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Association of elevated cytokines with childhood adversity in a sample of healthy adults

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Abstract

Objective—Childhood trauma has been associated adult stress-related disorders. However, little is known about physiologic alterations in adults with a history of early life trauma that do not have current psychiatric or medical diagnoses. In this study, the relationships between childhood adversity and cytokine and C - reactive protein (CRP) levels in healthy adults were examined.

Method—Participants included men (n=18) and women (n=20) who did not meet DSM-IV criteria for Axis I psychiatric disorders or any major medical illness. Cytokine and CRP levels were obtained from baseline blood samples. Subjects completed the Early Trauma Inventory Self Report (ETI-SR). The primary outcomes included serum interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), interleukin-1 β (IL1- β), and CRP levels. In addition, the mean numbers of traumatic experiences (sexual, physical, emotional, general, and the summed total) were measured.

Results—Significant positive associations were found between the total ETI score and IL-6 ($p = 0.05$), IL1- β ($p < 0.05$), and TNF- α ($p = 0.01$). Significant positive correlations were found between the number of general traumas and IL1- β ($p < 0.05$), TNF- α ($p < 0.05$), and IL-6 ($p < 0.01$). Neither the total number of traumas nor any of the trauma subscales were significantly associated with CRP levels.

Conclusions—The positive association between childhood trauma and basal cytokine levels supports the extant literature demonstrating the long-term impact of childhood trauma and stress on homeostatic systems. Importantly, this association was found in healthy adults, suggesting that

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these alterations may precede the development of significant stress-related psychiatric disorder or disease.

Keywords

life stress; biological stress; innate immunity; cytokines; C-reactive protein

Introduction

The association between early life stress and stress-related psychiatric disorders is well documented (Dube et al., 2001; Felitti et al., 1998; Mullen, Martin, Anderson, Romans, & Herbison, 1996). For example, exposure to childhood adversity and stress increases the risk for the development of depression and post traumatic stress disorder during adulthood (PTSD) (Chapman et al., 2004; Felitti et al., 1998; Widom, 1999). Despite these findings, the mechanistic connection between childhood adversity and stress-related psychiatric disorders is not well-delineated. However, an emerging literature suggests that prolonged and persistent pro-inflammatory signaling may play a role in the pathophysiology of stress related disorders in adults.

The cytokines interleukin-6 (IL-6), interleukin-1beta (IL-1 β) and tumor necrosis factor-alpha (TNF- α) the acute phase protein c-reactive protein (CRP) mediate the acute inflammatory response to psychological stress (Steptoe, Hamer, & Chida, 2007). Immobilization or open field exposure increases plasma levels of IL-6 in rodents (LeMay, Vander, & Kluger, 1990; Zhou, Kusnecov, Shurin, DePaoli, & Rabin, 1993). Clinical studies have found that cognitive and psychosocial stress tasks increase plasma CRP (Hamer et al., 2006b), TNF- α , IL-1 β (Altemus, Rao, Dhabhar, Ding, & Granstein, 2001) and IL-6 (Brydon et al., 2005; Maes et al., 1998) levels. The change in mononuclear IL-1 β gene expression was positively correlated with plasma IL-6 levels, subjective stress and anxiety (Brydon et al., 2005). Similarly, Maes and colleagues found that students with the highest subjective stress response to an academic exam exhibited significantly higher stimulated IL-6 and TNF- α levels than students with low subjective stress (Maes et al., 1998). Importantly, IL-6 and CRP fail to habituate to repeated psychosocial stress and are elevated in individuals exposed to chronic stress (Alley et al., 2006; Hamer, Gibson, Vuononvirta, Williams, & Steptoe, 2006a; Kiecolt-Glaser et al., 2003; von Kanel, Kudielka, Preckel, Hanebuth, & Fischer, 2006). A convergence of evidence suggests that prolonged pro-inflammatory signaling is a critical component of the pathophysiology underscoring stress-related psychiatric disorders (Maes et al., 1999; Straub, 2006).

Functional alterations in limbic brain regions have been associated with symptoms of stress and anxiety disorders. Cytokines increase noradrenergic transmission to limbic brain regions which may underscore the altered limbic tone that has been linked with hyperarousal in PTSD (Shin et al., 2005; Zalcman et al., 1994). In addition, central administration of an IL-1 receptor antagonist attenuated c-fos expression in the amygdala and reduced depressive-like behaviors to bacterial lipopolysaccharide (LPS) challenge (Konsman et al., 2008). Elevated basal and LPS stimulated cytokine and CRP levels in individuals with PTSD (Baker et al., 2001; Gill, Vythilingam, & Page, 2008; Spitzer et al., 2010; Spivak et al., 1997), depression (Himmerich et al., 2008; Howren, Lamkin, & Suls, 2009; Maes, Twisk, & Ringel, 2012) and myalgic encephalomyelitis (ME/cfs) (Fletcher, Zeng, Barnes, Levis, & Klimas, 2009). Plasma cytokine levels were significantly greater in individuals with comorbid depression and ME/cfs than in individuals with depression alone (Maes et al., 2012). Of note, individuals with depression, PTSD or comorbid depression and PTSD exhibited significantly greater serum IL-6 and soluble IL-6 receptor (sIL-6R) levels than healthy controls suggesting that elevated pro-inflammatory cytokine signaling plays a critical role in

the pathophysiology of stress-related psychiatric disorders (Maes et al., 1999; Maes et al., 1995; Sluzewska et al., 1996). Despite these findings, the role of cytokines and CRP in mediating risk for the development of stress and anxiety disorders as a consequence of childhood abuse and maltreatment is unclear.

A prospective study demonstrated that maltreated children are at risk for developing clinically relevant CRP levels (Danese, Pariante, Caspi, Taylor, & Poulton, 2007). Unfortunately, the prevalence of PTSD among study participants was not measured and therefore it is difficult to discern whether the CRP levels were a function of childhood maltreatment or PTSD. Elevated CRP levels have also been found in adults who were raised in harsh family environments and low childhood socioeconomic status (Taylor, Lehman, Kiefe, & Seeman, 2006). However, CRP levels were also associated with BMI and psychosocial dysfunction. Another study found that healthy adults with a history of childhood trauma exhibited greater IL-6 levels in response to a psychosocial stressor than healthy adults without a history of childhood trauma (Carpenter et al., 2010). Thus, childhood trauma may indeed be linked to long-term dysregulation in the IL-6 response to acute stress. Given the reciprocal and dynamic relationship between IL-6, TNF- α , IL-1 β and CRP, understanding the impact of childhood trauma on multiple cytokines may provide additional insight into the pathophysiology of psychiatric disorders. To our knowledge surprisingly little is known about TNF- α and IL-1 β levels in healthy adults with a history of childhood maltreatment.

The objective of this study was to examine the impact of exposure to adverse events during childhood on basal cytokine and CRP levels in a cohort of healthy adult subjects free of current psychiatric and medical illness. We hypothesized that healthy subjects exposed to more adversity during childhood would have significantly greater IL-1 β , IL-6, TNF- α , and CRP levels as compared to those without exposure to significant adversity during childhood.

Materials and Methods

Subjects

This secondary analysis was conducted from a larger study on gender differences in stress response among individuals with and without cocaine-dependence. These data have been presented in separate manuscripts (Brady et al., 2009; Waldrop et al., 2010). Only non cocaine-dependent healthy control subjects were included in the present analysis. Plasma was missing from seven control participants, thus these individuals were not included in the present analysis. The analysis was conducted using data from 38 healthy controls. Subjects were recruited from a 50-mile radius of the Charleston area, via media advertisements over a 48-month period. All procedures were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki, and received Institutional Review Board approval. Informed consent was acquired prior to study participation. General exclusion criteria included (1) current major depressive disorder (MDD) (2) current post traumatic stress disorder (PTSD); (3) current or lifetime history of other major Axis I disorders such as bipolar disorder, schizophrenia, somatoform disorder, etc. (4) history of or current medical conditions that might interfere with safe conduct of the study or impact HPA activity, including ischemic heart disease, chronic obstructive pulmonary disease, ME/cfs, fibromyalgia, endocrine and autoimmune disorders; (5) history of or current psychotic, eating, or bipolar affective disorders; (6) synthetic glucocorticoid steroid therapy within one month of testing; (7) current benzodiazepine, antidepressant, antipsychotic, beta-blocker and other medication use that might interfere with HPA axis activity or psychophysiologic measurement; (8) pregnancy, nursing, or ineffective means of birth control; (9) body mass index ≥ 35 ; or (10) DSM-IV criteria for substance dependence except caffeine, nicotine or marijuana within the past 60 days. Study procedures were conducted at the Clinical and

Translational Research Center (CTRC) of the Medical University of South Carolina. Subjects meeting inclusion criteria and failing to meet exclusion criteria were admitted to an inpatient unit at approximately 2000 hr the evening prior to testing. Subjects were rescheduled if there was any indication of acute infection or injury. Subjects dependent on nicotine were provided with a nicotine patch.

Plasma Cytokine Analysis

Blood samples were drawn from each participant at 1640 hr. which was 20 minutes prior to a corticotropin releasing hormone challenge. Blood was collected in EDTA-prepared tubes and immediately placed on ice. Plasma was obtained by centrifugation under refrigeration and the sample frozen at -70°C until assayed in duplicate. Measurements of cytokine levels were done using multiplex bead-array kit from Affymetrix according to manufacturer instructions with few modifications. A total of 16 assays ($n=8$ plates CRP; $n=8$ plates cytokines) were run by the same operator who was blinded to the data. Samples were run undiluted for IL-6, TNF- α and IL1- β and at 1:1000 dilution for CRP. Beads were incubated with the samples (50 μl , diluted 1:1 in assay buffer) for 60 minutes and then rinsed and incubated with detection biotinylated antibody and phycoerythrin-conjugated streptavidin. Detection was done using a BioRad Bio-Plex 200 machine. Each cytokine level was compared to a standard curve supplied in the kit. The inter-assay variability (% CV) were 10, 5.5, 5.5 and 16% for CRP, IL1- β , IL-6 and TNF- α respectively. Limits of detection (pg/ml) were 2.2–40,000, 0.2–516, 1.7–16,058 and 0.2–1.0 for CRP, IL1- β , IL-6 and TNF- α respectively. Cross reactivity was less than 5%.

Assessment

Subjects were screened prior to study participation with a physical exam, blood chemistry panel, and EKG. Physical health, prescription and over the counter medication and supplement use were reviewed by the clinician. Each subject was asked to fill-out the Early Trauma Inventory (ETI) (Bremner, Vermetten, & Mazure, 2000). The ETI is a 56-item self-report form which is used to evaluate early life trauma, including physical, sexual, emotional, and general forms of trauma. The ETI assesses the number, frequency, duration, and subjective impact (i.e., functional, emotional and relational) of traumatic experiences. The appropriate items endorsed were summed to create five variables of interest: total number of traumas, physical, emotional, sexual, and general traumas. The general trauma subscale consists of 21 items including questions such as exposure to natural disasters, serious personal injury or illness, parental separation, death of loved one, exposure to domestic violence, assault, combat etc. Experiences such as slaps in the face, burns, and choking are included in the 9-item physical trauma subscale. The 7-item emotional trauma subscale reflects experiences of ridicule, verbal abuse, and emotional neglect. The sexual trauma subscale includes 15 questions varying from inappropriate comments about sex or sexual parts to rape. High test-retest reliability, internal consistency, and external validity have been reported for the ETI (Bremner et al., 2000).

Stress and anxiety ratings were obtained at baseline using a modified Distress/Mood Scale, (Childress, McLellan, & O'Brien, 1986). This 100-mm visual 10-point Likert scale is anchored with adjectival modifiers (0) “not at all” to (10) “extremely”.

Statistical Analysis

The primary hypothesis was that the total number of adverse events endorsed on the ETI would positively correlate with baseline blood plasma cytokine concentration. To test this hypothesis, a linear regression model was fit with the log of the baseline cytokine as the outcome and total number of traumas as the predictor. Covariates controlled for in regression analysis included smoking status, gender, and the interaction between gender and

the total number of traumas. If the interaction was insignificant, it was removed from the model. Secondary analysis considered trauma subscales - number of physical, sexual, emotional, and general traumas as predictors of baseline cytokine levels, also controlling for covariates. Separate regression models were fit for each trauma subscale and the analytic procedure was the same as for the primary outcome. Residual analysis indicated violations of normality, and a log transformation of cytokines was necessary. Results are presented in terms of type III sums of squares F-tests, degrees of freedom, and associated p-values. Results concerning demographic and potential confounding variables are presented in terms of means and standard errors (SE). Type I error rate was set at $\alpha = 0.05$. Bonferroni adjusted α was set at 0.0125 for trauma subscales listed in Table 2. All analyses were performed in SAS (SAS/STAT software, Version 9.1.3, SAS Institute Inc., Cary, NC, USA).

Results

Demographic and trauma characteristics of the sample are displayed in Table 1. All of the participants were in general good health. The most commonly listed minor medical problem was seasonal allergies ($n=4$). Occasional use of ibuprofen or similar non-steroidal anti-inflammatory drugs was reported by four individuals. No one reported taking an antioxidant, omega-3, statin, or other medications and supplements expected to alter the inflammatory system. The mean (SE) number of general, sexual, physical, and emotional traumas reported by the group was 6.4 (0.9), 1.6 (0.5), 2.8 (0.33) and (0.42) respectively. One female reported 21 childhood traumas and statistically confirmed to be an outlier. Data from this subject was removed from subsequent analyses. The mean level of IL-6, IL1- β , TNF- α , and CRP were 1.74, 0.70, 4.10, and 711.5 pg/ml respectively. There were no differences in gender or age between people reporting exposure to traumatic experiences ($n=35$) and those who did not ($n=4$). The percentage of participants with a past history of depression was 21.1%. Five participants of the participants rated their stress and anxiety levels above zero. Within these individuals stress scores ranged from one (lowest) to four (highest) and anxiety scores ranged from one (lowest rating) to five (highest rating). Plasma levels of IL-6, TNF- α , IL-1 β and CRP in the individual with the highest stress and anxiety scores were 1.13, 0.07, 1.74 and 254.3 pg/ml respectively.

IL-6

The adjusted regression model indicated the total number of traumas was associated with IL-6 levels ($F_{1,30} = 4.05$; $p = 0.05$) (Figure 1A). When trauma subscales were considered, there was a significant and positive relationship between the number of general traumas and IL-6 levels ($F_{1,30} = 13.65$, $p < 0.01$) (Table 2).

IL1- β

The adjusted regression model indicated that the total number of traumas was positively and significantly associated with IL1- β levels ($F_{1,29} = 5.24$; $p < 0.05$) (Figure 1B). When trauma subscales were considered, the number of general traumas was found to be independently associated with IL1- β levels ($F_{1,29} = 6.04$; $p < 0.05$) (Table 2). However, when the data were analyzed using a Bonferroni adjusted $\alpha=0.0125$, there was no association between general trauma and basal IL1- β .

TNF- α

The adjusted regression model indicated the total number of traumas was associated with TNF- α ($F_{1,25} = 7.86$; $p = 0.01$) (Figure 1C). When trauma subscales were considered, the number of general traumas found to be independently associated with TNF- α ($F_{1,25} = 5.47$; $p < 0.05$) (Table 2). However, when the data were analyzed using a Bonferroni adjusted $\alpha=0.0125$, there was no association between general trauma and basal TNF- α .

CRP

The adjusted regression model indicated the total number of traumas was not significantly associated with CRP ($p > 0.05$) (Figure 1D). When trauma subscales were considered, the number of emotional traumas was found to be independently associated with CRP ($F_{1,30} = 4.42$, $p = 0.04$) (Table 2). However, when the data were analyzed using a Bonferroni adjusted $\alpha = 0.0125$, there was no association between emotional trauma and CRP.

Discussion

Studies of individuals with a significant history of adverse childhood experiences and stress-related psychiatric disorders have demonstrated dysregulation in neurobiologic systems, but it is difficult to determine if this dysregulation is involved in the connection between childhood adversity and the adult disorder or is simply a manifestation of the disorder (Heim & Nemeroff, 2001a; Heim, Newport, Bonsall, Miller, & Nemeroff, 2001b). In the present study, a significant and positive relationship was found between childhood trauma and basal IL-6, TNF- α , and IL-1 β levels in healthy adults who were free of any significant psychiatric and medical illness. The percentage of participants with a past history of depression was 21.1% and consistent with the lifetime prevalence rates of depression for adults aged 30–44 reported in the National Comorbidity Study (Kessler et al., 2005). In addition, no one met criteria for current or past PTSD or any psychiatric disorder and participants were free of anti-inflammatory medications and supplements that would alter pro-inflammatory cytokine levels. In this regard, the discovery of a significant and positive relationship between pro-inflammatory cytokine levels and childhood adversity in a healthy group of adults provides some insight into a potential biologic mechanism through which childhood adversity may be connected to stress-related psychiatric disorders in adulthood.

Data from developmental neuroscience studies suggest that early life stress may program an organism's sensitivity to subsequent stress throughout the lifespan (Ladd et al., 2000; Meaney, 2001). The finding of a significant positive association between early life stress and basal cytokine levels is consistent with the literature. For example, healthy adults with a history of early life stress exhibited altered HPA axis hormonal responses to laboratory stress tasks (Heim et al., 2001b; Heim et al., 2000; Moran-Santa Maria et al., 2010). In addition, early life stress has been associated with a reduction in hippocampal volume and a sensitized amygdala response to aversive social cues (Dannlowski et al., 2012). Interestingly, a growing literature suggests that over expression and amplification of the innate inflammatory response to acute stress plays a critical role in the pathophysiology of psychiatric disorders (Leonard & Maes, 2012). Sensitized noradrenergic tone in limbic brain regions has been implicated stress-associated psychiatric disorders (Bloom, 1995). Stress and norepinephrine stimulate cytokine production in limbic brain regions (Hueston et al., 2011; Johnson et al., 2008; Nguyen et al., 1998). Moreover, pro-inflammatory cytokines levels fail to habituate to repeated stress exposure (Porterfield, Gabella, Simmons, & Johnson, 2012; von Kanel et al., 2006). Preclinical studies have found that prolonged and elevated pro-inflammatory signaling attenuates neurogenesis, exacerbates oxidative and nitrosative stress pathways, promotes glutamatergic excitotoxicity and hippocampal neurodegeneration; cellular mechanisms that have been implicated in symptoms of depression and anxiety disorders (Duman & Monteggia, 2006; Tilleux & Hermans, 2007; Viviani et al., 2006; Wang et al., 2012; Zou & Crews, 2005). In addition, data from both clinical and preclinical studies have linked elevated cytokine levels with symptoms of depression and anxiety disorders. For example, exogenous IL-6 administration in limbic brain regions increases anxiety-like behaviors in rodents (Wu & Lin, 2008). Basal cerebrospinal fluid levels of cytokines were positively associated with the clinical severity of depression (Martinez, Garakani, Yehuda, & Gorman, 2012).

The present findings may have significant implications for stress-associated medical disorders. For example, cytokines have been implicated in the pathophysiology of chronic inflammatory disorders (Boekholdt et al., 2006; Danesh et al., 2008; Popivanova et al., 2008; Saxne, Palladino, Heinegard, Talal, & Wollheim, 1988). Childhood maltreatment and abuse are associated with an elevated risk for cancer, autoimmune disorders, cardiovascular and chronic obstructive pulmonary diseases (Anda et al., 2008; Dube et al., 2009; Felitti et al., 1998). Of note, the prevalence of depression and anxiety disorders among individuals with chronic inflammatory diseases is high and suggests that stress-associated psychiatric disorders and inflammatory diseases share a common pathophysiology (Chapman, Perry, & Strine, 2005). For example, elevated levels of TNF- α have been found in individuals with a history of myocardial infarction (MI), and there is a high prevalence of depression among MI patients (Halaris, 2009; Odeh, 1993; Ziegelstein, 2001). In addition, plasma levels of IL-6, TNF- α , IL-1 were significantly greater in individuals with comorbid depression and ME/cfs than in individuals with depression alone (Maes et al., 2012). Thus, prolonged pro-inflammatory signaling as a result of early life stress may play a critical role in the risk for the development of stress-associated psychiatric and inflammatory disorders. This connection is clearly speculative and longitudinal assessment of biomarkers is necessary.

While the strength of the relationship between cytokines and childhood adversity varied depending on the cytokine and the type of adverse event, the relationship was consistently in a positive direction. The total trauma score has the largest number of items and therefore the greatest statistical power. Significant associations were found between all three cytokines and general trauma. The association between IL-6 and general trauma remained significant after adjusting for multiple tests. Although the adjusted analysis failed to find significant associations between IL-1 β , TNF- α , and general trauma, a similar positive trend was observed indicating that general trauma may be a significant mediator of adult cytokine levels. The general trauma subscale contains a substantially larger number of items than the other scales (21 vs. 15, 9 and 7). Therefore, the positive association between the number of general traumas and IL-1 β , TNF- α and IL-6 may partly reflect the greater statistical power of this subscale. Additionally some items within the general trauma subscale are common occurrences. For example, as no-fault divorce laws were enacted, divorce rates rapidly climbed during the 1970s and early 1980s when the majority of the sample were children.

There was no association between emotional abuse and basal cytokine levels. The finding of an inverse association between plasma CRP levels and emotional trauma was insignificant after adjusting for multiple tests. Previous studies have linked early emotional abuse and neglect with dysregulation in the oxytocin system (Fries, Shirtcliff, & Pollak, 2008; Heim et al., 2009; Meinlschmidt & Heim, 2007). Thus, early emotional abuse and neglect may trigger a cascade of physiologic events that are independent of pro-inflammatory signaling.

Intuitively, one might expect sexual and physical traumas to be among the most severe trauma types and therefore most likely to be positively associated with long-term sequelae. However, the number of possible items to be endorsed on both of these subscales was small, limiting the statistical power of these analyses. In addition, the sexual trauma items on the ETI are heterogeneous and include items such as inappropriate sexual comments which are weighted as heavily as the “completed rape” item. Moreover childhood physical and sexual abuse is commonly under-reported even in self-reported surveys. Therefore, subjects may have been reluctant to disclose a history of victimization.

Income and education exhibit strong associations with health outcomes including health behaviors, morbidity, and mortality (Kawachi, Adler, & Dow, 2010). Taylor and colleagues found a positive association between low childhood socioeconomic status (SES) and CRP levels mitigated through BMI and psychosocial dysfunction (Taylor et al., 2006). In the

present study, childhood adversity was not associated with adult CRP levels. However, our study participants were free of psychosocial dysfunction which may explain the disparate findings. A recent study found that childhood adversity was positively associated with several inflammatory markers in African Americans (Slopen et al., 2010). In contrast to our study, Slopen's (2010) study included subjects who had a history of diabetes and cardiovascular disease and medications which may alter basal cytokine levels. In support of the present findings, no association was found between plasma CRP levels and childhood adversity in healthy adults (Carpenter, Gawuga, Tyrka, & Price, 2012).

There are a number of study limitations. Information impacting the inflammatory system such as sleep and exercise were not carefully assessed and may have influenced the cytokines levels. While the highest level of education obtained and employment serve as a rough proxy for current socioeconomic status (SES), information about childhood SES was not collected. As a result the impact of this childhood SES could not be included as a covariate in the statistical analysis. It is important to note however, that we did find an association between three cytokines and childhood trauma in a population of adults that appear to be in a higher SES. Although current SES data were not directly collected in the present study, 30 (77%) of the subjects were employed and 32 (84%) reported "some" college education. These findings are indeed intriguing and suggest that the impact of childhood trauma leaves a long-term physiological footprint that remains independent of adult socioeconomic status. Maes and colleagues found a significant association between perceived stress and stimulated cytokine levels (Maes et al., 1998). In the present study, only five of the 38 participants rated their stress or anxiety levels above zero. In addition, plasma IL-6 and TNF- α levels from the participant with the highest stress and anxiety ratings were below the group mean. Thus, it is unlikely that basal cytokine levels measured in the present study were due to stress or anxiety associated with anticipation of the task. In this preliminary investigation, the study may be statistically underpowered due to the small sample size. Thus similar studies with larger sample sizes are warranted. Similar studies assessing other biomarkers of inflammation and cellular immunity including plasma haptoglobin, neopterin and anti-cytokine levels may provide a more comprehensive understanding of the scale of immune system dysregulation. In addition, given the evidence supporting sensitization of pro-inflammatory cytokine signaling in the pathophysiology of stress-associated disorders, studies assessing soluble IL-6, IL-1 and TNF receptor levels and cellular markers of oxidative and nitrosative stress may provide critical insight into the mechanistic link between childhood adversity and stress-related disorders in adults.

In conclusion, this is the first study to our knowledge to demonstrate a significant positive association between childhood adversity and basal cytokine levels. This association is consistent with the extant literature supporting long-term adaptations in homeostatic systems as a consequence of childhood stress and adversity. Moreover, these findings may have important health implications both in terms of understanding disease process and the nature of resilience.

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Figure 1. Comparison of basal cytokine levels and total ETI score in healthy control subjects. (A) IL-6 (B) IL1- β (C) TNF- α (D) CRP. The sum of ETI items endorsed in each of the four domains (sexual, physical, emotional, and general trauma) was compared with basal cytokine levels.

Table 1

Study Demographics

Variable ¹	
n	39
Age	35.69 (12.0)
Number of early traumatic experiences ³	12.24 (9.8)
BMI	26.8 (4.3)
Male, n (%)	19 (48.7)
Some college, n (%)	32 (84.2)
Employment, n (%)	30 (76.9)
Caucasian, n (%) ²	27 (69.2)
Married, n (%)	8 (20.5)
Smokers, n (%)	23 (59.0)

¹Descriptive statistics are listed as mean $\pm$ standard deviation unless otherwise noted.

²Caucasian group contains two pacific islanders.

³Represent the total number of childhood traumas reported by the ETI-SR.

Table 2

Comparison of trauma subtype with cytokine and CRP levels

Cytokine	Number of General Traumas β (p-value)	Number of Sexual Traumas β (p-value)	Number of Physical Traumas β (p-value)	Number of Emotional Traumas β (p-value)
IL-1 β	0.05 (0.02)	0.04 (0.56)	0.03 (0.65)	0.03 (0.11)
TNF- α	0.07 (0.03)	0.11 (0.14)	0.14 (0.24)	0.06 (0.36)
IL-6	0.07 (0.001) *	-0.04 (0.41)	0.01 (0.88)	-0.02 (0.65)
CRP	-0.01 (0.52)	0.00 (1.00)	-0.07 (0.16)	-0.07 (0.04)

* denotes a significant effect following the Bonferroni adjustment.

Bonferroni corrected level of significance is $p < 0.0125$