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Associations Between Maternal Caregiving and Child Indicators of Toxic Stress Among Multiethnic, Urban Families

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Abstract

Introduction: Our purpose is to examine associations between maternal caregiving and child indicators of toxic stress among multiethnic, urban families with children at early school age.

Method: We conducted an exploratory cross-sectional analysis of 54 maternal-child dyads. Mothers reported on parenting behaviors and parental reflective functioning (PRF). Child indicators of toxic stress included hair/salivary biomarkers, anthropometric characteristics, and maternally-reported health and behavior.

Results: Hostile/coercive parenting behaviors were associated with child externalizing behavioral problems ($r=.43$, $p=.001$), but lower interleukin-6 levels ($r=0.31$, $p=.03$). High PRF was associated with fewer child emergency department visits ($\rho = -0.43$, $p=.009$), while impaired PRF was associated with more behavioral problems ($\rho = 0.52$, $p<.0001$).

Discussion: PRF and supportive parenting behaviors may protect against toxic stress among vulnerable families, but additional research is needed to better understand these relationships. Resources are available to help clinicians screen for family risk factors and model responsive caregiving in pediatric settings.

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Keywords

Parenting; family relations; stress; physiological; child health

Multiple studies demonstrate that caregivers can play an important role in buffering the harmful effects of toxic stress (Hostinar, Sullivan, & Gunnar, 2014). Toxic stress describes chronic activation of the stress-response-system, which occurs in response to persistent environmental stressors, such as poverty or community violence, and alters development of the brain and multiple physiological systems (Johnson, Riley, Granger, & Riis, 2013; Shonkoff et al., 2012). Over time, toxic stress may lead to poor health and developmental outcomes in childhood, including growth delay, obesity, and impaired cognitive, social-emotional and language skills, and sets the stage for impaired physical and mental health in adulthood (Garner, 2013; Shonkoff et al., 2012). Understanding the aspects of human caregiving that best protect against toxic stress is essential for the development of clinical interventions and policies that aim to promote health and reduce health inequities, especially among vulnerable families living in stressful environments.

Research with animal models demonstrates that maternal care quality influences development and regulation of stress-response systems in offspring, including changes in the hypothalamic-pituitary-adrenocortical (HPA) axis and autonomic nervous system (Anacker, O'Donnell, & Meaney, 2014; McEwen, 2008; Tang, Reeb-Sutherland, Romeo, & McEwen, 2014). In humans, evidence for the protective role of caregiving is largely found in studies of children who have experienced a *lack* of supportive caregiving, including exposure to maltreatment, parental depression, hostility, and loss due to divorce (Bloch, Peleg, Koren, Aner, & Klein, 2007; Danese & McEwen, 2012; De Bellis, 2005; Dougherty, Tolep, Smith, & Rose, 2013; Gershoff, 2016; Pears, Kim, & Fisher, 2008). These studies provide important evidence of the potential for supportive caregiving to prevent physiological disruptions in childhood; however, the specific caregiving patterns that best protect against toxic stress remain largely unexplored.

Two aspects of caregiving with important implications for child development are parenting behaviors and parental reflective functioning. Parenting behaviors include observable actions that may be supportive (e.g. praising or comforting a child) or hostile (e.g. use of threatening language or corporal punishment). Generally speaking, parenting behaviors have been linked with a range of psychosocial outcomes for children including cognitive development, behavior, and academic readiness, as well as weight status and risk for injury (Ahun & Côté, 2018; Jaques, Weaver, Weaver, & Willoughby, 2018; Ruberry, Klein, Kiff, Thompson, & Lengua, 2018; Ryan & Ollendick, 2018; Shloim, Edelson, Martin & Hetherington, 2015). Examination of the relationship between parenting behaviors and child stress physiology has been limited, however, and largely has focused on very young children in low-risk, homogenous samples (Jansen, Beijers, Riksen-Walraven, & De Weerth, 2010).

Also of great importance to child development is parental reflective functioning (Slade, 2005). Reflective functioning, or mentalizing, refers to an ability to understand the mental states of both the self and others, including thoughts, feelings, and intentions (Fonagy, Steele, Steele, Moran, & Higgitt, 1991). Parental reflective functioning (PRF), therefore,

describes a caregiver's capacity to not only reflect on his or her own mental states, but also the child's internal world, and connect this to the child's behavior in meaningful ways (Slade, 2005). Highly reflective parents recognize their own mental states as they relate to parenting, such as feelings of frustration, worry, or joy, and that these feelings affect how the parent relates to their child. Reflective parents are also highly interested in and curious about their child's mental states, but acknowledge the opacity of their child's inner world. In other words, reflective parents recognize that they can reflect on the child's experience, but will never completely understand the child's mind (Luyten, Mayes, Nijssens, & Fonagy, 2017; Slade, 2005). These two hallmarks of PRF, recognizing opacity of mental states and interest and curiosity in mental states, are crucial for the development of secure attachment relationships, emotion regulation, and ultimately the child's own reflective capacity (Luyten et al., 2017; Slade, 2005; Slade, Grienberger, Bernbach, Levy, & Locker, 2005).

As reflective functioning develops through early relationships, it may be impaired in parents with a history of insecure attachment, child maltreatment, or other forms of trauma (Fonagy et al., 1991; Slade et al., 2005; Stacks et al., 2014). Often these parents are unable to, or not yet able to, think about and understand their child's thoughts, feelings and intentions. This stance is described as *prementalizing*, and may be expressed as over-certainty about the child's mental states, or with the parent resorting to malevolent attributions to explain the child's behavior (Luyten et al., 2017). As PRF is critical for development of children's self-regulatory capacities, PRF may also influence development and regulation of the child's stress-response-system, especially for children who are exposed to persistent stressors. However, associations between parents' reflective capacity and physiologic stress in their children have not been explored.

The purpose of this study is to describe and examine relationships among maternal caregiving (namely, parenting behaviors and PRF) and child indicators of toxic stress in a multiethnic, urban sample of mothers and children at early school age (4-9 years). The ecobiodevelopmental (EBD) model provides a framework for the study, and describes connections among a child's ecology (social and physical environment), biology, and health and development (Figure 1; Shonkoff et al., 2012). We examine indicators of toxic stress across a range of physiological systems: primary neuroendocrine and immune mediators of the stress response, secondary cardiovascular outcomes associated with chronic stress, and tertiary health and behavioral outcomes that represent the downstream effects of chronic HPA-axis activation (Author blinded, 2018a; Garner, 2013; Johnson et al., 2013). As measurement of chronic stress biomarkers has been limited in low-income and ethnic minority children (Juster, McEwen, & Lupien, 2010), this study offers an innovative approach to examining toxic stress among children at risk. While much research in this area has been conducted with very young children, the downstream effects of stress are more likely to be measurable as children age, and thus an examination of school-age children is likely to provide important insight into risk and protective factors for toxic stress.

Identifying factors that protect against toxic stress in childhood is essential for the provision of pediatric primary care activities that focus on health promotion, disease prevention, and reduction of disparities among vulnerable families. Using a biobehavioral approach, our goal is to determine effect sizes and generate hypotheses that will inform future research studies

designed to evaluate protective factors and health outcomes among families living in environments of adversity.

Methods

Design, Sample & Setting

We use data from a larger cross-sectional, exploratory study conducted by this research team to examine risk and protective factors for toxic stress among low-income families (Authors blinded, 2018b). For this study, maternal-child dyads were recruited following participation in the control group arm of an early home visiting intervention, *Minding the Baby*® (MTB). In the original MTB randomized controlled trial (RCT), first time mothers with risk factors including poverty, a history of trauma, or young maternal age were enrolled (Ordway et al., 2014; Sadler et al., 2013; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT01458145) Identifier: NCT01458145). In the current study, participants were eligible for inclusion if (i) the child was between 4-9 years of age at the time of data collection, (ii) the mother had custody or regular contact with the child, (iii) the dyad was residing within the state of Connecticut, and (iv) the dyad participated in the control group arm of the MTB RCT. We successfully recruited and enrolled 65% (N=54) of the 83 families eligible for participation. Mothers who did not enroll (N=29) were more likely to be Latina ($p=.03$), but families did not differ by maternal age at enrollment, education level, or child gender [see (Authors blinded, 2018b) for additional information on recruitment and enrollment procedures].

Procedures

We obtained [University blinded] Institutional Review Board approval, and parents provided informed consent and permission to talk with the child. All children were informed about the study using age-appropriate materials, and children ages 7 to 9 years provided assent (Kohrman et al., 1995). Data were collected at private locations including participants' homes (N=21), the [Name blinded] Biobehavioral laboratory (N=25), and community libraries (N=8). Mothers were compensated \$50 for their time, consistent with the original RCT, and children were given an age appropriate book or toy.

Variables and Measures

Maternal caregiving.

Parenting behaviors.: We measured parenting behaviors using the 20-item self-report Parent Behavior Inventory (PBI) (Lovejoy, Weis, O'Hare, & Rubin, 1999). The PBI was developed for use by parents of early school age children and has demonstrated validity in at-risk populations (Dallaire et al., 2006; Lovejoy et al., 1999). The PBI includes two subscales that showed adequate internal consistency for the current sample: supportive/engaged parenting ($\alpha = .69$) and hostile/coercive parenting ($\alpha = .69$). Supportive/engaged parenting was indicated by positive responses to items such as "I try to teach my child new things" and "I laugh with my child about things we find funny." Examples of items related to hostile/coercive parenting included "I grab or handle my child roughly" and "When I am disappointed in my child's behavior, I remind her/her about what I've done for him/her" (Lovejoy et al., 1999).

Parental reflective functioning.: We measured PRF with the 18-item version of the Parental Reflective Functioning Questionnaire (PRFQ) (Luyten et al., 2017). The PRFQ is a self-report measure that includes three subscales: Interest and Curiosity in Mental States (PRFQ-IC), a measure of high PRF (e.g. “I try to see situations through the eyes of my child”); Certainty about Mental States (PRFQ-CM), which describes a parent’s capacity to recognize the opacity of his/her child’s mental states; and Prementalizing Modes (PRFQ-PM), which refers to impaired or low PRF (e.g. “when my child is fussy, he or she does that just to annoy me”) (Luyten et al., 2017). We re-coded the PRFQ-CM scale to aid interpretation (e.g. “I can always predict what my child will do”): the mid-range responses were scored highest to reflect *appropriate* certainty about mental states, and the ends of the Likert scale (*too much* or *too little* certainty) received the lowest scores. Reliability was low for both the original and re-coded versions of the PRFQ-CM ($\alpha = .44$), but adequate for PRFQ-IC ($\alpha = 0.65$) and PRFQ-PM ($\alpha = .70$).

Children’s indicators of toxic stress.

Neuroendocrine functioning.: We evaluated neuroendocrine functioning with hair cortisol, a noninvasive indicator of long-term HPA axis activity (Russell, Koren, Rieder, & Van Uum, 2012). We collected a 3-cm sample of hair from the posterior vertex of the child’s scalp, representing systemic cortisol exposure from the past three months. Hair cortisol was analyzed using a high-sensitivity enzyme immunoassay kit, and information on hair characteristics, hair care habits, and corticosteroid use was recorded (Meyer, Novak, Hamel, & Rosenberg, 2014; Russell et al., 2012).

Immune functioning.: We measured salivary C-reactive protein (CRP) and a panel of four proinflammatory cytokines [interleukin-1 beta (IL-1 β), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF)] to assess children’s immune functioning (Cook et al., 2000; Haddad, Saadé, & Safieh-Garabedian, 2002). Saliva was primarily collected using a passive drool device (N=47), but oral swabs were used when necessary based on developmental capabilities (N=7). Prior to saliva collection, the principal investigator (PI), an advanced practice nurse, conducted a gross oral exam and recorded notable findings (sores, dental caries, loose/missing teeth) (Riis et al., 2016). Salivary CRP was analyzed via enzyme immunoassay and the cytokine panel was analyzed using a 4-plex electrochemiluminescence immunoassay. Salivary biomarker intra-assay coefficients of variability were acceptable (2.8-6.9%). See [author blinded] et al. (2018) for discussion of biomarker collection and storage procedures.

Cardiovascular functioning.: We measured children’s systolic (SBP) and diastolic (DBP) blood pressure to assess cardiovascular risk (Muntner, He, Cutler, Wildman, & Whelton, 2004). After 5 minutes of rest, the PI measured children’s blood pressure with a calibrated manual sphygmomanometer. Blood pressure was measured three times at least 1 minute apart, and SBP and DBP percentiles were calculated based on age, height and gender (Muntner et al., 2004). Efforts were made to obtain measurements for all biomarkers at the same time of day (late afternoon after school) to account for diurnal variation (Bird & Michie, 2008).

Physical Health.: The PI measured children's height and weight with a calibrated stadiometer and scale, and determined body mass index (BMI) percentiles and z-scores based on age and gender-appropriate CDC growth charts (Kuczmarski RJ et al., 2002). Mothers reported on children's health history, including chronic illnesses, medication use, and frequency of emergency department (ED) visits, injuries/accidents, and hospitalizations.

Behavior and Academic Performance.: We assessed child behavior using age-appropriate parent-report versions of the 99-item Child Behavior Checklist (CBCL), a questionnaire designed to assess total, internalizing (anxious, depressive) and externalizing (aggressive, hyperactive) behavior problems (Achenbach & Ruffle, 2000). Cronbach's alpha was high for this sample ($\alpha=.90-.95$). We collected information on school performance using the CBCL academic background section (Achenbach & Ruffle, 2000).

Data Analysis

Descriptive statistics.—Univariate statistics (means, medians, frequencies) were used to describe sample characteristics and all study variables. Data were normally distributed for the PBI hostile/coercive scale, child BMI, DBP percentile, total behavior problems, and internalizing behaviors. Data transformations were applied to the following variables to improve normality of the distributions: salivary cytokines, hair cortisol, and externalizing behavior problems (natural-log transformations), and the PRFQ-IC scale (cube-transformation). Distributions of the remaining variables did not improve with transformations and thus nonparametric tests were used when these variables were examined.

Group comparisons.—Using two-sample t-tests, we compared salivary biomarkers levels for children with and without missing teeth, loose teeth, unfilled caries, recent dental work (past 1 week), and other mouth issues (crowns, fillings, braces). Using two-sample t-tests (t ; if comparing two means) or analysis of variance tests (F ; if comparing more than two means), we compared hair cortisol levels for differences by hair shape, color, style, washing frequency, product use, and corticosteroid use. We also used two-sample t-tests to compare child biomarkers and anthropometric measures for differences by child gender, age, and race/ethnicity. Child age was dichotomized into two groups (4-6 years and 7-9 years) based on developmental stage and data distribution. Race/ethnicity was categorized as Hispanic and non-Hispanic Black; the other/mixed race group was not used for comparison analyses due to small sample size ($N<5$).

Correlation and regression analyses.—We used Pearson correlations (r ; if both variables normally distributed) and Spearman's rank (ρ ; if at least one variable non-normally distributed) to examine associations between maternal caregiving and child indicators of toxic stress. Due to the exploratory nature of the study, we did not adjust for multiple hypothesis testing due to the risk of missing an association. For all correlations with a p -value of less than 0.1, regressions were then conducted with maternal caregiving as the independent variable and child indicators of toxic stress as the dependent variable. Simple linear regressions were conducted for continuous outcome variables (biomarkers, BMI, blood pressure, CBCL) and simple logistic regressions were conducted for dichotomous

outcome variables (health and academic history). Due to lack of variance on the PBI supportive/engaged scale, scores were dichotomized at the mean (high and low supportive parenting) for regression analyses. Because the number of ED visits is inherently a count variable, and our data followed a non-normal distribution with many zeros ($N=19$; 35%), regression models better-suited for count variables (Poisson, negative binomial, zero-inflated Poisson, and zero-inflated negative binomial) were tested and model fit was selected based on the smallest Akaike Information Criterion (AIC) value.

Sample size and power.—The goal of this exploratory study was to examine the size of correlational effects to inform future research studies on toxic stress prevention, rather than to obtain statistically significant effects. Though the associations in this study have not previously been examined, we expected correlations analyses to be underpowered for the eligible sample based on related correlations, such as between hair cortisol and maternal depression ($r=.22$) in a multiethnic sample of young children (Palmer et al., 2013). We considered a p -value of .05 to be the significance level for this study; however, correlations with p -values of less than .1 will also be highlighted, as these findings may also be useful for future research.

Results

Description of the Sample

Fifty-four maternal-child dyads participated in the study, and all reported receiving public assistance (Table 1). Mothers reported high levels of supportive/engaged parenting and interest/curiosity in children's mental states (Table 2). Descriptive statistics for the child biologic, health and developmental measures are presented in Tables 3 and 4. Almost half (44%) of the children were overweight or obese, and 14.9% had prehypertensive or hypertensive blood pressure levels. Asthma (27.8%), seasonal allergies (25.9%) and eczema (35.2%) were the most commonly reported diagnoses, and ED visits (64%) and learning problems (18.5%) were also commonly reported (Table 2).

Missing biomarker data.—One family opted out of biomarker collection, and salivary measures were excluded for one child due to a diagnosis of streptococcal pharyngitis within 2 days of the research visit. Saliva quantity was not sufficient for analysis for one child on all salivary biomarkers and one child on CRP only, resulting in sample sizes of $N=51$ for cytokines and $N=50$ for CRP. Forty-one hair samples were included in analyses; 4 were excluded due to reported corticosteroid use, one family refused biomarker collection, and 8 were not obtained due to short hair length.

Group comparisons.: Children with unfilled caries had significantly higher IL-6 levels ($t=2.34$, $p=.02$) than children without caries; thus this was included as a covariate for all regression analyses including IL-6. There were no significant differences in salivary biomarker levels for children with missing teeth ($n=13$), loose teeth ($n=18$), unfilled caries ($n=6$), recent dental work ($n=5$) or other mouth issues ($n=6$). Hair cortisol levels differed by hair shape ($F=9.49$, $p=.001$) and frequency of hair washing ($F=4.15$, $p=.008$), but not by hair color, product use, or styling habits.

There were no significant differences in child indicators of toxic stress by gender. Very few measures were significantly different by child age or race/ethnicity, and of these, none were included in correlations that met criteria for conducting regression analyses (*p-value* less than .1). For this reason and the small study sample size, we did not adjust for these characteristics in the regression models.

Associations between Maternal Caregiving and Child Indicators of Toxic Stress

We present a correlation matrix in Table 5 and regression models in Table 6. Results are discussed with respect to correlation analyses unless the regression models contribute useful information; for example, reporting odds ratios for associations with dichotomous outcome variables (health/school history).

Parenting behaviors.—Hostile/coercive parenting behaviors were associated with significantly higher total behavior problems ($r=.29$, $p=.04$) and log-transformed externalizing behavior problems ($r=.43$, $p=.001$) (Table 5) in children. Contrary to expectations, hostile/coercive parenting behaviors were also associated with lower log-transformed IL-6 levels ($r=.31$, $p=.03$) and lower TNF levels ($r=-.27$, $p=.053$) in children, though these relationships were not significant in the regression models (Table 6). Supportive/engaged parenting was associated significantly with lower odds of reporting a child receiving special education services (OR=0.77, 95% CI=0.62, 0.96). Supportive/engaged parenting was also correlated with reporting a history of ED visits and child accidents, but these relationships were not significant in the regression models (Table 6).

Parental reflective functioning.—More appropriate certainty about mental states was associated with significantly fewer ED visits for children ($\rho =-.43$, $p=.009$). Small effect sizes were also detected between more appropriate certainty about mental states and lower log-transformed child IL-6 levels ($\rho =-.27$, $p=.053$), as well as between interest/curiosity in mental states and elevated child CRP levels ($\rho =.26$, $p=.07$), though these relationships were not significant in the regression models (Table 6). Prementalizing modes, a measure of impaired PRF, was significantly associated with higher total behavior problems ($\rho =.52$, $p<.0001$), internalizing behavior problems ($\rho =.42$, $p=.002$), and log-transformed externalizing behavior problems ($\rho =.49$, $p=.0002$) in children, as well as increased odds of child hospitalization (OR=1.17, 95% CI=1.01, 1.37), surgery (OR=1.16, 95% CI=1.01, 1.35), and history of learning problems (OR=1.20, 95% CI=1.02, 1.41).

Discussion

The findings of this study suggest that previously unexamined protective components of caregiving, such as parental reflective functioning, may help to buffer a toxic stress response among children living in socioeconomically disadvantaged environments. Though the effect sizes detected were generally small, this was expected due to the complexity of factors that influence developing physiology (Lupien, McEwen, Gunnar, & Heim, 2009). However, that small to medium effects were detected at all in this small sample suggests that parental reflective functioning and parenting behaviors are likely to be important avenues for future research on toxic stress prevention. These results also suggest that a comprehensive profile

including biomarkers, health, and behavioral measures may be a useful strategy for understanding toxic stress in children, but further investigation is needed to understand the best measures for use in pediatric research studies (Author blinded, 2018x).

Maternal Caregiving and Toxic Stress in Children

Parenting behavior.—In examining associations with child indicators of toxic stress, the parenting behaviors yielded some unexpected results. While hostile/coercive parenting behaviors were associated with significantly higher behavior problems in children as expected, hostile/coercive behaviors were also associated with lower levels of two inflammatory markers, salivary IL-6 and TNF, suggesting a possible protective effect. Upon closer examination of the PBI hostile/coercive scale, we found the most frequently reported items were those that might be described in terms of authoritarian parenting styles, such as “I demand that my child does something (or stops doing something) right away” or “when my child misbehaves, I let him/her know what will happen if s/he doesn’t behave.” In comparison, items related to corporal punishment, such as “I spank or use physical punishment with my child,” were reported at very low frequencies. While this requires further investigation, these results suggest that for some families living in highly stressful or unsafe environments, some aspects of traditionally viewed negative parenting behaviors, like hostile or authoritarian parenting, may also be protective because they are necessary for child survival. Additionally, though the PBI has been used in diverse samples, it is possible that this instrument was not sensitive to cultural nuances or norms that influence parenting in the study sample (Dallaire et al., 2006; Lovejoy et al., 1999). The unexpected findings related to supportive/engaged parenting and child accidents and ED visits also points to the need for additional research on parenting behaviors among diverse populations. Culturally specific parenting behaviors and attitudes should be considered in future research studies in order to accurately examine protective caregiving patterns in families at risk for toxic stress.

Parental reflective functioning.—The results of this study indicate that parental reflective functioning may be an important protective factor for toxic stress in children. The results related to prementalizing modes are particularly compelling, as this measure of impaired PRF was associated with significantly higher learning problems, accidents, surgeries, and total, internalizing, and externalizing behavior problems in children. It is unsurprising that prementalizing modes were associated with maternally-reported child behavior problems, as a mother who is unable to enter her child’s subjective world may indeed interpret her child’s behavior as problematic, and thus the relationship may be at least partially due to bias in maternal reporting. However, children’s behavioral problems may also stem from a lack of reflectiveness from their mother, as impaired PRF is known to be associated with insecure attachment relationships and underdeveloped self and affect regulation (Slade, 2005). The detected associations with accidents and surgeries are also of interest, as these histories were reported at fairly low frequencies but significant relationships were nonetheless detected. If mothers with impaired PRF have difficulty anticipating their child’s behavior, they may fail to set appropriate boundaries or intervene when necessary to promote safety. As many of the reported surgeries were related to dental caries, this finding also may reflect larger health issues in the home environment. Future

research in this area could provide important insight into the role of PRF in promoting health and safety among vulnerable families.

The findings related to measures of high PRF, appropriate certainty about mental states and interest and curiosity in mental states, are also of interest. Appropriate certainty about mental states reflects recognition of the opacity of children's mental states; in other words, that we can never fully know what another is thinking and feeling, and this was associated with lower salivary IL-6 and significantly fewer ED visits among children in the study (Luyten et al., 2017; Slade, 2005). As mothers reported that over 70% of ED visits were for acute illnesses, the relationship with child ED visits suggests that reflective mothers may be better able to detect subtle symptomatic changes in their children and intervene earlier and more appropriately, preventing the need for an ED visit. The association between appropriate certainty about mental states and lower child IL-6 levels further suggests a protective role of PRF. IL-6 is involved in inflammatory, metabolic, and infection response processes, and elevated IL-6 levels have been associated with child psychosocial risk factors including environmental adversity, maltreatment history, and sleep disturbances (Author blinded, 2018x; Scheller, Chalaris, Schmidt-Arras, & Rose-John, 2011). Thus, our findings suggest that in addition to influencing children's self-regulatory capacities, PRF may also be related to regulation of the physiologic stress response. Future research with other measures of physiologic stress, such as diurnal cortisol rhythms or laboratory stress-response tasks, are necessary to better understand this link.

Contrary to expectations, interest and curiosity in children's mental states was associated with elevated CRP among children in the sample. CRP is a nonspecific marker of inflammation, and though measurement of CRP as an indicator of chronic stress has been limited in children, elevated CRP levels have been associated with neighborhood risk and cumulative adversity in other pediatric research studies (Broyles et al., 2012; Slopen et al., 2013). It is difficult to know whether this unexpected relationship was a consequence of the multiple comparisons explored or can be explained by other factors not measured in this study. Additionally, the results related to certainty about mental states and interest and curiosity in mental states should both be interpreted with caution, as internal reliability of these subscales was low to moderate. Additional research using other measures of PRF, such as the Parent Development Interview, is necessary to better understand the relationship between PRF and toxic stress among socioeconomically disadvantaged children (Slade, Aber, Bresgi, Berger, & Kaplan, 2004; Sleed, Slade, & Fonagy, in press).

Strengths and Limitations

As there are currently no standardized pediatric reference ranges for the hair and salivary biomarkers explored in this study, the results of this study make a valuable contribution to biomarker science, especially regarding levels in ethnic minority children as biomarker research has been very limited with this population (Gray et al., 2018; Riis, Granger, DiPietro, Bandeen-Roche, & Johnson, 2015). Further investigation of potential confounders, such as the presence of oral inflammation, with larger sample sizes and among different populations is necessary to improve future pediatric research studies in which hair and salivary biomarkers are collected (Riis et al., 2015).

Although this study is innovative in its use of biological, health, and behavioral measures to evaluate toxic stress, it is limited by the use of self-report measures to evaluate caregiving and child health and behavior. Though the instruments selected have been validated in similar samples, internal consistency was low for the PRFQ-CM and variance was very limited on the PBI supportive/engaged scale. This, paired with the small sample size, may have prevented detection of meaningful relationships in the study. Additionally, a single investigator collected all biomarkers and anthropometric measures; though this approach may increase measurement consistency across participants, it may also create a risk for measurement bias. Future research would be strengthened by the inclusion of additional objective measures to evaluate caregiving and child outcomes, as well as biomarker collection by multiple investigators and strategies to enhance inter-rater reliability. As noted previously, more complex physiological indicators of stress, such as measuring heart rate variability to evaluate cardiovascular risk or salivary cortisol diurnal curves to evaluate neuroendocrine functioning, would also strengthen future research in this area.

Although the goal of this study was to evaluate protective components of caregiving, it is notable that the most robust results were related to negative caregiving, such as hostile/coercive parenting behaviors and prementalizing modes. While our findings indicated that supportive/engaged parenting and parental reflective functioning may be important protective factors, additional research is necessary to better understand the underlying mechanisms that are most protective against toxic stress in vulnerable families. Future research is also needed to better understand how these protective characteristics interact with negative caregiving, the presence of stressors, and parental characteristics such as poor mental health or a history of adverse childhood experiences (Author blinded, 2018). While many self-report measures are available to evaluate negative or risky caregiving characteristics, these findings also highlight the need to develop reliable and culturally sensitive self-report measures of positive parenting and protective characteristics. Greater availability of these research measures will improve our understanding of protective factors for toxic stress by allowing for valid and feasible research with large, diverse samples.

Clinical Implications

The results of this study suggest that assessment of parenting and family risk factors is a critical component of pediatric care. The National Association of Pediatric Nurse Practitioners (NAPNAP) advocates for this approach, stating in a recent position statement on child maltreatment, “pediatric-focused advanced practice registered nurses (APRNs) are in a strategic position to assess for the presence of risk and protective factors and provide primary prevention interventions” (NAPNAP, 2016, p.26A). The American Academy of Pediatrics suggests a number of screening instruments that can be used by clinicians to evaluate caregiver and child risk factors, including the Parental Screening Questionnaire and the Bright Futures Pediatric Intake Form (American Academy of Pediatrics, 2018; Dubowitz et al., 2007; Kemper & Kelleher, 1996). Early screening and intervention not only has the potential to support healthy parent-child relationships, but also prevent the short and long-term health and behavioral problems related to among children who experience chronic physiological stress in childhood.

The results of this study also provide evidence to support encouragement of nurturing, responsive caregiving as a routine part of clinical practice for pediatric healthcare providers. Positive parenting behaviors can be encouraged during pediatric office visits by actively recognizing supportive and engaged interactions (e.g. “I love the way you’re looking and smiling at her right now”). Clinicians can also strive to enhance caregiver-child relationships by modeling a reflective stance during primary care visits. Developmental assessments, in particular, offer an opportune moment to encourage reflection on the child’s behavior. By wondering aloud what the child might be thinking (e.g. “I wonder why he is wiggling so much”), or ‘speaking for the baby’ by providing a verbal description of what the child’s physical or emotional cues might mean (e.g. “it must be frustrating for her when she can’t keep up with her big sister!”), the clinician can encourage a better understanding or new perspectives regarding the child’s behavior. For specific strategies, we refer the reader to a paper by Ordway and colleagues (2015) regarding modeling PRF in primary care practice.

Conclusion

The results of this study provide an important foundation for future research studies aiming to understand the complex mechanisms that may mitigate the effects of toxic stress in vulnerable families. Future research examining the causal relationships among these phenomena with large, diverse samples of caregivers and children will provide greater insight into the mechanisms that may prevent toxic stress in families at risk. Incorporating a genomic approach, including exploration of the epigenetic transmission of protective caregiving and the role of genes in physiologic responses to chronic stress, is also essential for a robust understanding of these complex relationships. These empirical investigations are necessary to ultimately inform the development of tailored interventions and policies aiming to reduce health disparities and promote lifelong health for children living in vulnerable families.

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Figure 1:
 Conceptual framework of the study. Solid boxes indicate variables examined in this report.
 CRP, C-reactive protein; PTSD, posttraumatic stress disorder. Reprinted with permission
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Hostile/Coercive Parenting	• Lower inflammatory cytokines levels (IL-6, TNF) • Higher total and externalizing behavior problems
Supportive/Engaged Parenting	• Higher odds of ever visiting the emergency department or experiencing an accident • Lower odds of using special education services
High Parental Reflective Functioning	• Lower inflammatory markers (IL-6, CRP) • Fewer emergency department visits
Impaired Parental Reflective Functioning	• Higher total, internalizing and externalizing behavior problems • Higher odds of hospitalization and surgeries • Higher odds of learning problems

Figure 2.

Summary of detected relationships between maternal caregiving and child indicators of toxic stress. Bold font indicates relationship was statistically significant after regression analysis.

Table 1

Characteristics of Mothers and Children in the Study Sample

Characteristic	Mothers (n=54)	Children (n=54)
Age in years, <i>M (SD)</i>	26.79 (3.32)	6.68 (2.08)
Years education <i>M (SD)</i>	12.98 (1.56)	3.23 (1.97)
Grade level, <i>n (%)</i>		
Not enrolled/Other		6 (11.1)
Pre-K to First grade		27 (50.0)
Second to Fourth Grade		21 (38.9)
Race, <i>n (%)</i>		
White	14 (25.9)	9 (16.7)
Black	26 (48.1)	27 (50.0)
Other	14 (25.9)	18 (33.3)
Hispanic Ethnicity, <i>n (%)</i>	27 (50)	28 (51.9)
Hispanic Cultural Group, <i>n (%)</i>		
Puerto Rican	21 (77.8)	20 (71.4)
Mexican	2 (7.4)	2 (7.1)
Other/Multiple Groups	4 (14.8)	6 (21.4)
Marital Status, <i>n (%)</i>		
Single	37 (68.5)	
Married	12 (22.2)	
Living Together	5 (9.3)	

Note: *M*, mean; *SD*, standard deviation. Participant characteristics originally reported in (authors blinded, under review).

Table 2

Descriptive Statistics for Maternal Caregiving Self-Report Measures

Variables	N	Mean	SD	Scale Range
Parent Behavior Inventory				
Hostile/Coercive Scale	54	14.7	6.2	0 - 50
Supportive/Engaged Scale	54	47.0	3.4	0 - 50
Parental Reflective Functioning Questionnaire				
Certainty About Mental States	54	32.6	2.5	6 – 42
Interest/Curiosity in Mental States	54	34.1	5.7	6 – 42
Prementalizing Modes	54	10.3	4.8	6 – 42

Note: *SD*, standard deviation.

Table 3

Descriptive Statistics for Continuous Child Indicators of Toxic Stress

Variables	N	Mean	SD
Salivary IL-1B	51	79.24	108.27
Salivary IL-6	51	9.13	11.74
Salivary IL-8	51	903.03	978.42
Salivary TNF	51	5.37	5.71
Salivary CRP	50	14413	24195
Hair cortisol	41	57.25	112.67
Child Behavior Checklist (t-scores)			
Total Score	54	52.46	11.06
Internalizing Behaviors	54	51.64	9.87
Externalizing Behaviors	54	51.09	10.94
BMI z-score	54	0.75	1.13
SBP Percentile	53	63.73	22.16
DBP Percentile	53	71.24	15.71
Number of ED visits	54	3.03	2.84

Note: SD, standard deviation; IL, interleukin; TNF, tumor necrosis factor-alpha; CRP, c-reactive protein; ED, emergency department; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure. BMI calculated according to CDC Guidelines for age and gender (Kuczmarski, et al., 2002). To be consistent with previously published data from this study, blood pressure percentiles were calculated according to the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (Falkner et al., 2004). Data originally reported in (authors blinded, under review).

Table 4

Descriptive Statistics for Categorical Child Indicators of Toxic Stress

Variables	N	%
BMI Category		
Underweight (<5%)	2	3.7
Normal weight	28	51.8
Overweight (85-94%)	11	20.3
Obese (>=95%)	13	24.1
Blood Pressure Category	3	
Prehypertension	5	5.56
Hypertension		9.36
Health History		
Asthma	15	27.8
Food Allergies	11	20.4
Seasonal Allergies	14	25.9
Eczema	19	35.2
Healthcare Utilization		
Ever Visited ED	35	64.8
Ever Hospitalized	6	11.1
Ever Had Accident	9	16.7
Ever Had Surgery	9	16.7
Academic History		
Learning Problems	10	18.5
Repeated Grade	6	11.1
Special Education Services	8	14.8

Note: BMI, body mass index. BMI calculated according to CDC Guidelines for age and gender (Kuczmarski, et al., 2002). To be consistent with previously published data from this study, blood pressure categories are reported according to the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (Falkner et al., 2004). Data originally reported in (authors blinded, under review).

Table 5

Correlations between Maternal Caregiving and Child Indicators of Toxic Stress

Measure	PBI Hostile	PBI Supportive	PRFQ CM	PRFQ IC ^b	PRFQ PM
IL-1B ^a	-.13 ^c	.12	-.13	-.13 ^c	-.21
IL-6 ^a	-.31 ^{*c}	.05	-.27 ^{**}	-.11 ^c	-.04
IL-8 ^a	-.07 ^c	-.04	-.16	-.11 ^c	-.05
TNF ^a	-.27 ^{**c}	-.02	-.17	-.13 ^c	-.11
CRP	-.08	-.17	.03	.26 ^{**}	.14
Hair cortisol ^a	-.09 ^c	-.02	-.07	.10 ^c	-.25
CBCL Total	.29 ^{*c}	-.09	.001	.15 ^c	.52 [*]
CBCL Internalizing	.12 ^c	-.06	-.09	.19 ^c	.42 [*]
CBCL Externalizing ^a	.43 ^{*c}	-.09	.07	.12 ^c	.49 [*]
BMI	-.12 ^c	.08	.13	.06 ^c	.06
SBP %	.03	-.12	-.06	-.05	.21
DBP %	.10 [†]	.19	-.06	.05 ^c	.01
Asthma	.08	-.11	-.05	.12	.11
Seasonal Allergies	-.12	-.01	-.15	-.15	.11
Eczema	.01	.21	-.09	-.07	.18
Ever Visited ED	.06	.25 ^{**}	-.23 ^{**}	.01	-.12
No. of ED Visits	-.21	.08	-.43 [*]	.14	-.19
Ever Hospitalized	-.06	.01	-.06	.04	.31 [*]
Ever Had Accident	-.06	.26 ^{**}	-.14	-.11	-.01
Ever Had Surgery	.17	.04	-.19	-.11	.24 [*]
Learning Problems	.08	.05	-.19	.01	.27 [*]
Repeated Grade	.10	.06	-.19	-.11	.02
Special Education Services	.19	-.32 [*]	.05	-.02	.19

Note:

*
 $p < .05$;**
 $p < 0.1$;^a = variable was log transformed;^b = variable was cube transformed;

^c = Pearson correlation conducted, all other correlations conducted using Spearman's rho; BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; IL = Interleukin; TNF = Tumor Necrosis Factor-alpha; CRP = C-reactive Protein; ED = Emergency Department; CBCL = Child Behavior Checklist; PBI=Parent Behavior Inventory; PRFQ=Parental Reflective Functioning Questionnaire; CM=Certainty about Mental States; IC= Interest/Curiosity in Mental States; PM=Prementalizing Modes.

Table 6

Regression Analyses between Maternal Caregiving and Child Indicators of Toxic Stress

Independent Variable	Dependent Variable	N	B	p	Regression model	Odds Ratio (95% Confidence Interval)
PBI Hostile	IL-6 ^a	51	-0.35	.08	Linear ^c	
	TNF	51	-0.04	.053	Linear	
	CBCL Total	54	0.51	.03	Linear	
	CBCL Externalizing	54	0.02	.001	Linear	
PBI Support	Ever visited ED	54	0.16	.07	Logistic	1.17 (0.98, 1.38)
	Ever had accident	54	0.34	.09	Logistic	1.40 (0.94, 2.08)
	Special Education	54	-0.26	.02	Logistic	0.77 (0.62, 0.96)
PRFQ-CM	IL-6 ^a	51	-0.07	.13	Linear ^c	
	Ever visited ED	54	-0.18	.13	Logistic	0.83 (0.66, 1.05)
	ER visit frequency	54	-0.2	.006	Negative Binomial	
PRFQ-IC ^b	CRP	50	-8.14	.06	Linear	
PRFQ-PM	CBCL Total	54	6.83	<.001	Linear	
	CBCL Internalizing	54	5.1	.02	Linear	
	CBCL Externalizing	54	0.12	<.001	Linear	
	Ever Hospitalized	54	0.16	.049	Logistic	1.17 (1.01, 1.37)
	Ever Had Surgery	54	0.15	.04	Logistic	1.16 (1.01, 1.35)
	Learning Problems	54	0.18	.02	Logistic	1.20 (1.02, 1.41)

Note:

^a = variable was log transformed;^b = variable was cube-transformed;

^c =controlled for unfilled caries; SBP=systolic blood pressure; IL = Interleukin; TNF = Tumor Necrosis Factor-alpha; CRP = C-reactive Protein; ED = Emergency Department; CBCL = Child Behavior Checklist; PBI=Parent Behavior Inventory; PRFQ=Parental Reflective Functioning Questionnaire. Regression analyses only conducted for correlations with significant (<.05) or near significant (<.1) p-values. PBI-Support scale dichotomized at the mean due to lack of variance and non-normal distribution.