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# Association between Plasma IL-6 Response to Acute Stress and Early-Life Adversity in Healthy Adults

**Linda L Carpenter*[,1,2], Cyrena E Gawuga[3], Audrey R Tyrka[1,2], Janet K Lee[1], George M Anderson[4] and Lawrence H Price[1,2]**

*[1]Mood Disorders Research Program and Laboratory for Clinical Neuroscience, Butler Hospital, Providence, RI, USA; [2]Department of Psychiatry and Human Behavior, Alpert Medical School at Brown University, Providence, RI, USA; [3]Department of Molecular Pharmacology, Physiology and Biotechnology, Brown University, Providence, RI, USA; [4]Child Study Center, Yale University School of Medicine, New Haven, CT, USA*

Increased production of peripheral cytokines and other pro-inflammatory markers has been linked to psychiatric disorders such as major depressive disorder and post-traumatic stress disorder. Recent research has pointed to early-life stress, particularly childhood maltreatment, as an independent and preventable risk factor for systemic inflammation in adulthood. Some data suggest that adults with a history of childhood maltreatment exhibit a heightened inflammatory response to acute stress challenge. To further elucidate the relationship between childhood maltreatment and pro-inflammatory cytokine production, we examined plasma IL-6 response to the Trier Social Stress Test (TSST) in 69 healthy adult subjects without depression or post-traumatic stress disorder. Serial plasma IL-6 concentrations were measured during a standardized psychosocial stressor in $n = 19$ subjects with moderate–severe childhood maltreatment (MAL), and $n = 50$ controls without maltreatment (CTL), as indicated by self-ratings on the childhood trauma questionnaire (CTQ). CTQ total scores were positively correlated with overall change in IL-6 response, as well as the maximum IL-6 concentration during the TSST. Greater acute IL-6 release and higher IL-6 concentrations over time were observed for the MAL group relative to the CTL group. Inflammation may be an important developmental mediator linking adverse experiences in early life to poor adult physical and mental health. The results of this preliminary study warrant further investigation in a larger sample.
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## INTRODUCTION

A growing body of research has established that pro-inflammatory cytokines, such as interleukin-6 (IL-6), have systemic effects far beyond the canonical immune response. These immunomodulators have been implicated in a number of psychiatric disorders, particularly major depressive disorder (Groer and Morgan, 2007; Koo and Duman, 2008; O'Brien *et al*, 2004; Pace *et al*, 2006) and anxiety disorders (Bauer *et al*, 2010; Hoge *et al*, 2009; von Kanel *et al*, 2007). The pro-inflammatory response is not restricted to the pathological states; acute psychological stress produces a transient rise in peripheral cytokines in healthy adult humans (Miller *et al*, 2005; Steptoe *et al*, 2007).

*Correspondence: Dr LL Carpenter, Department of Psychiatry and Human Behavior, Alpert Medical School at Brown University, Butler Hospital, 345 Blackstone Boulevard, Providence, RI 02906, USA, Tel: +1 401 455 6349, Fax: +1 401 455 6534,
E-mail: Linda_Carpenter_MD@Brown.EDU
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However, early-life stress, such as childhood maltreatment, seems to be an independent risk factor for systemic inflammation in otherwise healthy adult humans (Danese *et al*, 2007). Neuroendocrine-immunological abnormalities that are established during a stressful childhood are thought to mediate the development of the pro-inflammatory phenotype in adulthood (Chida *et al*, 2007; Elenkov, 2008; Powell *et al*, 2009). In a study of stress-induced immune response in men with and without major depressive disorder (MDD), men with MDD and a history of early-life stress displayed an exaggerated IL-6 response to an acute psychosocial stressor as compared with non-depressed male subjects (Pace *et al*, 2006). We previously reported a finding of low cortisol response to stress among adults with exposure to childhood maltreatment (Carpenter *et al*, 2009), and others have reported an inverse relationship between cytokine release and cortisol release to mild psychological stress challenge (Kunz-Ebrecht *et al*, 2003). To further elucidate the role that childhood stress exposure has in the cytokine response to acute stressors encountered in adulthood, we examined the IL-6 response to the Trier

Social Stress Test (TSST) in a cohort of healthy adults without psychiatric disorders.

## MATERIALS AND METHODS

### Subjects

Subjects were 69 adults (42 women, 27 men) in the age group 18–64 years, who were selected from the community. The subjects in this study were a subset of a larger study cohort that we examined in previous studies (Carpenter *et al*, 2007, 2009). Voluntary written informed consent was obtained from healthy adults who were recruited to participate in a study about stress. The study was approved by the Butler Hospital Institutional Review Board. Subjects who scored in the 'moderate' to 'severe' range on at least one of the five subscales of the CTQ comprised the maltreated (MAL) group ($n = 19$). Subjects scoring 'minimal' or 'none' on all five CTQ subscales comprised the control group (CTL, $n = 50$). All subjects were free of pregnancy, significant medical illness, and recreational drug use, as evidenced by complete physical and neurological examination and standard laboratory tests, including electrocardiogram, complete blood count, serum electrolytes, thyroid-stimulating hormone, urine toxicology, and urinalysis. Oral contraceptives and estrogen-replacement therapies were allowed, and menstrual cycle phase at the time of testing was recorded for female subjects. Body mass index (BMI) was calculated as weight (kg) divided by height ($m^2$). Exclusion criteria included major medical illness, or use of any psychotropic medication or other drug thought to influence hypothalamic–pituitary—adrenal (HPA) axis function (including psychotropic medications, beta blockers, angiotensin-converting enzyme inhibitors, ketoconazole, metyrapone, and corticosteroids). Structured Clinical Interview for DSM-IV for Axis I Disorders (SCID-I) was used for psychiatric diagnostic assessments. Diagnoses leading to exclusion included a current or lifetime diagnosis of a primary psychotic disorder or bipolar disorder, current substance dependence or abuse, and current major mood or anxiety disorder. Subjects with prominent personality pathology, as detected through clinical interviews and interactions with research staff during the first two visits, were also excluded. Subjects were remunerated for their time and travel.

### Assessment of Maltreatment History, Current Mood/Anxiety Symptoms, and Well-Being

In addition to diagnostic interviews, subjects completed a battery of self-report assessments at baseline, including the Inventory for Depressive Symptoms—Self-Rated (IDS-SR) (Rush AJ *et al*., 1996), the State-Trait Anxiety Inventory (STAI) (Spielberger, 1983), the Perceived Stress Scale (PSS) (Cohen S and Mermelstein, 1983), the Quality of Life—Enjoyment and Satisfaction Questionnaire (QLESQ) (Endicott *et al*, 1993), and the CTQ (Bernstein *et al*, 2003). The CTQ Version 3 is a 28-item self-report instrument comprising five subscales (emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect).

### The Acute Stress Protocol

The TSST is a standardized laboratory psychosocial stress protocol that involves public speaking, role play, and mental arithmetic tasks in front of a panel of confederate judges (Kirschbaum *et al*, 1993). The protocol consists of an anticipation period followed by a 10-min test period, during which the subject must deliver a monologue speech about his/her qualifications for a chosen vocation and perform mental calculation and recitation of serial subtraction by 13's. Blood samples, heart rate, and blood pressure data were obtained from subjects before, during, and after the role-play/arithmetic stressor to monitor for safety and physiological arousal ($-30$, 0, $+30$, and $+45$ min). An intravenous (IV) catheter was established at 1100 hours to allow enough time for subjects to accommodate to the biological testing suite environment. Plasma samples were collected by intravenous access at 0 min (1345 hours), and at $+15$ (1400 hours), $+30$ (1415 hours), $+45$ (1430 hours), $+60$ (1445 hours), $+75$ (1500 hours), and $+90$ (1515 hours) min. Subjects met briefly with the judges immediately after the 0th time point and were told about the public speech role play. They then prepared their speech during the anticipation period (1350–1400 hours). Subjects were debriefed after the role play. Self-ratings of emotional states, as described elsewhere (Carpenter *et al*, 2007, 2009), were completed at 0, $+30$, and $+75$ min. Subjects remained awake in bed for the remainder of the protocol.

### Assays

Plasma IL-6 was assayed using high-sensitivity ELISA available from R&D Systems (Minneapolis, MN). Quality assessment samples (concentration, 2.47 pg/ml) were determined with intra- and inter-assay CVs of 3.3 and 8.9%, respectively.

### Statistical Analyses

Analyses were conducted using SPSS 16.0.1. The IL-6 values and age (years) were log10 transformed to fulfill the requirements for normal distribution in statistical analyses. All tests were two-tailed with significance defined as $p$-value $< 0.05$. $\chi^2$ and $t$-test statistics were calculated to compare the two groups on baseline clinical and demographical variables. Baseline variables that differed significantly between groups were entered in *post-hoc* models as covariates. A final set of *post-hoc* analyses were performed with estrogen use ($n = 42$) and menstrual-cycle phase ($n = 37$) as covariates for women in the sample with available data.

To isolate the absolute magnitude of IL-6 rise in response to stress challenge, the summary variable 'delta(IL-6)' was calculated as change from time 0 (baseline) to peak IL-6 value after introduction of the stressor. Pair-wise bivariate Pearson's correlation matrices were run to evaluate relationships between IL-6 values (time 0, max, and delta) and baseline clinical and demographical variables, including the total CTQ score (continuous data). These were followed by partial correlation analyses, controlling for age and BMI, to examine the relationships between total CTQ score and IL-6.

Two types of general linear models (GLMs) were used to examine possible effects of maltreatment group on IL-6 response to the stress test. In the primary analysis, GLM univariate analysis was performed with delta(IL-6) as the dependent variable; group was defined as a fixed factor, and covariates in the model included those found to be statistically related to IL-6 (age and BMI). *Post-hoc* tests included the same model with the addition of several other covariates, including baseline characteristics that differed between groups and others that theoretically could impact the response to acute stress (sub-threshold depression symptoms, state and trait anxiety, level of perceived stress, menstrual cycle phase, and estrogen use). A similarly constructed GLM, with age and BMI as covariates, was also used to examine *post-hoc* group differences in IL-6 concentration at a single time point (time 0) before exposure to stress in the TSST protocol.

The second analysis strategy used repeated-measures GLMs to test the effects of the maltreatment group on IL-6 response to the TSST over time. The SPSS GLM repeated measures procedure uses analysis of variance (ANOVA) to model dependent variables measured at multiple times, and the predictor variables in the model may be categorical factors (maltreatment group in our case) or continuous covariates (we included age, BMI, and others). For our models, the dependent variable (IL-6 concentration) was represented by seven measurement times. Subgroups in the population and covariates are considered as 'control' variables in this analysis. In contrast to the summary variable delta(IL-6), which captures the maximal change in IL-6 concentration during the period of observation (time 0–90 min), the repeated measures in GLM analysis strategy permits comparisons within and between groups during the multiple phases of the response curve over time. The Huynh–Feldt correction was applied when sphericity assumptions were not met.

## RESULTS

Bivariate Pearson's correlation coefficients revealed significant positive relationships between indices of IL-6 and age, BMI, and CTQ total. No significant correlations emerged for any of the IL-6 measures and sex, depression symptoms, quality of life score, state anxiety, trait anxiety, or perceived stress level. After controlling for age and BMI, we found that CTQ total scores were positively correlated with delta(IL-6) ($r = 0.33$, $p = 0.006$) and with max IL-6 (0.37, $p = 0.002$), but not with baseline (time 0) IL-6 ($r = 0.15$, $p = 0.23$).

Clinical and demographical characteristics for the CTL and MAL groups are shown in Table 1. Results of *t*-tests showed that compared with controls, the group reporting childhood maltreatment was significantly older ($t = 2.4$, $p = 0.03$), had a higher mean BMI ($t = 2.4$, $p = 0.03$), and higher trait anxiety scores ($t = 2.1$, $p = 0.04$). There was a nonsignificant trend ($p = 0.09$) toward higher subthreshold depressive symptoms in the maltreated group. State anxiety, perceived stress, and quality of life scores did not differ significantly between groups. The proportion of women did not statistically differ across groups (56% *vs* 74%; $\chi^2 = 0.27$, $p = 0.14$).

**Table 1** Comparison of Clinical and Demographical Characteristics of Groups

| | Controls, CTL ($n = 50$) | Maltreated, MAL ($n = 19$) | *p* |
|---|---|---|---|
| Age, mean (SD) years | 24.50 (8.83) | 32.84 (13.89) | 0.03 |
| Range (years) | 18–64 | 18–59 | |
| *Gender, n (%)* | | | |
| Male | 22 (44.0%) | 5 (26.3%) | NS |
| Female | 28 (56.0%) | 14 (73.7%) | |
| Body mass index, mean (SD) | 24.61 (3.77) | 28.11 (5.92) | 0.03 |
| Oral contraceptive or estrogen use, *N* (% of women/group) | 12 (42.8%) | 5 (35.7%) | NS |
| *Highest level of education, N (%)* | | | |
| Partial high school | 1 (2.0%) | 1 (5.3%) | NS |
| High-school graduate | 4 (8.0%) | 2 (10.5%) | |
| Technical degree | 0 (0.0%) | 1 (5.3%) | |
| Partial college | 27 (54.0%) | 9 (47.4%) | |
| College graduate | 13 (26.0%) | 4 (21.1%) | |
| Professional degree | 5 (10.0%) | 2 (10.5%) | |
| Perceived stress scale, mean (SD) | 17.76 (6.70) | 20.37 (6.31) | NS |
| IDS-SR total, mean (SD) | 8.86 (6.19) | 11.84 (7.24) | 0.09 |
| STAI state anxiety, mean (SD) | 30.00 (7.41) | 31.11 (6.54) | NS |
| STAI trait anxiety, mean (SD) | 32.41 (8.51) | 37.58 (8.93) | 0.04 |
| CTQ total score, mean (SD) | 5.98 (0.86) | 10.47 (1.81) | $<0.01$ |
| *CTQ subscales (categorical), N (%), moderate–severe* | | | |
| Emotional abuse | 0 (0%) | 11 (57.9%) | |
| Physical abuse | 0 (0%) | 8 (42.1%) | |
| Sexual abuse | 0 (0%) | 4 (21.1%) | |
| Emotional neglect | 0 (0%) | 9 (47.4%) | |
| Physical eglect | 0 (0%) | 8 (42.1%) | |

Abbreviations: IDS-SR, Inventory of Depressive Symptomatology—Self-Report; STAI, State-Trait Anxiety Inventory; CTQ, Childhood Trauma Questionnaire; S, symptomatology.
In the right column, 'NS' denotes *t*-test or $\chi^2$ test comparing CTL and MAL groups that was not significant at $p < 0.05$.

Results of the GLM analysis of delta(IL-6), controlling for age and BMI, showed a significant effect of group ($F = 8.5$, $p = 0.005$), such that greater stress-induced increase in IL-6 concentration was associated with a history of maltreatment. The independent effect of maltreatment group remained significant when all other covariates (depression, state and trait anxiety, quality of life, and perceived stress scale scores) were also included in the model ($F = 6.9$, $p = 0.01$). None of the other variables in the model had a significant effect on delta(IL-6). When menstrual cycle was examined in a subsample of female subjects, maltreatment group retained its significant effect on delta(IL-6), and menstrual phase did not emerge as a significant independent effect. Similarly, the main finding was unchanged when estrogen use was examined as a covariate; estrogen use was not a significant predictor of delta(IL-6). Comparison of

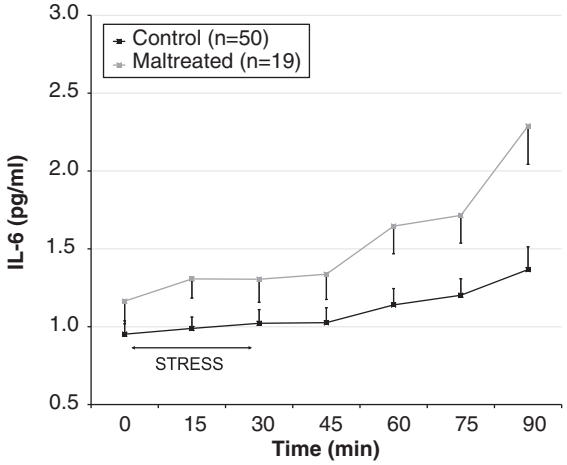


**Figure 1** Interleukin-6 (IL-6) response to the Trier social stress test in healthy adults without psychopathology, grouped according to the presence or absence of childhood maltreatment. The graph depicts untransformed data, with means adjusted for age and BMI.

IL-6 concentrations immediately before exposure to the stressor (time 0) revealed no significant baseline difference between MAL and CTL groups, after controlling for BMI and age ($p = 0.14$).

With the repeated-measures GLM model, we observed a significant between-groups effect on IL-6 response to TSST ($F = 4.6$, $p = 0.03$), after controlling for the effects of age and BMI. There was no significant interaction effect of time-group, indicating that the response curve generated by the MAL group was significantly elevated, but essentially parallel to that of the CTL group (Figure 1). When a *post-hoc* repeated-measures model was constructed to include the additional covariates listed above, the independent effect of maltreatment group was reduced to trend level ($F = 3.3$, $p = 0.07$), and a trend-level interaction effect of time × group emerged ($F = 1.9$, $p = 0.09$). None of the covariates produced a significant effect on IL-6 response except BMI (between-subjects effect, $F = 26.8$, $p < 0.01$) and depression score (multivariate effect, $F = 54$, $p = 0.02$). Estrogen use and menstrual cycle phase did not emerge as significant effects in the repeated-measures model.

## DISCUSSION

Previous studies found that subjects with MDD exhibit an exaggerated IL-6 response to acute psychosocial stress (Miller *et al*, 2005; Weinstein *et al*, 2010). However, the role of early-life environment in the stress-related inflammatory response has not been established. Pace *et al* (2006) demonstrated that men with MDD reporting childhood maltreatment were found to have a greatly increased IL-6 response to the TSST. This study sought to clarify the role of early-life stress in mediating the IL-6 response, and to disentangle the effects of MDD and early-life maltreatment by assessing the acute inflammatory response in adults without depression. The results of this small pilot study indicate that adverse early environment, measured here by self-reported childhood abuse or neglect, is significantly linked to pro-inflammatory response to acute psychosocial stress in otherwise healthy adults. Subjects in our sample with childhood maltreatment showed greater overall peripheral release of IL-6 during a standard stress challenge, and significantly elevated IL-6 concentrations throughout the TSST observation period, as compared with the control group.

Significant group differences in age and BMI were a limitation of this study. Recent studies have demonstrated that exposure to early-life stress increases adult obesity (Boynton-Jarrett *et al*, 2010; D'Argenio *et al*, 2009), while others have reported a relationship between BMI and cytokine response to stress (Benson *et al*, 2009; Brydon *et al*, 2008). The correlation between BMI and early-life stress was also robust in our sample ($r = 0.41$, $p < 0.01$). Our finding of heightened IL-6 response in the maltreatment group emerged after statistically controlling for the effects of BMI and age. However, insufficient power and collinearity between the variables precluded our ability to elucidate a possible interaction or mediating effect of BMI and childhood maltreatment in the generation of plasma IL-6 responses. Future investigation into this question, with larger groups of subjects matched by age and BMI, will be an important next step for unraveling the relationships among adverse early-life environment, obesity, and inflammatory response to acute stress. A larger sample size will also permit examination of different subtypes of childhood maltreatment as independent predictors of cytokine response to stress.

The clinical consequences of having an exaggerated cytokine response to stress are not clear, particularly in healthy adults without major medical disorders. IL-6 is produced by numerous tissues in the body, and identifying the original source of IL-6 that is measured in plasma is not a straightforward process. In the periphery, IL-6 is produced by leukocytes, skeletal myocytes (Keller *et al*, 2005), adipocytes (Fried *et al*, 1998), and splenocytes (Merlot *et al*, 2004). Animal models have demonstrated that exposure to acute stress increases the expression of pro-inflammatory cytokines both in the periphery (LeMay *et al*, 1990; Zhou *et al*, 1993) and within the central nervous system (Butterweck *et al*, 2003; Suzuki *et al*, 1997). Although there is evidence that peripheral cytokines can be transported across the blood–brain barrier (Threlkeld *et al*, 2010), the majority of relevant human studies have assessed basal or stimulated IL-6 production in the periphery, likely painting an incomplete picture of the dynamic interaction between the immune system and other physiological systems.

The mechanism by which cytokine response to acute stress might lead to development of mental and physical health disorders is unknown, but the findings of this study and the work of other research groups (Benson *et al*, 2009; Chen *et al*, 2006) provide some support for the notion that individuals with this phenotype may be predisposed to illness following repeated exposure to common psychosocial stressors. Elevated IL-6 response has been implicated in the pathogenesis of coronary heart disease through a combination of autocrine, paracrine, and endocrine mechanisms (Yudkin *et al*, 2000). A recent meta-analysis of studies measuring cytokine concentration in patients with major depression found that IL-6 concentrations were significantly higher in depressed subjects compared with

control subjects (Dowlati *et al*, 2010). The ability of proinflammatory cytokines to inhibit hippocampal neurogenesis was identified as one candidate mechanism for their detrimental effects on mood. Another mechanistic hypothesis, advanced to explain why children reared in unfavorable socioeconomic circumstances show increased susceptibility to chronic diseases of aging in adulthood, is that stress exposure in early life programs biological systems in a persistent and deleterious manner. Miller *et al* (2009) performed genome-wide transcriptional profiling in healthy adults and found that a history of socioeconomic stress during childhood was associated with upregulation of genes bearing response elements for the CREB/ATF family of transcription factors that convey adrenergic signals to leukocytes. Additionally, they found that subjects with high stress backgrounds had relative downregulation of genes with response elements for the glucocorticoid receptor, increased output of cortisol in daily life, heightened expression of transcripts bearing response elements for NF-$\kappa$B, and greater stimulated production of IL-6. Their results support the notion that exposure to socioeconomic adversity stress in early life leads to exaggerated adrenocortical and inflammatory responses through resistance to glucocorticoid signaling. Although such a phenotype could be adaptive during acute threats to well-being, over time increasing allostatic load on the body might contribute to chronic disease processes. Cross-sectional measurements of HPA and immune function in adulthood may thus vary greatly as a function of the relative age of an organism when stressed and/or the chronicity of exposure to a remote stressful environment. The relevance of timing and chronicity effects was illustrated by recent preclinical data demonstrating inverse changes in central IL1-$\beta$ and peripheral corticosterone concentrations, depending on whether stress exposure in rats was introduced in childhood or adulthood (Lu *et al*, 2010).

Consistent with this proposed mechanism, results from our past neuroendocrine investigations (Carpenter *et al*, 2007, 2009; Tyrka *et al*, 2008a, b) as well as those reported by many other research groups (reviewed by Bauer *et al*, 2010; Gunnar *et al*, 2009; Heim *et al*, 2008) have associated early-life stress with abnormal functioning of the HPA axis. We observed a pattern of relatively diminished cortisol response to the TSST among adults with histories of childhood-maltreatment (Carpenter *et al*, 2007), a subset of which comprise the sample for this study of IL-6. However, we had not previously analyzed our cortisol data in relation to inflammatory cytokines or other peripheral markers of immune function. Investigation into the complex relationships between IL-6 and cortisol in this small pilot study was limited by statistical considerations. However, we performed a cursory exploration with Pearson's correlation coefficients generated for the individual time point data (plasma cortisol and IL-6 concentrations from the same stress test) in these 69 subjects. Consistent with the patterns reported by others (Kunz-Ebrecht *et al*, 2003), we found cortisol concentrations to be inversely related to plasma IL-6 concentrations. The strongest and most statistically significant (negative) correlations emerged at the beginning and at the end of the 90-min protocol, and were generally persistent after the application of CTQ total score as a control variable, ie, in a partial correlation analysis controlling for early-life stress. It is possible that dampened cortisol response to acute stress in subjects with early-life stress is partially responsible for the enhanced IL-6 stress response observed in this group (Heim *et al*, 2000), but more definitive studies will be needed to properly elucidate a causal relationship or how they interact to mediate the link between early adverse environment and adult health outcomes.

Measuring concentrations of other potential mediators, such as norepinephrine, in future studies of early-life stress and inflammatory response to acute psychosocial stress will also be fruitful for parsing the complex interactions among the neuroendocrine, immune, and psychological systems (Bierhaus *et al*, 2003). An extensive literature documents a prominent role for sympathetic nervous system activation in both inflammatory and immunodepressive processes (Catania *et al*, 2009; Di Comite *et al*, 2007; Szelenyi and Vizi, 2007), and norepinephrine may offer some measure of neuroprotective effect by reducing brain infiltration of peripheral immune cells driven by increases in chemokine and cell adhesion molecule expression (O'Sullivan *et al*, 2010).

In conclusion, the results of this pilot study contribute to a rapidly growing literature that illuminates the complex relationships between stress and neuroimmune regulation in the pathoetiology of disease. Cytokines such as IL-6 are an integral part of the innate inflammatory response to a physical stressor (eg, infection, inflammation). The mechanisms by which psychosocial stress initiates cytokine response, as well as the clinical consequences of an exaggerated cytokine response to stress, remain to be determined.

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## DISCLOSURE

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