proteins that have integral roles in CVD development, such as fibrinogen and C-reactive protein [7, 16], thus making IL-6 an especially important early indicator of morbidity and mortality. Recent evidence also suggests that greater increases in IL-6 in response to an acute stressor (i.e., IL-6 stress reactivity) predict increased ambulatory systolic blood pressure 3 years later [17, 18]. Thus, not only are circulating IL-6 levels at rest important to cardiovascular health but also, potentially, IL-6 reactivity to stressors.

While associations between perceived social support and circulating levels of IL-6 have previously been reported [19, 20] (though not consistently [21]), it is unclear whether having

high levels of social support directly suppresses the typical elevations in IL-6 that occur in response to acute stressors. High perceived support in one's life is linked to reductions in cardiovascular [22] and cortisol reactivity [23]. In the current study, we examine whether social support can moderate IL-6 reactivity to acute stress.

In addition to examining whether social support moderates IL-6 stress reactivity, we were also interested in whether social support moderates the relationship between acute affective responses and IL-6 stress reactivity. Negatively valenced and high arousal states, such as anger, fear, and anxiety, are well known to impact cardiovascular [24] and cortisol [25] reactivity to and recovery from acute stress. Emerging work has also shown that these acute negatively valenced and high arousal affective responses to stressors are also associated with IL-6 reactivity to those same stressors. Carroll and colleagues [26] demonstrated that individuals with increases in anxiety and even small but significant increases in anger following an acute stressor have the greatest elevations in IL-6 during the stressor recovery period. In contrast, Moons and colleagues [27] found that fear, not anger, was related to IL-6 increase during stressor recovery.

We propose that perceived support may buffer the IL-6 reactivity to acute stress directly, but even more, it may dampen the relationship between negative affective responses and IL-6 stress reactivity. In the current study, we examined associations between trait perceived support and circulating IL-6 levels before, during, and after an acute stressor. We predicted a trait effect—that participants reporting higher levels of support in their life would demonstrate reduced IL-6 reactivity compared to those with low support. Furthermore, we tested whether previously established links between acute affective responses and IL-6 reactivity are moderated by higher levels of support. Specifically, we expected that high social support would mitigate the effects of anger, anxiety, and fear on IL-6 reactivity, should these affective states be related to IL-6 reactivity. In other words, we predicted that the relationship between anger, anxiety, and fear with IL-6 reactivity would be strongest among those reporting low levels of perceived support and mitigated in those reporting high levels of support.

## Methods

Postmenopausal women between 54 and 82 years old were recruited through flyers and posters in the community and from service providers serving the elderly in the San Francisco Bay Area for a prospective study on caregiving and its effects on health. Caregivers included healthy women providing a minimum of 4 h of daily care to a family member with dementia and reporting high levels of stress and age-matched non-caregiver controls reporting low daily stress. Participants were excluded if they reported major medical conditions such as heart disease, cancer, or diabetes; use of medications containing agents known to affect stress hormone levels; and regular smoking. The study protocol was approved by the Institutional Review Board of the University of California, San Francisco.

### Procedures

Women interested in the study were screened for eligibility by telephone. They received a physical exam, fasting blood draw, and provided written informed consent at the UCSF

Clinical and Translational Science Institute's Clinical Research Center (CCRC). They were then scheduled to return on a separate afternoon 1 week later to undergo a modified Trier Social Stress Test (TSST) [28]. On their return to the laboratory, they ate a standardized lunch provided by the CCRC metabolic kitchen and had an intravenous forearm catheter inserted at 1300 hours. After a 1-h resting baseline period with relaxation music in headphones, blood was drawn and the blood was assayed for interleukin-6 levels (time 0). A modified form of the TSST including performance of a speech and math task was administered. The phases of the stressor included four 5-min stressful periods (20 min total), including introduction to two trained evaluators who described the task (0–5 min); a preparatory period for the speech (6–10 min); a speech (about strengths and weaknesses, instead of a job interview, to fit the age group which includes many retirees; 11–15 min); and, lastly, a math task (serial subtraction of consecutive prime numbers; 16–20 min). Evaluators maintained neutral expressions and followed a script to provide neutral feedback throughout the tasks. Fifty women completed the TSST and blood draws, including 23 caregivers and 27 control women.

## Materials

**Socio-demographics—**Socio-demographics were assessed at first study visit with the use of self-report questionnaires. Date of birth (age), ethnicity, education level by years, and household income (16 levels, from less than US $10,000 to greater than US $200,000) were assessed.

**Interleukin-6—**Whole blood was collected into 10-ml SST tubes (Becton Dickinson, Franklin Lakes, NJ) at 0, 30, 50, and 90 min from start of the TSST. Blood was allowed to clot for 30 min at room temperature and then centrifuged at 1,300 rpm for 15 min. Serum was aliquoted, frozen, and stored at −80 °C for subsequent cytokine quantification. A high-sensitivity sandwich immunoassay was used to quantify IL-6 (Mesoscale Discovery). Assay sensitivity is 0.46 pg/ml and the average intra- and inter-assay coefficients of variation are 4 and 6 %, respectively. Two caregivers had extreme values of IL-6 at baseline (22 and 83 pg/ml) and, thus, were eliminated from the current analyses, reducing the sample size to 48.

## Psychological Measures

**Stressor-Related Affect—**Anger, anxiety, and fear were assessed with a one-item question for each individual affect 10 min after the completion of the TSST: "How (angry/fearful/anxious) did you feel during the speech and math tasks?" Participants selected the best option from a five-point Likert scale from 0 (not at all) to 4 (a great deal).

**Perceived Social Support—**The widely used and well-validated 12-item Interpersonal Support Evaluation List was used to measure perceived social support [29]. Participants indicated the extent to which 12 phrases that described the availability of different forms of perceived support (instrumental support, appraisals of available support, and sense of belonging) were either true or false. A four-item Likert-type scale was used, from 0 (definitely false) to 3 (definitely true). A mean score for the 12 items was used. Cronbach's alpha in the current study was 0.89.

## Statistical Approach

Hypotheses were tested with growth curve modeling [32]. In the growth curve models, the repeatedly measured outcome (IL-6) is regressed on time, providing estimates for baseline ($B_0$) and the rate of change ($B_{time}$) at the same time. In terms of the TSST, $B_0$ and $B_{time}$ are estimates of IL-6 levels at time 0 and its rate of change over the next 90 min until study completion. A significant $B_0$ suggests that IL-6 is at levels different from 0 pg/ml before the TSST begins, and a significant $B_{time}$ suggests that IL-6 rate of change over time is significant in response to the TSST. In other words, $B_0$ and $B_{time}$ represent cytokine reactivity in its complete form. Without covariates or predictors in the model, these estimations are called the unconditional growth curve and estimates are for the full sample of participants.

To test the effects of perceived support ($B_{support}$) and affect (i.e., anger, $B_{anger}$; fear, $B_{fear}$; anxiety, $B_{anxiety}$) on IL-6 stress reactivity, we examined separate models with interactions between (1) perceived social support (mean-centered) and time ($B_{support*time}$); (2) anger (mean-centered) and time ($B_{anger*time}$); (3) fear (mean-centered) and time ($B_{fear*time}$); and (3) anxiety (mean-centered) and time (Banxiety*time). A significant interaction between perceived support and time ($B_{support*time}$), for example, suggests that IL-6 increase over the course of the TSST significantly varies as a function of perceived support, and the direct effect of perceived support ($B_{support}$) estimates whether baseline is a function of perceived support. The follow-up approach [30, 32] is to test simple slopes—whether the growth in IL-6 over time is significant at one standard deviation above the mean of perceived support and then again at one standard deviation below the mean of perceived support (this is similar to testing interactions in ordinary least square regression models, as recommended by [30]).

A significant three-way interaction between perceived support, affect (for example anger), and time ($B_{support*anger*time}$) indicates that IL-6 reactivity varies differently as a function of affect at varying levels of perceived support. This, in turn, is followed up with simple interaction tests between anger and time at 1 SD above and below the mean perceived support. Significant simple interactions suggest that IL-6 reactivity is significantly different as a function of affect at that particular level of perceived support, and only then should we test to determine the rise in IL-6 at higher and lower levels of the affective state. Non-significant simple interactions suggest that at that level of perceived support, a particular affective state is unrelated to IL-6 reactivity. Thus, simple slopes are unexplored when simple interactions are not significant.

A random intercept model with restricted maximum likelihood (REML) estimation was fitted with an unstructured covariance matrix [32] in all models, allowing the proper handling of missing and skewed data, producing unbiased estimates [32]. A REML estimated growth model with unstructured covariance matrix overcomes the limitations of other statistical approaches in dealing with small sample sizes, skewed predictors, and non-independence in the outcome data, producing unbiased estimators [31, 32]. As mentioned previously, data from two caregivers were eliminated for high levels of IL-6, thus eliminating significant skew across all four time points in the mixed analyses (skewed statistic=0.83).

IBM's Statistical software, SPSS 20.0, was used for data analysis.

## Results

### Univariate and Bivariate Statistics

Table 1 presents the descriptive statistics for age, BMI, perceived support, anger, anxiety, and fear and the four IL-6 measurements at 0, 30, 50, and 90 min following the TSST for the full sample and split for caregivers and control participants.

Pearson product–moment coefficients were calculated for all data, and t tests examined whether caregivers were different from controls on any study variable. Caregivers reported significantly greater post-stress anxiety ($t(46)=2.11$, $p=0.04$), but were not different on post-stress anger or fear. Greater social support was marginally associated with lower fear (−0.28, $p=0.06$) and IL-6 at 30 min (−0.25, $p=0.09$) and 90 min (−0.25, $p=0.09$) post-TSST. Anger was related to anxiety ($r=0.44$, $p=0.002$) and fear ($r=0.30$, $p=0.04$), and anxiety was related to fear ($r=0.54$, $p<0.001$). The *t* tests did not reveal significant differences in IL-6 levels at any time point between caregivers and controls.

### Unconditional Means Model

We partitioned the between- and within-person variation in IL-6 reactivity in response to the TSST. The estimates of the residual and intercept unexplained covariance parameters were 1.34 (SE=0.16) and 1.68 (SE=0.43), respectively. The intra-class correlation was 0.55; in other words, 45 % of the variation in IL-6 reactivity occurred within person over time ($p<0.001$).

### Conditional Means Model for Covariates

Next, in a series of mixed models to determine covariates in the model, we tested the independent effects of age, BMI, and caregiver status on IL-6 output. Those variables that met $p<0.05$ were maintained in the analyses of interest. BMI was marginally significantly associated with elevated IL-6 ($B=0.07$, SE=0.04, $p=0.08$). Older participants and caregivers were not more likely to have elevated IL-6 across all samples ($B=0.60$, SE=0.41, $p=0.15$ and $B=0.02$, SE=0.04, $p=0.24$). Thus, the analyses reported below were conducted without any covariates, though follow-up analyses with these covariates were conducted, as indicated in the follow-up analyses section below.

### Unconditional Growth Models

We further examined the growth in IL-6 as a function of time alone to determine the extent to which the within-person variation was a function of the passing of time across the stressor. Including time into the model, the residual unexplained variation dropped from 1.34 to 0.79, suggesting that the stressor-induced IL-6 reactivity accounted for 41 % of the change in IL-6 within persons, leaving 59 % of the variation unaccounted for. The results indicated that across all participants, IL-6 followed a linear relationship ($B_0=1.70$, SE=0.23, $p<0.000$ and $B_{time}=0.02$, SE=0.002, $p<0.001$), such that for every minute after the TSST started, IL-6 rose an average of 0.02 pg/ml or an average of 1.80 pg/ml across the 90 min.

## Growth Models

**Perceived Support as a Predictor of IL-6 Rate of Change—**Growth modeling analyses revealed that the IL-6 rate of change was marginally associated with perceived support ($B_{support*time}$=−0.008, SE=0.004, $p$ =0.082).

**Affective States as Predictors of IL-6 Rate of Change—**Next, we examined three separate models for IL-6 rate of change and each affective state. Each model included all three affective states, but modeled the interactions with time individually in each model. Table 2 presents the results for these three analyses: (1) anger after the TSST was significantly related to IL-6 reactivity to the TSST, though not to baseline (intercept) levels; (2) anxiety was unrelated to baseline or reactivity; and (3) fear was related to the mean levels across the four samples.

**Perceived Support as a Moderator of Anger-IL-6 Relationship—**Finally, we examined whether perceived support moderates the association between anger and IL-6 reactivity since only anger was related to IL-6 change over time in earlier analyses. The results indicate that a significant three-way interaction existed between perceived support, anger, and time ($B_{support*anger*time}$=−0.01, SE=0.003, $p$ =0.007), such that the change in IL-6 across time that occurs as a function of anger varies at different levels of social support. To examine this further at different levels of social support, we examined the simple interactions between anger and IL-6 reactivity at one standard deviation above and below the mean of perceived support. The results revealed that for women who reported higher levels (one standard deviation above the mean) of perceived support, the IL-6 slope significantly increased ($B_{time}$=0.02, SE=0.00, $p$ <0.001); however, this increase was no longer associated with anger ($B_{anger*time}$= −0.002, SE=0.002, $p$ =0.45). In other words, IL-6 reactivity was unrelated to anger after the TSST in those reporting higher levels of support. On the other hand, at one standard deviation below the mean of perceived support, the simple interaction between time and anger was significant ($B_{anger*time}$=0.009, SE=0.003, $p$ <0.001). This suggests that for women at lower levels of perceived support, anger in response to the TSST had a significant effect on IL-6 reactivity.

Given the significant simple interaction at lower levels of support, we examined the simple slopes at one standard deviation above and below the means of anger (i.e., higher and lower levels of anger, respectively) at this lower level of support. Simple slope analyses revealed that for women who reported lower levels of support and responded to the TSST with elevated levels of anger, IL-6 significantly increased across time ($B_0$=−0.77, SE=1.23, $p$ =0.53, and $B_{time}$=0.03, SE=0.004, $p$ <0.001, respectively). For those lower in support and lower in anger, IL-6 increased significantly across time, but to a lesser extent than for those at higher levels of anger ($B_0$=−0.77, SE=1.35, $p$ =0.57, and $B_{time}$=0.01, SE=0.005, $p$ =0.03, respectively). In other words, at lower levels of support, change in IL-6 over time was a function of anger—greater anger in response to the TSST was related to significantly greater increases in IL-6 compared to the increase in IL-6 for those at lower levels of anger. Figure 1 demonstrates the significant differences in slopes revealed by the interaction of anger and time at lower levels of social support.

**Follow-Up Analyses, Including Covariates—**We repeated the above series of analyses with covariates age, BMI, and caregiver status in the models. All the results were unchanged compared to the models without covariates.

## Discussion

Chronic elevations in circulating levels of pro-inflammatory proteins, including IL-6, promote the development of cardiovascular and related diseases [9–11, 33]. IL-6 reactivity to acute stress is also related to the development of CVD risk [17, 18] and appears responsive to affective states that occur following acute stress [26, 27]. Here, we examined whether perceived support mitigates the relationship between co-occurring negatively valenced and high arousal affect and IL-6 reactivity in response to acute stress.

In the current study, the levels of IL-6 at baseline and increases in response to acute stress in the controls and caregivers were similar to the levels reported in previous studies in healthy individuals [34–38]. Our results further indicate that even low levels of anger after acute stress are related to IL-6 reactivity, as found in the study of Carroll and colleagues [26], whereas anxiety and fear were not related to reactivity—in contrast to previous studies which used younger samples [26, 27]. Fear was related to baseline levels of IL-6. Furthermore, while social support only marginally mitigated IL-6 reactivity ($p$ =0.08) to an acute stressor directly, social support significantly moderated the relationship between acute stress-related anger and IL-6 reactivity. These findings add to the literature on the classic buffering role that social support plays in health—that it matters more for well-being and health in the context of high stress or distress [3, 5].

It is of theoretical interest to consider why, in this study, small elevations of the negatively valenced and high arousal affective state of anger, but not anxiety or fear, were associated with greater IL-6 reactivity to acute stress. Anger reactivity may have a different evolutionary purpose and unique physiological sequelae. Anger is thought to be an approach-related emotion, whereas fear and anxiety are avoidance emotions and are evidenced to have different neural correlates [39–43]. In lab studies, anger responses are characterized by higher cardiac output [44] and lower cortisol output than fear [45]. Although speculative, it may be that short-term stress-induced increases in IL-6 and other pro-inflammatory cytokines confer a survival advantage by facilitating acute stress-induced enhancement of innate immune responses, as reported in preclinical and human subject studies [46–52]. Individuals with low social support may be more likely to be “out on their own” and have to fend for themselves and, as a result, be more susceptible to attack and/or injury. Therefore, such individuals may mount a more robust immunological stress response. Furthermore, an angry individual may be more likely to engage in an aggressive encounter, i.e., choose to fight rather than flee, and, as a result, may be more likely to need enhanced immune defenses to heal wounds (incurred during the fight) and to defend against accompanying pathogen entry. These evolutionary underpinnings may at least partially explain the association among social support, anger, and IL-6 reactivity as reported here. As with most psychological and biological processes, activating this response too frequently or for too long (especially in the absence of a wound or infection) may result in higher exposure to pro-inflammatory factors and their deleterious health consequences. It is of little

surprise then that elevations in baseline IL-6 levels [9–13, 33] and increasing levels of other pro-inflammatory markers [53] are typically related to various features of cardiovascular disease and early mortality. At present, little is known about what are normative versus prolonged recoveries of reactivity in autonomic, endocrine, or inflammatory responses to stress, though it is well established that acute increases, relative to a given sample, in autonomic [54–56] and endocrine hormones [57] are related to increased cardiovascular disease risk and mortality.

Although these ideas need to be further tested and verified, our findings suggest that what nature may have designed as an adaptive response, i.e., acute stress-induced enhancement of immune function to protect an organism during times of ongoing/potential challenge, may have harmful consequences when activated too frequently in the absence of wounding or pathogen entry, contributing to inflammatory-related disease processes.

Furthermore, while some evidence suggests that IL-6 reactivity to acute stress is predictive of future elevated ambulatory blood pressure [17, 18], there is clearly a need for more research on understanding the role that acute elevations of IL-6 play in the development of hypertension and other clinical risk factors of cardiovascular disease.

Anger is of particular importance to CVD development [58, 59]. Mittleman et al. [60] evidenced a 2.3-fold increase in myocardial infarction incidence within 2 h following an increase in experienced anger. These findings have been confirmed in other reports [61–64]. Those who tend to ruminate, or perseverate, on past events that trigger anger (i.e., angry rumination) have particularly poor physiological recovery following stress. For example, angry rumination is associated with prolonged endothelin-1 increases, which in turn may mediate endothelial dysfunction and atherosclerotic plaque formations [65]. IL-6 and endothelin-1 are significantly related [66], and in fact, endothelin-1-treated cells in culture have increased IL-6 mRNA and protein [67]. It is likely then that a possible pathway through which anger induces increased circulating IL-6 levels (as seen here) is through increased endothelin-1 and that angry rumination may very well lead to even greater increases in IL-6 mRNA and protein.

Our findings indicate that anger-related IL-6 stress reactivity is dampened in those with higher levels of support. This is consistent with evidence suggesting that perceived social support buffers associations between anger and metabolic risk factors [68]. Field studies monitoring daily events and ambulatory blood pressure also show that perceived support and positive interpersonal interactions buffer the link between negative affect and increased blood pressure [22, 69]. Perceived support dampens daily rumination and negative affect in trait ruminators [70], indicating that perceived support has both psychological and physiological benefits in those who tend toward negative affect in general and anger in particular.

Tightly bound to the emotional experience of anger is the cognitive experience of hostility. Neural correlates of anger, hostility, and rumination include, but are not limited to, the dorsal anterior cingulate cortex and anterior insula [71]. These neural correlates are also activated during social rejection stress and, in fact, mediate social rejection and IL-6

reactivity [72]. Eisenberger and colleagues [73] demonstrated that viewing photos of a romantic partner reduces activation in these neural regions. The presence of a supportive partner also attenuates acute stressor-induced cardiovascular responses [74]. A stable perception of available support may thus promote successful neurobiological adaptation to negative affect via the use of effective coping and self-regulation strategies [75, 76]. Future research should delineate the differential moderating effects of general perceived support versus actual received support in the laboratory on the associations between negative affectivity and physiological reactivity, as suggested by Uchino and colleagues [77].

## Limitations

The current study has several limitations. First, our sample included only postmenopausal, healthy women, and research demonstrates varying IL-6 reactivity as a function of sex, age, and health status (see review [18]). Furthermore, caregivers varied in IL-6 reactivity, similar to previous studies [78]. Yet, the effects in the present study suggest that social support as a buffer of the anger/IL-6 reactivity relationship remained significant even after the effects of caregiver on IL-6 reactivity were covaried. Our findings are also based on a small sample size, though mixed modeling techniques with REML estimation when repeated measures are available provide unbiased and robust estimates. REML mixed modeling has significant estimation advantages over other statistical procedures, such as log transformations, repeated-measure ANOVAs, or change scores [31, 32, 79]. Of course, follow-up studies with larger sample sizes, more diverse groups and ages, and varying health status may prove important to delineating possible group differences.

An important limitation of the current study is the use of a one-item self-reported affective response question. As a result, we were unable to examine its validity, though the face validity of the one question item is apparent. The ability to test for emotion specificity is limited by people's emotional clarity—the ability to notice and report small changes in emotions—and report these. The changes in anger during a lab stressor of this type tend to be small, as found in other studies [26, 44]. This suggests that even small changes in reported anger may reflect changes in underlying inflammatory responses. Furthermore, since we only have affective states measured after the TSST, it is impossible to address which stressor specifically, the math or presentation task, caused the increases in negative affect. However, the measurement appeared satisfactory in that the affective responses were significantly related to one another, as expected. Other studies have used change scores in affect pre- and post-stressor or direct anger induction by recalling a previously angering event, and our results are, in general, consistent with those in the present study [26, 27, 65, 80, 81]. Our design included affect 10 min after the stressor, which may have included residual recovery, not peak anger responses. This may be part of why anger measured at this one time point was so predictive of reactivity, a topic for future studies that have repeated measures of mood reactivity and recovery. Finally, the current study only examined negatively valenced and high arousal affective states and did not assess low arousal or any positively valenced affective states. Future studies could expand the inquiry by also including stress responsive emotions of different valence and arousal.

In summary, our study revealed significant moderating effects of social support on the association between anger and increased IL-6 reactivity during acute stress. Social support significantly mitigated anger/IL-6 reactivity associations. These findings have significant clinical implications for individuals at risk of CVD, especially in those inclined to anger [60, 62]. While genetic factors may contribute to IL-6 reactivity [82], supportive networks are an important modifiable factor that can significantly reduce the deleterious effects of negative affect reactivity, and in particular anger, on cardiovascular functioning. We conclude that the important protective effects of social support may act in part through an anger-buffering model.

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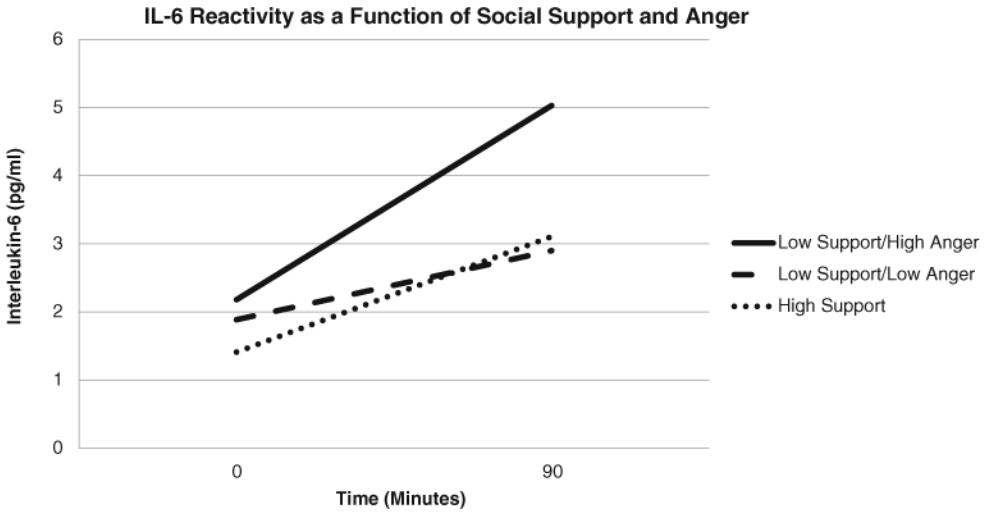


**Fig. 1.**

IL-6 reactivity as a function of anger in women with low support. The results revealed that in women with lower social support (−1 SD below the mean of social support), IL-6 reactivity is significantly more pronounced at higher levels of anger compared to lower levels. *0 min*, start of the TSST; *90 min*, 90 min from start or 70 min from the end of the TSST

## Table 1

Descriptive statistics (mean, SD) for all participants and separated for caregivers and controls

| | Mean (SD) | Caregivers (*N* = 22) Mean (SD) | Controls (N = 24) Mean (SD) |
|---|---|---|---|
| 1. Age (years) | 63.33 (8.22) | 64.81 (6.10) | 64.78 (5.87) |
| 2. BMI (kg/m$^2$) | 25.85 (4.99) | 25.98 (4.88) | 26.09 (5.32) |
| 3. Social support | 3.35 (0.47) | 3.25 (0.46) | 3.50 (0.40) |
| 4. Anger | 0.72 (1.11) | 0.90 (1.02) | 0.59 (1.19) |
| 5. Anxiety[a] | 2.04 (1.30) | 2.47 (1.17) | 1.70 (1.32) |
| 6. Fear | 0.90 (1.22) | 1.24 (1.44) | 0.63 (0.97) |
| 7. IL-6 0 Min (pg/ml) | 1.74 (1.09) | 1.78 (1.36) | 1.69 (0.86) |
| 8. IL-6 30 Min (pg/ml) | 2.12 (1.39) | 2.37 (1.75) | 2.01 (1.05) |
| 9. Il-6 50 Min (pg/ml) | 2.54 (1.53) | 2.68 (1.97) | 2.44 (1.10) |
| 10. IL-6 90 Min (pg/ml) | 3.42 (2.24) | 4.04 (2.94) | 2.97 (1.34) |

[a]Caregivers reported significantly greater anxiety ($p$ <0.05)

**Table 2**

Mixed model results for post-TSST affective states predicting IL-6 reactivity

| | No interaction with time | | Anger*time | | Anxiety*time | | Fear*time | |
|---|---|---|---|---|---|---|---|---|
| | ***B*** | **SE** | ***B*** | **SE** | ***B*** | **SE** | ***B*** | **SE** |
| Intercept | **1.61** | **0.36** | **1.72** | **0.36** | **1.62** | **0.38** | **1.70** | **0.36** |
| Affective states | | | | | | | | |
| Anger | 0.28 | 0.19 | 0.12 | 0.20 | 0.28 | 0.19 | 0.28 | 0.19 |
| Anxiety | −0.33 | 0.18 | −0.33 | 0.18 | −0.34 | 0.20 | −0.33 | 0.18 |
| Fear | **0.65** | **0.19** | **0.65** | **0.19** | **0.65** | **0.19** | 0.28 | 0.19 |
| Time | **0.02** | **0.002** | **0.02** | **0.002** | **0.02** | **0.002** | **0.02** | **0.002** |
| Interaction effect | – | – | **0.004** | **0.002** | 0.000 | 0.001 | 0.003 | 0.002 |

Separate models examined the relationship between (1) anger, (2) anxiety, and (3) fear with IL-6 growth over time (interaction effects). Intercept and time indicate the baseline and growth over 90 min in IL-6. Interaction effects indicate the relationship between each affective state and growth over time in IL-6 while including the other affective states as covariates. Terms in bold are significant results ($p$ <0.05). When covarying age, BMI, and caregiver status, the results are completely consistent with the results shown in this table.