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Adversity in Preschool-Aged Children: Effects on Salivary Interleukin-1β

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Abstract

Exposure to early life adversity is linked to impaired affective, cognitive, and behavioral functioning and increases risk for various psychiatric and medical conditions. Stress-induced increases in pro-inflammatory cytokines may be a biological mechanism of these effects. Few studies have examined cytokine levels in children experiencing early life adversity, and very little research has investigated cytokines or other markers of inflammation in saliva. In the present study, we examined salivary IL-1β and C-reactive protein (CRP) levels in relation to stress exposure in 40 children aged 3 to 5 years who were enrolled in a larger study of early life adversity. Childhood maltreatment status was assessed via review of child welfare records, and contextual stress exposure, traumatic life event history, and symptoms of psychopathology were assessed via caregiver interviews at a home visit. In a subsequent visit, salivary IL-1β and CRP were obtained before and after participation in four emotion-eliciting tasks. Number of past month contextual stressors, lifetime contextual stressors, and traumatic life events each demonstrated a significant main effect on IL-1β. Baseline IL-1β was positively associated with each of the significant main-effect adversities. Post-challenge IL-1β displayed positive associations with each adversity variable, but were not significant. CRP was not significantly associated with any of the adversity variables. Given evidence suggesting involvement of IL-1β in the neuropathology of psychiatric conditions, these results may have important implications for developmental outcomes.

Keywords

childhood maltreatment; cytokine; IL-1β; stress; preschool aged children

It is well established that exposure to childhood maltreatment and other adverse experiences undermine adaptive developmental outcomes in children (Appleyard, Egeland, van Dulmen, & Sroufe, 2005; Sameroff, Seifer, Baldwin, & Baldwin, 1993). Early adversity impairs

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affective, behavioral, cognitive and interpersonal functioning, and increases risk for psychiatric conditions including depressive, anxiety, and substance-use disorders (Brown & Anderson, 1991; Bryer, Nelson, Miller, & Krol, 1987; Burns et al., 2004). There is now increasing recognition that early environment also modifies risk for the development of several medical conditions, including hypertension, obesity, diabetes, heart disease, and pain syndromes (Price, Kao, Burgers, Carpenter, & Tyrka, 2013; Shonkoff & Garner, 2012). In fact, early stress appears to increase risk for early mortality, with one recent study showing that adults with six or more adverse experiences in childhood died nearly 20 years earlier than those without adversity (Brown et al., 2009).

Children in poverty are disproportionately exposed to adverse circumstances through direct and indirect mechanisms embedded within several levels of the environment including families, neighborhoods and communities, and the larger culture (Bronfenbrenner, 1977; Cicchetti & Lynch, 1993). Lack of resources directly impacts the physical environment, including the availability, stability, and quality of nourishment, shelter, neighborhood environment and schooling. Poverty also influences the social environment directly and indirectly, through effects on emotional stability and availability of caregivers and others in the community. Within *families*, children in poverty may be exposed to harsh or neglectful parenting and maltreatment, and parental mental illness, substance use, and incarceration. Within the immediate *communities* in which they live, children in poverty face neighborhood violence, a lack of employment options for their caregivers, low-quality childcare, and underfunded educational systems. The early-life health consequences of developing in poverty are well documented. For example, chronic diseases such as asthma and diabetes have long been known to be more prevalent and have disparate morbidity among impoverished individuals (Gaskin et al., 2013; Koinis-Mitchell et al., 2007). These wide-ranging effects of early adversity may result in part from constitutional changes in the inflammatory system.

Acute Stress Response and Inflammation

Exposure to acute stress or trauma initiates the inflammatory response, which involves increases in pro-inflammatory cytokines, as well as chemokines, adhesion molecules, and acute phase reactants. Cytokines are a large and diverse group of messenger proteins that act through intercellular signaling to regulate immune responses (Lacy & Stow, 2011; Robles, Glaser, & Kiecolt-Glaser, 2005). Pro-inflammatory cytokines play a vital role in mobilizing the immune response to infectious agents and injuries, and it is now clear that cytokines are also activated in response to acute psychological stress. Inflammatory proteins serve as part of an adaptive response that serves to minimize injury and promote healing in response to acute toxins, threats or injuries. However, excessive inflammation with prolonged and persistent elevation of pro-inflammatory cytokine levels is associated with major depression (MDD) and post-traumatic stress disorder (PTSD) in addition to other psychiatric and other medical conditions.

Inflammation and Psychopathology

A wealth of literature describes findings from clinical and epidemiologic samples showing that adults with MDD have elevated inflammatory responses or peripheral concentrations of cytokines, most commonly interleukin (IL)-6, IL-1β, and TNF-α, as well as the acute phase protein C-reactive protein (CRP). Meta-analyses have confirmed these associations (Dowlati et al., 2010; Hiles, Baker, de Malmanche, & Attia, 2012; Liu, Ho, & Mak, 2012). There is now also substantial evidence in adults that PTSD is associated with inflammation (Baker, Nievergelt, & O'Connor, 2012; Gola et al., 2013; O'Donovan et al., 2011; Pace et al., 2012). Few studies of children with psychiatric disorders have been conducted. Findings from a small number of studies of adolescent depression have been mixed (Mills, Scott, Wray, Cohen-Woods, & Baune, 2013), however a recent large study found that externalizing behavior at age 8 predicted elevated CRP at age 10, and age 8 internalizing and externalizing behaviors predicted elevated IL-6 at age 10 (Slopen, Kubzansky, & Koenen, 2013a).

Several lines of evidence implicate cytokine activity as a mechanism of these disorders. A recent meta-analysis found that IL-6 and CRP concentrations were significant predictors of the subsequent development of depressive symptoms (Valkanova, Ebmeier, & Allan, 2013). Inflammation is associated with decrements in learning and memory (Krishnadas et al., 2013; Nikas, 2013; Phillips et al., 2011; Teunissen et al., 2003; Wright et al., 2006; Yaffe et al., 2003), and therapeutic use of interferon for Hepatitis C can cause depression (Udina et al., 2012) Animal models show that peripheral administration of endotoxin or cytokines elicits "sickness behavior" including social withdrawal, and reduction of food intake and other activities (Dantzer, 2009). Cytokines do not passively cross the blood-brain barrier, but several direct and indirect routes for cytokines to act on the brain have been documented (Dantzer, 2009; Mills et al., 2013).

Role of Inflammatory Cytokines in Neuroplasticity

Further evidence supports a role for cytokine activity on the growth and development of neurons (Kohman & Rhodes, 2013). As with many physiological systems, there is some evidence that low levels of inflammatory cytokines may have salutary effects, while high levels may be deleterious. A number of studies have examined effects of cytokine exposure on neural progenitor cells. At relatively low concentrations, IL-6, IL-1β, and TNF-α induce neuronal differentiation and proliferation, but at high concentrations, pro-inflammatory cytokines reduce neurogenesis and cell survival (Araujo & Cotman, 1995; Barkho et al., 2006; Bernardino et al., 2008; Cacci, Claasen, & Kokaia, 2005; Monje, Toda, & Palmer, 2003; Zunszain et al., 2012). IL-1β may play a particularly important role in the brain (Dantzer, 2009). In animal models, central administration of IL-1β activates the HPA axis, reduces hippocampal brain-derived neurotrophic factor (BDNF), and impairs hippocampal-dependent learning (Koo & Duman, 2008). Furthermore, there is evidence from animal models that activation of the IL-1β receptor is necessary for stress to impair neurogenesis (Koo & Duman, 2008).

Childhood Adversity and Inflammation

There is currently a great deal of interest in the hypothesis that early stress exposure may lead to chronic inflammation. Several studies have shown that childhood adversity is linked to higher peripheral levels of inflammatory cytokines in adults with MDD, and there is some evidence for an effect of early stress in other conditions such as drug abuse, schizophrenia, and migraine (for a review, see Coelho, Viola, Walss-Bass, Brietzke, & Grassi-Oliveira, 2013).

Other work has examined associations of early experience with inflammatory markers in healthy subjects or those recruited from the community. This is a relatively new area of research and published findings are limited. Most of the studies on this topic have examined CRP in peripheral blood samples. CRP is an acute phase reactant produced by the liver in response to cytokines. In a large longitudinal birth-cohort study, Danese and colleagues (2007) found that childhood maltreatment was predictive of significantly higher plasma CRP levels in adulthood. Depression was associated with significantly elevated levels of CRP but childhood maltreatment accounted for much of this effect, and those with depression and maltreatment had the highest CRP levels (Danese et al., 2008). Additional large studies of adults have confirmed associations of childhood adversity or socioeconomic status and CRP (Appleton et al., 2012; Matthews, Chang, Thurston, & Bromberger, 2013; Pollitt et al., 2007) and CRP and IL-6 (Bertone-Johnson, Whitcomb, Missmer, Karlson, & Rich-Edwards, 2012; Rooks, Veledar, Goldberg, Bremner, & Vaccarino, 2012), however, two small studies of healthy adults did not find an effect of early stress on CRP levels (Carpenter, Gawuga, Tyrka, & Price, 2012; Hartwell et al., 2013).

Several studies have measured CRP in childhood and found positive associations with either adverse events (Slopen, Kubzansky, McLaughlin, & Koenen, 2013b) or socioeconomic adversity (Broyles et al., 2012; Dowd, Zajacova, & Aiello, 2010; Howe et al., 2010; McDade et al., 2005; Murasko, 2008). However, one study found that the link between CRP and adversity varied as a function of chronic interpersonal stress (Marin, Martin, Blackwell, Stetler, & Miller, 2007), another found an association of high SES and high CRP when those with very high CRP were included (Thomas, Cooper, Williams, Baker, & Davies, 2005), and other studies found no association of CRP with childhood economic status (Cook et al., 2000; Gimeno et al., 2008). Thus, it appears that the effect of childhood adversity that is seen on elevated levels of CRP in adulthood is more variable in studies of childhood CRP.

Only a few investigations have examined associations of early adversity with basal or induced cytokine levels in healthy participants. Stressful life events were associated with higher levels of plasma IL-6 in 10-year-old children (Slopen et al., 2013b) and TNF-α in children ages 5–10 (Dixon, Meng, Goldberg, Schneiderman, & Delamater, 2009), parental divorce or separation was linked to higher IL-4 levels (Herberth et al., 2008). Miller and Chen (2010) studied 135 female adolescents longitudinally over 1.5 years and found that those with harsh families had increasingly higher IL-6 responses to immune challenge but no effect on circulating IL-6 levels. In a study of adults, those with lower childhood SES had higher in vitro IL-6 responses to stimulation (Miller et al., 2009). Our group found that IL-6 response to a standardized psychosocial challenge task, was greater in healthy adults with a

history of childhood maltreatment, although no difference in baseline IL-6 was observed (Carpenter et al., 2010). In a recent small study of healthy adults, Hartwell and colleagues (2013) found that reports of early trauma were correlated with basal levels of serum TNF-α, IL-6, and IL-1β.

Other than this small study of adults by Hartwell and colleagues, no studies have examined the relationship between childhood adversity and IL-1β concentrations, despite the important role of this cytokine in the inflammatory cascade, and evidence that it is implicated in the pathophysiology of MDD possibly due to inhibitory effects on neuroplasticity. Animal models of stress exposure show increases in IL-1β (e.g., Bailey, Kinsey, Padgett, Sheridan, & Leblebicioglu, 2009; Caso, Moro, Lorenzo, Lizasoain, & Leza, 2007; Nguyen et al., 1998; Porterfield, Gabella, Simmons, & Johnson, 2012; You et al., 2011), and in humans, there is evidence that IL-1β increases acutely in response to stress challenge, including cognitive, social, and sleep-deprivation paradigms (Brydon et al., 2005; Mastrolonardo, Alicino, Zefferino, Pasquini, & Picardi, 2007; Steptoe, Hamer, & Chida, 2007; Yamakawa et al., 2009).

None of the prior studies on this topic focused on the pre-school period, so it is not known whether stress-induced inflammation might begin during this early developmental stage. Blood sampling is very difficult with young children, and recent research has begun to examine inflammatory markers in saliva. Salivary cytokines are produced locally in the oral mucosa, however some studies have documented correlations of IL-1β and CRP in saliva and peripheral blood (Byrne et al., 2013; Megson, Fitzsimmons, Dharmapatni, & Bartold, 2010; Ouellet-Morin, Danese, Williams, & Arseneault, 2011; Riis et al., 2013). One study found that salivary IL-1β increased in response to psychosocial stress challenge (Mastrolonardo et al., 2007).

In the present study, we examined the hypothesis that salivary IL-1β and CRP would be elevated in association with stress exposure in a sample of pre-school-aged children.

Methods

Participants

Forty families who were enrolled in a larger study of child maltreatment and other adversities participated in this study. All families consented to examination of child welfare records to determine maltreatment status. Families with a maltreated child who remained at home with the caregiver (n=18) were identified from the local child welfare agency and an emergency maltreatment assessment service via record review as described below. Families with no documented episodes of maltreatment (n=22) were recruited at a low-income pediatric medical clinic during a well-child visit and at childcare centers.

Children ranged in age from 3 to 5 years (M = 50 months; SD = 9.6 months), were racially and ethnically diverse (15 White non-Hispanic, 11 Hispanic, 6 Black, 8 other races), and 22 were male. Most caregivers (n=36) were biological mothers. Nine caregivers had less than a high school degree, 15 completed high school, 11 some post-secondary education, and 5 had a bachelor's degree. Twenty-one caregivers were unemployed and 38 of the families

qualified for public assistance. Based on review of available medical records and parent report, children with chronic illness, medication use, obesity, and failure-to-thrive were excluded. Those with acute illness or medication use were included no less than 2 weeks following resolution of illness and medication use.

Child maltreatment status—Trained research staff coded child welfare records using the System for Coding Subtype and Severity of Maltreatment in Child Protective Records (Barnett et al., 1993). Five maltreatment subtypes and severity scores ranging from 1 (least severe) to 5 (most severe) were derived, and children with a case of moderate to severe levels of maltreatment (score of 3–5) within the prior 6 months were eligible for participation. Four children had substantiated cases of physical abuse, 4 sexual abuse, 4 physical neglect/failure to provide, 4 physical neglect/lack of supervision, and 10 emotional maltreatment.

Procedure

Families completed a series of two home visits and a battery of questionnaires in between visits. During the first visit, caregivers completed interviews on child stress exposure and symptoms of child psychopathology. The second home visit occurred in the afternoon. After a 15-minute period of free play, a baseline pre-challenge saliva sample was collected with a Salimetrics Children's Swab (State College, PA). Children then participated in four emotion-eliciting tasks from the Lab-TAB Laboratory Temperament Assessment Battery (Lab-TAB) including two one-minute fear episodes (stranger approach and scary mask), a two-minute frustration episode (attractive toy in a transparent box) and a one-minute exuberance episode (pop-up snakes). After another period of free play, a post-challenge saliva sample was collected at the end of the visit, approximately 30 minutes after completion of the Lab-TAB.

Measures

Socioeconomic adversity—Three indicators of low socioeconomic status were obtained via questionnaire (parental education < high school degree, parental unemployment, and single parenthood) and summed to create a socioeconomic adversity variable.

Contextual stress interview—Caregivers completed a semi-structured interview developed in our laboratory to assess the child's experience of contextual stressors in the past month and in the child's lifetime. Categories were: death of a caregiver, separation from a caregiver, frequent change of residence or homelessness, inadequate food or clothing, and other events including witnessing neighborhood violence or parental arrest. Each domain was scored positive if at least one episode occurred, and domains were summed for past month and lifetime.

Traumatic life events and child symptoms—The Diagnostic Infant and Preschool Assessment (DIPA; Scheeringa, & Haslett, 2010) interview was conducted with caregivers to assess child experiences of traumatic life events and symptoms of PTSD and MDD. Interviews were conducted by trained clinical social workers and a PhD level psychologist, reviewed in a group supervision format, and scored based upon group consensus. Traumatic events in each domain were dichotomized (no trauma versus ≥ 1 trauma), then summed to

create a scale for number of types of traumas experienced in the child's lifetime. Physical and sexual abuse were not included because they were assessed as maltreatment (above). Possible scores ranged from 0 to 8.

Symptoms of PTSD and MDD experienced within the past month were summed. None of the children met DSM-IV criteria for PTSD or Major Depression, and only two children met Research Diagnostic Criteria for PTSD, thus diagnostic status was not considered.

Parenting stress—Caregivers completed the 36-item Parenting Stress Index Short Form (Abidin, 1995), and the total score was used to assess stress associated with parenting.

Inflammatory markers—The baseline saliva sample was assayed for IL-1β and CRP. IL-1β was also assayed in the post-challenge saliva sample (given evidence that it may increase in response to stress). Saliva samples were assayed in duplicate at the Salimetrics Laboratory (State College, PA) using high sensitivity enzyme immunoassays. For IL-1β the intra-assay coefficient of variation was <3% and the inter-assay coefficient of variation was <5%. For CRP, the intra-assay coefficient of variation was <3.9% and the inter-assay coefficient of variation was <7.5%. Values were log transformed and winsorized prior to data analysis to adjust for skewed distributions and outliers.

Results

Preliminary Analyses

Descriptive statistics are displayed in Table 1. Child age, gender, race and ethnicity were not associated with IL-1β at baseline, IL-1β following the challenge task, or CRP and were considered no further. A repeated measures general linear model (GLM) tested change in IL-1β over the challenge task. There was not a significant effect of time on IL-1β, $F(1, 39) = .06$, *ns*).

Associations of Adversity Variables with IL-1β

Associations of each adversity variable with IL-1β were tested with repeated measures GLMs. The number of contextual stressors in the past month ($F(1, 38) = 6.07$, $p = .018$) and in the child's lifetime ($F(1, 38) = 4.67$, $p = .037$), and the number of traumas ($F(1, 38) = 4.73$, $p = .036$) each exerted a significant between-subjects effect on IL-1β. The socioeconomic adversity variable showed a trend-level main effect ($F(1, 38) = 3.29$, $p = .078$). There were no between-subjects effects of child maltreatment status ($F(1, 38) = .48$, *ns*) or parenting stress ($F(1, 38) = .10$, *ns*). None of the adversity measures showed within-subjects effects.

Correlations were used to examine the effects of the significant adversity measures on IL-1β at each time point. As shown in Table 2, baseline IL-1β was positively associated with each of the significant main-effect adversities. Post-challenge IL-1β showed positive correlations with each adversity variable but these did not reach significance. Figure 1 depicts the mean IL-1β values for each time point according to the number of lifetime contextual stressors.

Post Hoc Analysis of Differences in IL-1β Based Upon Specific Stress Experiences

In exploratory post-hoc analyses, several individual stressors were found to be associated with higher levels of baseline IL-1β at each time-point (Table 3).

IL-1β and Child Symptoms

Repeated measures GLM was used to test for effects of child symptoms of PTSD and MDD on IL-1β over time. There were no between- or within-subjects effects.

CRP, Contextual Stressors and Child Symptoms

There were no associations of CRP at the single time point with any of the adversity variables or symptom measures.

Discussion

These findings indicate that salivary IL-1β is increased in association with adverse experiences in early childhood. To our knowledge, this is the first study to show an association of this important pro-inflammatory cytokine with stress exposure in children, and the first to examine any inflammatory markers in relation to stress exposure in children of preschool-age. As discussed above, evidence from animal and human studies supports a role of inflammatory cytokines in the development of MDD and PTSD as well as the broad-ranging health effects of stress-induced inflammation. Exposure to stress increases IL-1β in several brain regions including the hippocampus, and administration of IL-1β in the brain activates the HPA axis, reduces hippocampal BDNF, and impairs hippocampal-dependent learning, suggesting important effects on neuroplasticity (Kohman & Rhodes, 2013; Koo & Duman, 2008). Consistent with the hypothesis that IL-1β and other inflammatory proteins are involved in the neuropathology of psychiatric conditions, a study of adolescent suicides found increased activity of IL-1β, IL-6, and TNF-α in the prefrontal cortex (Pandey et al., 2012).

To our knowledge, this is the first study to examine childhood adversity in relation to salivary cytokine levels. Salivary cytokines are produced by oral mucosal cells and may not be indicative of systemic inflammation. However, some evidence indicates that there are at least modest correlations of some inflammatory proteins in saliva and peripheral blood in adolescents (Byrne et al., 2013; Riis et al., 2013), including IL-1 β (Riis et al., 2013) and in adults (Ouellet-Morin et al., 2011; Out, Hall, Granger, Page, & Woods, 2012; Williamson, Munro, Pickler, Grap, & Elswick, 2012). That IL-1β increased acutely in response to a psychosocial stress challenge (Mastrolonardo et al., 2007) indicates that this cytokine can be responsive to central nervous system activation and does not simply reflect the oral mucosal response to local infection or injury. Our findings of an association with childhood adversity provide further support for a brain-saliva connection. Unfortunately we did not have a measure of oral hygiene, so it is possible that the association with stress exposure is due to an effect of stress on oral hygiene and associated dental caries. However, that exposure to stressors was linked to salivary IL-1β in a sample in which nearly all families qualified for public assistance suggests that the findings are unlikely to be explained by an effect of poverty overall on oral hygiene. Tooth eruption has also been linked to elevations of salivary

cytokines, however, most children have a full set of primary teeth by age 3 (American Dental Association, 2005) and permanent teeth do not begin to erupt until age 6–7 (American Dental Association, 2006), so this is unlikely to explain our findings.

Given the association of IL-1β with other adversities, it is somewhat surprising that we did not find an effect of documented childhood maltreatment in this preliminary study. In this sample, non-maltreated children were exposed to significant economic and other adversity, so effects of maltreatment may have been obscured by these other influences. In addition, the maltreated children included in this study remained in the home with their primary caregiver. This occurs when it is determined by the local child welfare agency that the environment can be made safe for the child, either by preventing further contact with the perpetrator, or by providing services to a caregiver who is considered to be able to maintain a safe and nurturing environment. Thus, the most severe and chronic forms of maltreatment would not be included in this study. In addition, the maltreated children were exposed to different types of abuse and neglect, and the nature of these experiences may be determinants of the biological sequelae (Cicchetti, 2013). Due to the small numbers of children with each maltreatment type, we were not able to assess this in this preliminary study. In addition, because the sample as a whole was impoverished and exposed to a variety of contextual stressors, it is also possible that undocumented cases of maltreatment, such as neglect, may have occurred in the non-maltreated group.

It is of note that while stress exposure was linked to IL-1β, neither IL-1β nor CRP was linked to psychiatric symptoms in this modest-sized sample. It is possible that IL-1β will be predictive of the future development of mood or anxiety symptoms. Indeed, a study by Miller and Cole (2012) revealed that among subjects with childhood adversity, but not those without adversity, high IL-6 forecasted depression 6 months later. We also did not see an increase in salivary IL-1β over our sampling period. In healthy adults, Mastrolonardo et al. (2007) did observe increases in salivary IL-1β from baseline to 10 minutes following a psychosocial stress test. In the present study, it is possible that the second saliva sample was not taken early enough to detect a rise in this cytokine or that the Lab-TAB vignettes were not sufficiently challenging to arouse a cytokine stress response.

Salivary CRP was not associated with adversity in our sample of preschool-aged children. This is in contrast to findings of elevated plasma or serum CRP in recent large studies of older children and adults with a history of childhood adversity or maltreatment, although findings for CRP in children are mixed with some showing no association as reviewed above. The effect in positive studies tends to be modest in size, so that larger sample sizes may be required. In addition, some evidence indicates that elevated CRP in association with early stress may be highest, or may only be evident, in those who also have depression (Danese et al., 2011; Danese et al., 2008; Miller & Cole, 2012) or behavioral or affect dysregulation (Appleton et al., 2012). The association of CRP with childhood adversity has been reported exclusively in plasma or serum, so it is possible that salivary CRP is not elevated in association with early stress, however, recent work suggests at least modest correlations between blood and saliva measures of CRP (Byrne et al., 2013; Ouellet-Morin et al., 2011). Alternatively, given that findings on the effects of adversity on CRP measured

in childhood CRP have been variable, it is possible that consistent basal elevations of CRP do not occur until later in childhood.

Limitations of our study include the modest sample size and the lack of a contemporaneous blood sample to validate our findings with systemic measures of inflammation. In addition, both poverty and early adversity have been linked to obesity and adipocytes are one source of peripheral cytokines. Associations of BMI with childhood adversity account for at least some of the effects for CRP and TNF-α in peripheral blood (Dixon et al., 2009; Matthews et al., 2013; Slopen et al., 2013b). It is not clear whether obesity influences inflammatory proteins in saliva, however. We excluded obesity and failure-to-thrive when identified in the records or by caregivers during screening. BMI, available from chart review for 24 children, was not associated with salivary IL-1β or CRP in this study (data not shown), so this is unlikely to account for our findings. However, future work with larger samples is needed to determine whether obesity or adiposity influences saliva cytokines or CRP.

Strengths of this study include the careful measurement of adverse experiences including documented evidence of maltreatment from child welfare records, in-home assessments and a standardized challenge protocol, and the use of an at-risk, impoverished sample. In addition, we examined IL-1β over time during a stress challenge, but did not find stress-induced changes. Finally, we carefully excluded children with chronic illness and medication in order to avoid these confounds, and children with acute illness or medications were studied after resolution of the condition.

It important to note that our findings occurred in the context of poverty, and that among other stressors, unemployment and food insecurity were linked to increased levels of IL-1β. However, poor health outcomes among impoverished children are neither universal nor impervious to change. The majority of children developing in poverty do not have identifiable health problems during childhood or early adulthood. In addition to differential exposure to stressors, protective processes play a role. For example, Brody and colleagues (2013) found that among individuals developing in poverty during childhood, those with the least supportive environments have the highest allostatic load (as indexed by blood pressure, catecholamine levels, and body mass index) in late adolescence. Chen and colleagues (2011) found that among adults with a history of low childhood SES, those who reported high maternal warmth during childhood had lower inflammatory responses to immune challenge suggesting that supportive family environments may buffer these negative effects of environment.

Finally, interventions may produce change. For example, there is evidence that providing opportunities for individuals living in poverty to move to better neighborhoods reduces the risk of obesity (Ludwig et al., 2011). Although we are not aware of similar data regarding change in inflammatory markers, given the effects of stress on inflammation, improvements in social environments are likely to be beneficial. Medications that target inflammation, including nonsteroidal anti-inflammatory drugs (NSAIDS), TNF-alpha antagonists, and antibiotics are being examined as possible treatments for mood disorders (Tyrka et al., 2013). Emerging data indicate that exercise, weight loss, yoga, and meditation may have anti-inflammatory effects (e.g., Rosenkranz et al., 2013; Bhasin et al., 2013); these

approaches may be particularly appropriate components of an intervention for children exposed to adversity.

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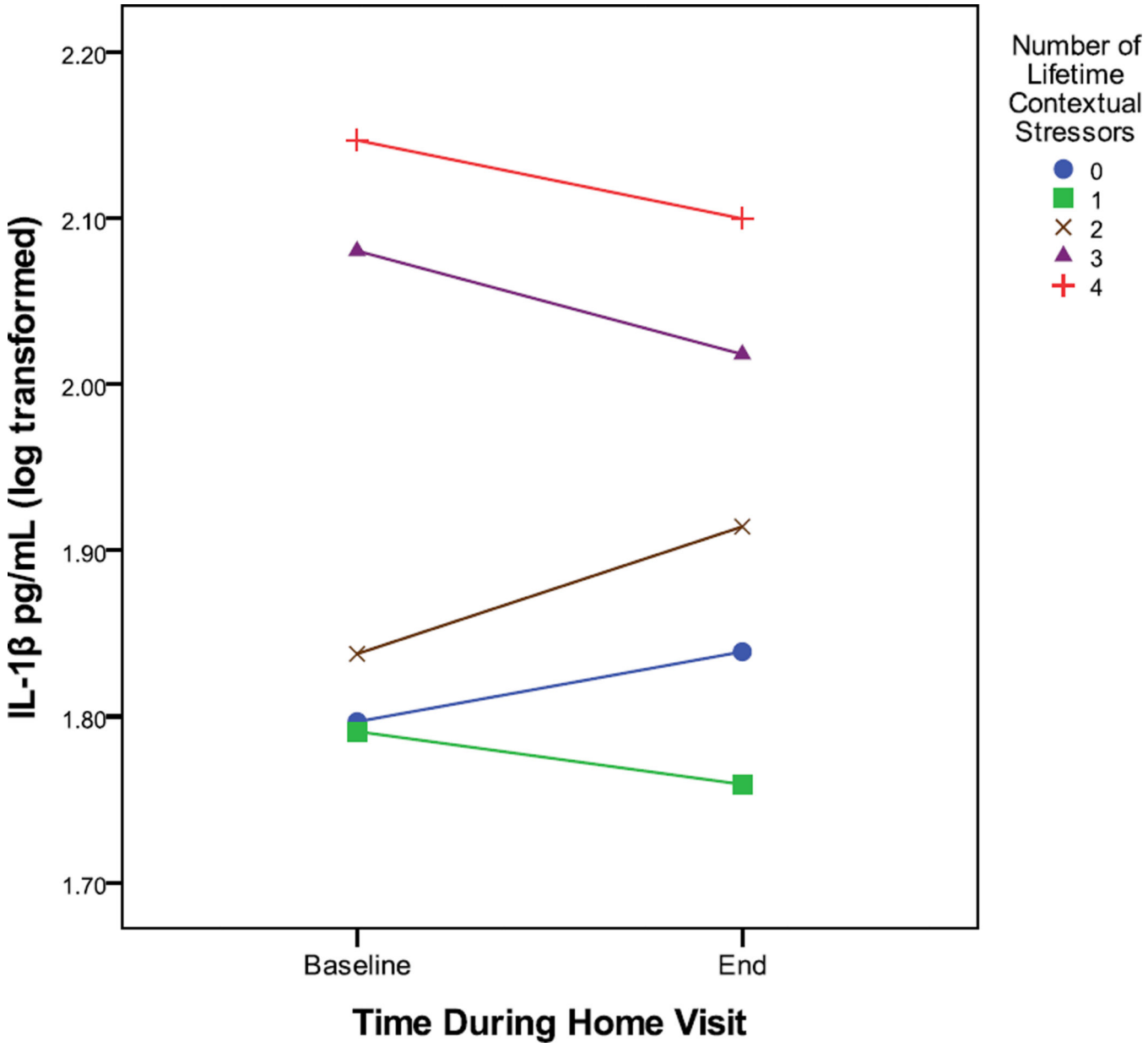

Figure 1.

Table 1

Descriptive statistics

	Mean	*SD*	Range
Baseline IL-1β pg/mL	93.0	68.6	16.4 – 336.0
Post Challenge IL-1β pg/mL	94.6	69.6	19.3 – 318.4
CRP ng/mL	3.0	1.7	1.2 – 6.84
Socioeconomic Adversity	1.5	1.0	0.0 – 3.0
Contextual Stressors Past Month	0.6	0.9	0.0 – 3.0
Contextual Stressors Lifetime	1.4	1.2	0.0 – 4.0
Traumatic Events	0.8	1.1	0.0 – 3.0
Parenting Stress	40.2	35.2	1.0 – 95.0
PTSD Symptoms	2.6	6.4	0.0 – 35.0
MDD Symptoms	1.0	2.8	0.0 – 15.0

Note: n=40

Table 2

Correlations of continuous adversity variables and IL-1β

	Baseline IL-1β	Post Challenge IL-1β
Socioeconomic Adversity	.35*	.15
Contextual Stressors Past Month	.45**	.21
Contextual Stressors Lifetime	.32*	.27t
Traumatic Events	.36*	.24

Note: n=40.

t $p < .10$.

* $p < .05$.

** $p < .01$

Table 3

Baseline IL-1β (log transformed) and individual adversity variables

		Experienced	Not Experienced
	t	**Mean(*SD*)**	**Mean(*SD*)**
Socioeconomic Adversity			
Parental education	1.64	1.9 (0.3)	1.8 (0.3)
Parental unemployment (*n*=21)	2.33*	2.0 (0.3)	1.7 (0.3)
Single parent family (*n*=15)	0.52	1.9 (0.4)	1.8 (0.3)
Contextual Stressors Past Month			
Caregiver separation (*n*=10)	1.66	2.0 (0.3)	1.8 (0.3)
Food insecurity (*n*=3)	2.01*	2.2 (0.1)	1.8 (0.3)
Other stressor (*n*=7)	3.88**	2.2 (0.2)	1.8 (0.3)
Contextual Stressors Lifetime			
Death of a caregiver (*n*=7)	−0.72	1.8 (0.3)	1.9 (0.3)
Caregiver separation (*n*=16)	2.05*	2.0 (0.4)	1.8 (0.3)
Housing/homelessness (*n*=6)	0.67	1.9 (0.3)	1.8 (0.3)
Food insecurity (*n*=4)	6.80**	2.2 (0.0)	1.8 (0.3)
Other stressor (*n*=15)	2.57**	2.0 (0.3)	1.8 (0.3)
Traumatic Life Events			
Car accident (*n*=4)	2.06*	2.2 (0.33)	1.8 (0.3)
Witnessing violence (*n*=7)	3.37**	2.2 (0.21)	1.8 (0.3)
Accidental burning (*n*=4)	−0.43	1.8 (0.28)	1.9 (0.3)
Hospitalization (*n*=9)	2.10*	2.1 (0.36)	1.8 (0.3)
Other trauma (*n*=8)	−0.67	1.8 (0.33)	1.9 (0.3)

Note:

* $p < .05$.

** $p < .01$.

Parental education was dichotomized; *n*=24 had a high school degree or less education.