HHS Public Access

Author manuscript

Brain Behav Immun. Author manuscript; available in PMC 2021 May 01.

Published in final edited form as:

Brain Behav Immun. 2020 May ; 86: 22–29. doi:10.1016/j.bbi.2019.05.001.

Early Childhood Risk Exposures and Inflammation in Early Adolescence

Thomas G O'Connor[1], **Michael T Willoughby**[2], **Jan A Moynihan**[1], **Susan Messing**[3], **Ana Vallejo Sefair**[4], **Jennifer Carnahan**[5], **Xiajuan Yin**[6], **Mary T Caserta**[5]

[1]Department of Psychiatry, University of Rochester Medical Center

[2]RTI International

[3]Department of Statistics and Bioinformatics, University of Rochester Medical Center

[4]Department of Psychology, University of Rochester

[5]Department of Pediatrics, University of Rochester Medical Center

[6]Frank Porter Graham Child Development Institute, University of North Carolina at Chapel Hill

Abstract

There is now reliable evidence that early psychosocial stress exposures are associated with behavioral health in children; the degree to which these same kinds of stress exposures predict physical health outcomes is not yet clear. We investigated the links between economic adversity, family and caregiving stress in early childhood and several markers of immune function in early adolescence. The sample is derived from the Family Life Project, a prospective longitudinal study of at-risk families. Socio-demographic and psychosocial risks have been assessed at regular intervals since the children were first assessed at 2 months of age. When the children were early adolescents, we conducted an in-depth health assessment of a subsample of families; blood samples were collected from venipuncture for interleukin(IL)-6, Tumor Necrosis Factor (TNF)-alpha, and C-reactive protein (CRP), as well as glucocorticoid resistance. Results indicated limited but reliable evidence of an association between early risk exposure and inflammation in adolescence. Specifically, caregiver depressive symptoms in early childhood predicted elevated CRP almost a decade later, and the prediction was significant after accounting for multiple covariates such as socio-economic adversity, health behaviors and body mass index. Our findings provide strong but limited evidence that early stress exposures may be associated with inflammation, suggesting one mechanism linking early stress exposure to compromised behavioral and somatic health.

Correspondence to: Thomas G. O'Connor, Wynne Center for Family Research, Department of Psychiatry, University of Rochester Medical Center, 300 Crittenden Blvd, Rochester, NY 14642; Tom_OConnor@URMC.Rochester.edu; ph: +1 585-273-1221.

1. Introduction

A large and rapidly growing research base links early psychosocial stress exposure or adverse childhood experiences to health outcomes in adulthood (Brown et al., 2009; Felitti et al., 1998a; Slopen, McLaughlin, Dunn, & Koenen, 2013; Taylor, Way, & Seeman, 2011). An important and more recent extension of this literature is the replicated finding that the putative effects of early stress exposure on health outcomes are observable in childhood (Caserta et al., 2008; Dube et al., 2006; Flaherty et al., 2006). This latter finding is notable because it implies that there may be a particular influence of early stress exposures on health outcomes, and that mechanisms of health and disease are stress-responsive in children. Not yet resolved in the pediatric literature is the identification of mechanisms which may explain how early stress may have adverse health effects. The current study examines the association between early stress exposures and immune function outcomes in early adolescence. The data are based on a prospective longitudinal study that has followed a large, diverse and low-income sample from early infancy; markers of immune function were collected when the children were early adolescents.

Many studies of adults support the hypothesis that inflammation is one mechanism by which early stress exposure may predict subsequent adverse health outcomes (Fagundes, Glaser, & Kiecolt-Glaser, 2013; Felitti et al., 1998b; Taylor, Lehman, Kiefe, & Seeman, 2006; Wegman & Stetler, 2009), with the strongest evidence deriving from prospective studies linking childhood stress with specific immune markers later in development (Caspi, Harrington, Moffitt, Milne, & Poulton, 2006; Danese et al., 2009; Miller & Chen, 2010; Pedersen et al., 2018; Slopen, Kubzansky, McLaughlin, & Koenen, 2013). The majority of studies in this area assessed inflammatory markers in adulthood; very few studies have assessed inflammatory markers in children, and limited data are available on inflammatory markers in adolescence (Broyles et al., 2012; Caserta, Wyman, Wang, Moynihan, & O'Connor, 2011; Miller & Chen, 2010; Slopen, Kubzansky, et al., 2013). As a result, the degree to which early stress exposure has childhood-onset effects on the immune system remains a key developmental question, with sizable clinical application. Opposing expectations might be proposed. On one hand, it might be that effects of stress exposure on the child's immune system are not evident because there has not yet been sufficiently prolonged stress exposure, which is suggested by, for example, an allostatic load model (Korte, Koolhaas, Wingfield, & McEwen, 2005). Alternatively, there may be a lack of association because younger individuals have more cellular immunological reserves (e.g., less immunosenescence) and therefore greater capacity to adapt to early stress. A further possibility is that the young immune system may be comparatively more vulnerable to early stress, and so the effects may be exaggerated relative to findings reported in adults.

Research findings do suggest that the child's immune system may be at least somewhat responsive to (prior) stress exposures. However, as recent empirical and conceptual reviews note (Kuhlman, Chiang, Horn, & Bower, 2017; O'Connor, Moynihan, & Caserta, 2014), the limited – and diverse – literature leaves open core questions about the types of early stress exposure that may have long-term effects, which types of immune function may be altered, and the mechanisms involved. The current study sought to contribute to each of these areas by reporting novel data from a study with several methodologically advantageous features.

Specifically, in response to a recent report documenting a lack of high-quality longitudinal studies (Elwenspoek, Kuehn, Muller, & Turner, 2017), we report data from a prospective study that collected detailed stress exposure data since early infancy on repeated occasions; our assessment investigates immune outcomes in early adolescence. Second, existing reviews also make clear that different kinds of immune outcomes are plausible targets for studies on the effects of early stress exposure (Elwenspoek et al., 2017; O'Connor et al., 2014). We focus on inflammation by measuring circulating cytokines associated with innate immune function, IL-6 and TNF-alpha, and the acute phase reactant C-reactive protein, a non-specific marker of inflammation. We focus on these markers because they have attracted considerable attention in prior research and because they have known associations with multiple health outcomes in pediatric and adult samples.

Other factors also require additional explication. One is the nature of the stress exposure. Many different kinds of early psychosocial stress may instigate biological changes leading to alterations in the immune system. To date, socio-economic status is among the most common targets (Chiang et al., 2015; Pietras & Goodman, 2013); however, it has important limits for understanding mechanisms and identifying plausible intervention targets because it is a broad index that signals exposure to a wide range of confounded risks. Economic deprivation is, nonetheless, a leading candidate marker, and so in the current analyses we include poverty based on the income to needs ratio, a specific measure of low economic and social resources in the family. A second measure of early risk commonly included in studies of child health is family violence. Family violence, often assessed in terms of inter-parental conflict or aggression, is associated with a wide range of poor behavioral and physical health outcomes and select biomarkers such as cortisol in children and adolescents (Holt, Buckley, & Whelan, 2008; Hughes et al., 2017; Suglia, Enlow, Kullowatz, & Wright, 2009; Towe-Goodman, Stifter, Mills-Koonce, & Granger, 2012); its association with child inflammation is not yet clear but the prior research on other health outcomes warrants its inclusion in this study.

We also examine caregiver depression, one of the most well-documented risks for poor child behavioral and health outcomes (Goodman & Gotlib, 1999; E. Raposa, Hammen, Brennan, & Najman, 2014), as a predictor of inflammation in early adolescence. We target caregiver depressive symptoms because of the sizable literature linking it with biomarkers in the child or adolescent that may relate to inflammation, such as stress physiology indexed by salivary cortisol (Essex, Klein, Cho, & Kalin, 2002; Halligan, Herbert, Goodyer, & Murray, 2004). There is, in addition, a small but growing research base providing more direct evidence that maternal depression may be associated with child immune health; studies of childhood asthma provide one example (Wood et al., 2018). Furthermore, a somewhat related literature indicates that caregiving quality, which is impaired by depression, is associated with inflammatory markers (Fuligni et al., 2009), stimulated cytokine production (E. Chen, Miller, Kobor, & Cole, 2010), and antibody response to vaccine (O'Connor et al., 2015). That is, multiple lines of evidence provide at least indirect evidence that caregiver depressive symptoms may be associated with inflammation in childhood and early adolescence; we test this hypothesis directly. In summary, we target several *a priori* stress exposures in infancy and early childhood (under 2 years of age) that are prominent in developmental and health

studies; we also consider if the prediction of inflammation from psychological stress exposures can be differentiated from broader indicators of early economic disadvantage.

We also examined possible mechanisms of influence. One notable mechanism linking early stress exposure and later inflammation is health behavior. Adult studies suggest that a sizable portion of the effect of early life stress on later inflammation can be explained by – or at least not de-confounded from – health risk behaviors, including poor diet, obesity, and lack of exercise (M. Chen & Lacey, 2018; Pedersen et al., 2018). That may also be so in pediatric studies. One study of adolescents found that obesity partly explained the association between socio-economic status and IL-6 (Pietras & Goodman, 2013); additionally, adiposity and health behaviors largely accounted for an association between lower family income and CRP in the NHANES study (Dowd, Zajacova, & Aiello, 2010; Schmeer & Yoon, 2016) and between life stress and CRP in late adolescence in the TRAILS study (Jonker, Rosmalen, & Schoevers, 2017). Analyses of the MUSP study (E. B. Raposa, Bower, Hammen, Najman, & Brennan, 2014) indicated that early life stress, which included maternal depression, low income and parental discord, was associated with BMI in early adulthood, which was associated with CRP. Accordingly, in the current study we include multiple measures of health behaviors concurrent with immune markers, including sleep, obesity, and exercise, to examine if the effects of early life stress on later immune functioning is secondary to these health behaviors.

Alongside health behaviors, we examine glucocorticoid resistance as a possible mechanism linking stress exposure and inflammation. As suggested by studies of animals and humans (Avitsur, Stark, & Sheridan, 2001; Miller & Chen, 2010), early stress exposure may be associated with persisting elevated inflammation because of a diminished glucocorticoid receptor sensitivity, which would otherwise downregulate the immune response. We test that hypothesis in the current study.

2. Methods

2.1 Participants

The Family Life Project (FLP) is an ongoing longitudinal study of rural poverty that involves families who had a child born between September 2003-August 2004 in one of six counties in Eastern North Carolina (NC) and Central Pennsylvania (PA). Sampling procedures were employed to recruit a representative sample of 1,292 children from rural counties, with over-sampling of low-income families in both states and of African American families in NC (Vernon-Feagans, Cox, & Investigators, 2013). Following hospital screening, participants who were selected and agreed to participate were formally enrolled into the study by completing a home visit when the target child was approximately 2 months old. Participating families completed additional home visits conducted when the child was 6, 15, and 24 months. Data for the current study of child immune system function are based on a subset of FLP families who were seen when the children were approximately 11 years old. That is, we did not intend to include all FLP families in this assessment. Of the 1,292 families in the study, a phone screen was administered to determine the child's eligibility based on the absence of a) chronic illness b) immune disorders and c) known contraindications for blood sampling because of a medical or blood disorder; this screening

identified 939 eligible children, of whom 814 agreed to be considered for the immune study. These eligible and interested families were stratified by poverty (using income to needs ratio of 1.8, the threshold for Head Start) and race (African-American/Caucasian) to create distinct groups of poor and non-poor African-American and Caucasian families in the NC sample; because of the absence of African-American families in the rural PA sample, only poor and non-poor Caucasian families were available from PA. The final sample 470 families (226 from NC, 244 from PA) represents 30–50% of children/families who were eligible and agreed to be considered for the immune substudy. However, of these n = 470 families, a blood draw was not attempted if the child had a previously non-disclosed medical complication, if there was a contraindication identified at the visit (e.g., high blood pressure, acute illness), or if the subject refused; a blood sample was obtained on n=337. Visits were re-scheduled if the child was acutely ill. Information on quality assurance and quality control are described in the measures section. The study was approved by the IRB of UNC Chapel Hill; parents provided informed written consent; adolescents provided assent. Families were compensated for participation.

2.2 Procedures

The primary caregiver completed measures of early stress exposures and socio-demographic information from home visits conducted up to and including the 24-month visit (see 2.3.1). Data at the early adolescent assessment was composed of health behavior and biological sample collection and a psychosocial assessment conducted in the home; in some cases the psychosocial and health (including blood sample) data were conducted on separate, closely-spaced visit. Ten ml of whole blood was collected in SST vacutainer tubes (Becton Dickinson, cat# 367985) and the serum was separated on site using a portable centrifuge following a 30-minute clotting period within 1 hour of collection. Serum was transferred to pre-labeled cryovials. In additional sample of 10–20 ml of whole blood was collected in heparinized vacutainer tubes. The serum cryovials and whole blood samples were packaged on site into absorbent sleeves in biohazard specimen bags cushioned with gel packs that were reconstituted on site with tap water (cool to tepid in summer and warm in winter). A LogTag TRIX-8 Temperature Data Recorder inside a LogTag LTI-CASE Protective Case was activated and inserted into the outer sleeve of the specimen bag. The temperature recorder read temperatures at 5-minute intervals following activation with alerts for a lower limit of 50°F (10°C) and an upper limit of 85°F (29.4°C). Using the LogTag USB Docking Station, data were downloaded from each recorder. The recorders were then checked, re-set, and returned to the field for reuse. Samples were shipped overnight from the family home to the research lab in non-insulated smaller shipping boxes when outdoor temperatures were above 55°F; lower temperatures required the use of an insulated box. These samples were received by the lab and processed within 24 hours. Serum samples were frozen at −80°C until assayed. Visits were scheduled at a time that was convenient for the families and were typically conducted within two weeks of each other. (See below for details on blood processing and quality control.)

2.3 Measures

2.3.1 Early stress exposures

Socio-economic and demographic risk.: Household poverty was defined by summing the income of anyone who resided in the household and dividing it by the federal poverty threshold for a given family size to create the income/needs ratio (INR). Household income information was collected at the 6, 15, and 24-month home visits. The correlations between the measurements were > .80; accordingly, the mean INR value across these time points was used to index household poverty. Single-parent status was included as a dummy code to index socio-demographic risk.

Family violence.: Primary caregivers completed the short form of the Conflict Tactics Scale (Straus & Douglas, 2004; Strauss & Gelles, 1990), a widely-used and validated measure of interparental violence with considerable links to child behavioral and psychological development (Gustafsson, Cox, & the Family Life Project Key, 2012; Hibel, Granger, Blair, & Cox, 2009). This is a 19-item self-report instrument to assess receipt and perpetration of physical (e.g., "My partner pushed, shoved or slapped me") and psychological aggression (e.g., "My partner insulted or swore or shouted or yelled at me") between partners; each item was rated on a 7-point Likert scale concerning frequency. Data were composited across primary caregiver reports of received and perpetrated violence from assessments completed at 6, 15 and 24 months of age to derive a total exposure index in early childhood. Cronbach's alphas were >.80 at each assessment.

Caregiver depressive symptoms.: Primary caregivers (principally mothers) completed the 6-item depression subscale of the Brief Symptom Inventory (BSI) (Derogatis, 2000) to assess depressive symptoms. Items on the scale were rated on a 5-point Likert scale; an example item is: "How much were you distressed by feeling hopeless about the future?" Correlations between time points ranged from .39 to .58; we used a mean score from assessments at 6, 15, and 24 months and converted to a T score to index clinical severity. Cronbach's alphas were >.80 at each assessment.

2.3.2 Early adolescence

Inflammatory markers.: Serum was thawed and assayed in duplicate for human IL-6, human TNF-alpha, and c-reactive protein (CRP) using Quantikine ELISA kits (high sensitivity kits were used for IL-6 and TNF-alpha) (R&D Systems, Minneapolis, MN) according to manufacturer's instructions. Absorbance was measured at wave lengths 490nm and 650nm. A four parameter logistic curve of the standard was used to extrapolate the concentrations of the samples using SoftMax Pro v. 6.2 (Molecular Devices, Sunnyvale, CA) software for analysis. Results that were undetectable or that fell below the minimum detectable concentration established for each kit by the manufacturer were assigned a value half of the lowest standard concentration; for IL-6 it was 0.078 pg/ml; for TNF alpha it was 0.25 pg/ml; for CRP it was 0.39 ng/ml. Samples that tested above the standard range were diluted and repeated as were samples with variance coefficients greater than 10%. For intra-assay precision, three samples of known concentration were tested 20 times on 1 plate. Intra-assay values were: IL-6, 6.9–7.8%, TNF-alpha, 3.1–8.7%, CRP, 3.8–8.3%. For inter-assay

precision, three samples of known concentration were tested in 40+ separate assays by at least 3 technicians using 2 different lots of components. Inter-assay values were: IL-6, 6.5–9.6%, TNF alpha, 7.2–10.4%, CRP, 6.0–7.0%. Details on how outliers/extreme scores were managed are provided in the Data Analysis section.

Glucocorticoid receptor insensitivity or glucocorticoid resistance.: Based on a previously published protocol (Miller & Chen, 2010), whole blood from heparinized vacutainer tubes was diluted 1:10 in phosphate buffered saline and cultured with and without the endotoxin lipopolysaccharide (LPS, 50 ng/ml). A range of concentrations of hydrocortisone (0, 2.76×10^{-5} M, 2.76×10^{-6} M, 2.76×10^{-7} M, 2.76×10^{-8} M) was added to additional cultures containing LPS. Supernatants were collected and IL-6 concentration was measured in duplicate using ELISA (Human IL-6 DuoSet, R&D Systems, Minneapolis, MN). A standard range of 9.38 pg/ml to 1200 pg/ml was included on each plate and supernatants from cultures with LPS were diluted 1:10 prior to assaying while those without were assayed neat. Absorbance at wavelengths 450nm and 540 nm were measured (correction wavelength) (Molecular Devices, Sunnyvale, CA). Samples that tested above the standard range were diluted further and repeated as were samples with variance coefficients greater than 10%. Multiple measures of GRA could be constructed from the protocol, e.g., based on area under the curve, slope, inhibitory coefficient, or difference score. Analyses indicated a very high degree of overlap across these alternative measures; the GRA score used in analyses is the difference between the LPS without hydrocortisone and the LPS with the highest hydrocortisone concentration.

Child health behaviors.: Height was assessed using a stadiometer; weight was measured using a standard digital scale. Child body mass index (BMI) was measured using the conventional formula of weight in kilograms divided by the squared height measured in meters; children whose BMI was at or above the 95% for BMI for children of the same age and sex were classified as obese (we include obesity in the analyses below; findings were substantively identical for the continuous BMI measure). Pubertal development (stages 1–5) was measured using Tanner stages based on self-report. Exercise was measured using the School-Based Nutrition Monitoring Questionnaire (Hoelscher, Day, Kelder, & Ward, 2003); we include in these analyses an index of heavy exercise lasting at least 30'. Sleep was measured using the Sleep Habits Survey (Wolfson et al., 2003); we include self-reported sleep quality, number of occasions of wake after sleep onset (WASO), and total sleep hours collected over two routine days/nights.

Socio-economic, demographic and psychosocial risk.: Income from all sources was assessed using a categorical measure with 8 categories. Primary caregivers reported their education level; the highest obtained level of education was classified into one of 3 categories: approximately 10% of the sample did not complete their high school degree, 69% graduated from high school but did not obtain a higher degree, and 21% completed a bachelor's degree or greater. Two dummy codes were created indicating (1) whether or not the caregiver completed high school and (2) whether or not the caregiver completed college. Home ownership was measured as rent/own. The primary caregiver completed the

depression subscale of the BSI, as in early childhood, to assess depressive symptoms; T scores were calculated as at the early childhood assessment.

Additional covariates.: Parents reported on prescribed and over the counter medications for the child, noting the medication name, dose/frequency, and reason for taking the medication. Medications were reviewed for pharmacological action and classified according to drug mechanism. Four classes of medications were excluded on an *a priori* basis because they (or the medical condition for which they were described) had known interference with immune markers or because they demonstrated a marked empirical association with immune markers. The four drug categories were: corticosteroids, leukotriene receptor antagonists, anticonvulsants, antihistamine antagonist. Presence of other medications, dose, and reason for prescription were also assessed and considered as possible covariates. Recent illness in the past two weeks (coded yes/no) was also included as it may be associated with elevated inflammation (Caserta et al., 2011). Family size (the total number of persons residing in the household), as a possible index of illness exposure, was collected from maternal interview. Additional socio-demographic factors considered were child sex, race (the two categories of race were African-American and Caucasian), and location (PA or NC). Time of blood draw was recorded; minimum and maximum temperatures of the package containing the blood throughout the shipping process were also recorded (as described above).

2.4 Analysis strategy

We first present descriptive data on the sample and information from a series of quality control checks on the blood samples. Bivariate associations are then presented between early risk exposure and key adolescent follow-up measures. A series of ordinary least squares regression models were estimated to test the hypothesis that early life stress exposures were reliably related to inflammatory markers in early adolescence. Initially, we considered the focal predictors as main effects. Subsequently, we tested whether any of these effects were moderated by child gender or race. This included the introduction of six two-way interaction terms. Following conventional practice, non-significant interactions were culled and the model was re-estimated. Only covariates that were reliably associated with immune measures were considered in the final regression model, with the exception that we included, on an *a priori* basis, covariates that were central to the sampling design (PA vs NC); part of the quality control or a prior potential confounds (time of blood draw, temperature variation in transit, recent illness, household size); or considered essential or best practice given existing research on inflammatory markers (BMI, exercise, sleep quality). Although TNF-alpha was normally distributed, that was not the case for IL-6 and CRP and GRA, which were ln-transformed. A key consideration was how to define and manage potential outliers for IL-6, TNF-alpha, and CRP. Many approaches have been suggested and there is not yet a clear evidence-based best practice to differentiate a biased/biasing value from a "genuinely" high if extreme value; furthermore, values to define clinical extremes or thresholds for each of these markers have not been robustly established in pediatric samples. Our approach to derive robust estimates in the analyses was based on several non-exclusive procedures: a) we excluded on *a priori* statistical grounds values that were > 4 SDs above the mean; b) based on reports to a detailed medical interview, we excluded children on medications that would bias results (as described above and below); c) we did not conduct a visit if the child was

acutely ill; d) we instituted several quality assurance measures (e.g., samples with extreme or missing temperature data in transit were excluded (see below); e) we included several current covariates, notably BMI, sleep, exercise. For supplementary and sensitivity analyses, multiple imputation was used to address missing data for predictor variables (using 25 iterations); we did not impute missing data on inflammatory markers or GRA.

3. Results

3.1 Preliminary and descriptive results.

Of the 470 children in the immune substudy of the FLP, a blood sample was obtained on 337 (non-successful blood draws primarily attributed to refusal, n=50, or health concern detected at the visit, n=39). Of these 337 samples, we were able to derive reliable cytokine data on 329; however, of these, data from 36 children were excluded because the children were prescribed one of the 4 medications that would interfere with immune analyses, 5 samples were excluded because of extreme low or high temperature reported on the temperature tracking devices, and 6 samples were excluded because of missing temperature tracking data. The sample of families included were not different from those not selected for the immune study on poverty, child sex, caregiver education, marital status, but were less likely to be African-American (33% compared with 48%, $p<.01$). Table 1, which presents descriptive statistics for the sample included in analyses, indicates that the sample was at elevated psychosocial risk according to conventional indicators; approximately 25% of the early adolescents were obese. There are limited means of comparing our inflammatory markers with other samples, but it is notable that our CRP mean of 1.25 mg/L (n=329) is comparable to the mean CRP of 1.22 mg/L reported in the NHANES sample with an average age of approximately 10 years (Dowd et al., 2010); similarly, whereas 10.9% of our sample had a CRP >3 mg/L, the rate in NHANES was 8.5%.

3.2 Bivariate and prediction analyses.

Bivariate associations between early stress exposures and select early adolescent measures indicate modest to moderate overlap between targeted early stress exposure variables, and modest to moderate associations between biological measures in early adolescence; measures of *a priori* interest or those that were reliably associated with early risk are reported in Table 2. A marginal association between early symptoms and CRP was found; IL-6 in early adolescence was inversely associated with income to needs ratio and positively associated with having lived in single-parent household in early childhood. Note that the bivariate associations between early stress exposures and measures of early adolescent inflammation do not adjust for BMI or other confounds.

An OLS regression model was carried out to predict each inflammatory marker in adolescence from early stress exposure, concurrent stress exposure, and health behaviors. Analyses indicated that CRP was reliably associated with early stress exposures. Results from the OLS model for CRP are reported in Table 3. Results indicated that caregiver symptoms in early childhood predicted elevated concentration of CRP in early adolescence; this effect was significant after accounting income to needs ratio, violence exposure, and whether or not the family had ever been headed by a single parent in early childhood;

additionally, the prediction from caregiver symptoms to CRP in early adolescence was significant after also adjusting for concurrently measured psychosocial and socio-economic and demographic stresses, including contemporary caregiver depressive symptoms, as well as multiple health behaviors. Of the health behaviors assessed concurrently with CRP, BMI and recent illness were significantly positively associated, independently of other variables in the model. One artifact result in Table 3 is the negative association between CTS and CRP; given that the bivariate association between CTS and CRP was actually zero (Table 2), the association that emerged in the multivariable model is likely an artifact; this explanation is supported by the results from imputed data (see below) which indicated that the parameter estimate was both non-significant and substantially reduced.

OLS models using the same predictors as in Table 3 indicated that neither IL-6 nor TNF-alpha was significantly predicted from early childhood exposures after adjusting for covariates.

Analyses of possible mechanisms linking early stress exposure with inflammation targeted adolescent health behaviors and glucocorticoid resistance. Table 2 indicates that obesity but not glucocorticoid resistance was significantly associated with concurrently measured CRP. However, neither obesity nor glucocorticoid resistance (or other health behaviors collected in early adolescence) was significantly associated with early exposure to caregiver depressive symptoms, and so are unable to explain the longitudinal association between early caregiver symptoms and early adolescent CRP.

3.3 Supplementary and sensitivity analyses

Several sets of sensitivity and exploratory analyses were conducted. Analyses (not shown) indicated no reliable evidence that the prediction from early stress to CRP or other inflammatory markers or GRA differed significantly by child sex or child race. Analyses were re-analyzed using multiple imputation to address missing data for predictor variables. The parameter estimates for early risk exposure was comparable although mildly reduced for caregiver depressive symptoms (.03 [SE .017]) and substantially reduced for early violence exposure (−.15 [SE .16]); obesity and recent illness remained strongly associated with CRP (1.66 [SE .21]) and .90 [SE .23]), respectively) in the imputed model.

4. Discussion

Analyses of a comparatively large, diverse, at-risk sample that has been followed prospectively for over a decade indicated that caregiver psychological symptoms of depression in the early years (through age 2 years) predicted elevations in the acute phase reactant C-reactive protein, a non-specific marker of inflammation, in early adolescence. The effect size was small but statistically significant despite adjustment for potential confounding factors, including other measures of significant early childhood stress as well as health behaviors and risk exposures collected concurrently with inflammation. A prediction of CRP in early adolescence from early caregiver symptoms was, however, a somewhat isolated effect. We describe below how these findings expand on existing research.

Before interpreting the findings, we first consider the strengths and limitations to the study. Specific limitations include our focus on circulating levels of inflammatory markers; these results may not extend to other markers of immune functioning in the adolescent, e.g., from stimulated cytokines or antigen response to immunization. It is not clear how substantial that limitation (or lack of generalizability) is given that peripheral circulating markers of inflammation, such as the approach used in this study, have been linked to cardiovascular disease and related pathologies such as arterial wall pathology in pediatric and adult populations (Everett et al., 2013; Harrington, 2017). In addition, our assessment of inflammatory markers was limited to CRP, IL-6, and TNF-alpha; there is a tendency for research to report on a limited profile, including single markers in many papers. Further research will need to rely on more extensive analysis of the dynamic interplay of pro- and anti-inflammatory cytokines before clear conclusions can be drawn. A third limitation was the reliance on a single time point of measurement of inflammation. Future work will benefit from repeatedly measuring immune markers and analyzing sources of within-individual change. Lastly, the sample has particular characteristics that make it well-suited to study stress exposure and adverse health outcomes (e.g., high rates of rural poverty, high percentages of African-American families), but the findings may not generalize to economically more privileged or urban samples. These limitations are offset by several strengths of the study, including the long-term prospective design; comparatively large sample of families; high-risk design with detailed measures of risk exposure on multiple occasions; inclusion of multiple inflammatory markers; consideration of medical and health behavior confounds; and a detailed plan for insuring high-quality data from blood samples collected in family homes.

The need for high quality longitudinal studies to examine if, by what mechanisms, and in what contexts early stress exposure may influence immune outcomes in children was recently highlighted (Elwenspoek et al., 2017). Leverage for testing the hypothesis that early life stress predicts subsequent immune function and health derives from several design advantages of the FLP. One of these is the accounting of several major early life stresses widely researched in the adverse childhood experiences literature. One of these, caregiver symptoms of depressive symptoms, emerged as a robust predictor of inflammation measured approximately a decade later. There is a long-standing literature on the behavioral, emotional, and cognitive maladjustments in children associated with caregiver – both maternal and paternal – depression and other common forms of significant psychological distress (Goodman & Gotlib, 1999; Ramchandani et al., 2008); caregiver depressive symptoms have also been associated with biomarkers of health in children, such as cortisol (Essex et al., 2011). The addition of a marker of inflammation with application to major illnesses such as cardio-metabolic diseases is an important extension to prior research. Our findings also provide another kind of extension to prior work: whereas prior research suggested that early stress exposures may have immune health effects in adulthood (Danese et al., 2009), our results suggest that childhood predictors of inflammation are detectable by early adolescence. This implies that the adverse health outcomes observed in prior studies of adults may not require very many years of stress exposure. The current findings also extend existing evidence that children in high-risk environments have poor parent-reported health (Flaherty et al., 2013) and poorer health on objective measures of illness (Caserta et al.,

2008). Whether or not these effects persist, attenuate or exacerbate over time with additional and cumulative stress exposure will require further longitudinal follow-up of this sample.

The prediction from caregiver symptoms to CRP was robust, withstanding the inclusion of multiple confounds, including other types of early stresses (poverty, family violence) and concurrently assessed risk and confounders, including caregiver depressive symptoms and child health-related behaviors. It may be important that neither IL-6 nor TNF-alpha, other commonly identified markers of inflammation, was associated with early risk exposure after accounting for covariates. The mechanisms of effect connecting early stress exposure, specifically caregiver depressive symptoms, to early adolescent inflammation, specifically CRP, require further consideration. Prediction of CRP was particular to caregiver symptoms; that was so despite the confirmed overlap between symptoms and other stressors commonly associated with poor child health outcomes. Although we would not wish to argue that caregiver depressive symptoms have a privileged impact on child health, we would draw two potentially important implications. One is that caregiver depressive symptoms may have been the most reliable long-term predictor – among those studied – because it was a more direct index of the family and caregiving environment than, for example, poverty. The second implication is that the findings do not support compositing risks of many types, as is sometimes practiced. Evidence for particularly targeting caregiving-based risks in studies of stress and children's health has been available for some time, from the report of Meyer & Haggerty of a dose-response pattern between stress in the family and streptococcal infection in the child (Meyer, 1962) to more recent data showing that observed caregiving quality predicted antibody response to vaccination in early adolescence (O'Connor et al., 2015).

Quite why the prediction to adolescent inflammation was limited to CRP is not yet clear. It may reflect CRP as a further downstream and broader marker of inflammation, i.e., compared with IL-6 and TNF-alpha, and the different pathways and origins of markers of inflammation. Further research is needed to explain the differential mechanisms. One mechanism that did not receive support in these analyses is glucocorticoid resistance. The prediction to CRP from early risk exposures was not mediated via glucocorticoid resistance, which was not associated with early risk exposures. We also failed to find strong evidence that the impact of early caregiver symptoms on later inflammation was explained by health behaviors such as obesity, as some previous studies suggested (Broyles et al., 2012; Jonker et al., 2017). In fact, in contrast to some prior studies (Pietras & Goodman, 2013), we found only limited evidence that exposure to early stressors was associated with obesity; differences with other studies on this finding may be accounted for by the marked differences in racial and economic composition in the FLP study compared with most others.

Early risk exposure was somewhat arbitrarily targeted to the first 2 years. That decision can be justified by the existing literature emphasizing the potential privileged impact of infant and early childhood exposures to psychosocial, nutritional and other risks for child physical and neurodevelopment (Cusick & Georgieff, 2016; Fox, Levitt, & Nelson, 2010). There is also emerging evidence for behavior-immune system associations in infancy and early childhood (O'Connor et al., 2017). Admittedly, however, the definition of "early" varies considerably, and we are not aware of a particularly strong biological or psychological rationale for this or other cut-offs for defining "early" exposure: many could be defended.

Attempts to derive an impact of early stress exposure and its implicit timing effect will be undermined by the substantial stability of early risk exposures. More broadly, chronicity, severity, and timing of stress are inherently confounded for those major stressors prioritized in observational studies. Accordingly, although it clearly is of interest that early exposure to caregiver depressive symptoms predicted inflammation in early adolescence – independently of concurrently measured depressive symptoms, which did not – we would instead emphasize the value of collecting multiple occasions of measurement to improve reliability of assessment and the inclusion of multiple different but overlapping types of stress exposures.

Finally, we found no evidence that the prediction of inflammation in early adolescence from early stress measure varied by sex or race of the child; that is despite a likely sufficiently large sample size. Concerns about data quality do not seem a plausible explanation because we applied a multitude of quality control checks and because we do obtain expected associations between IL-6 and TNF-alpha and health behaviors, most notably obesity.

It is well-established that interventions to improve the caregiving environment may have lasting positive effects on children's behavioral well-being (Scott, Briskman, & O'Connor, 2014). A compelling clinical application of the current findings – which is just suggestive at this time – is that interventions to improve caregiver psychological health may promote not only child health, as has been suggested (Stein et al., 2018), but also child immune health. A less speculative and perhaps more immediate application is the value of instating a broader-based integrated assessment of both behavioral and physical health where interventions for child psychological and behavioral well-being are applied.

Acknowledgements:

This study is part of the Family Life Project [https://flp.fpg.unc.edu/] which was supported by NICHD (P01HD039667) with co-funding from National Institute on Drug Abuse. Support for this paper was provided by MH 097293 with a supplement funded by the ORWH and the Wynne Center for Family Research.

References

Avitsur R, Stark JL, & Sheridan JF (2001). Social stress induces glucocorticoid resistance in subordinate animals. Horm Behav, 39(4), 247–257. doi: 10.1006/hbeh.2001.1653S0018-506X(01)91653-8 [pii] [PubMed: 11374910]

Brown DW, Anda RF, Tiemeier H, Felitti VJ, Edwards VJ, Croft JB, & Giles WH (2009). Adverse childhood experiences and the risk of premature mortality. Am J Prev Med, 37(5), 389–396. doi: S0749–3797(09)00506–6 [pii]10.1016/j.amepre.2009.06.021 [PubMed: 19840693]

Broyles ST, Staiano AE, Drazba KT, Gupta AK, Sothern M, & Katzmarzyk PT (2012). Elevated C-reactive protein in children from risky neighborhoods: evidence for a stress pathway linking neighborhoods and inflammation in children. PLoS One, 7(9), e45419. doi: 10.1371/journal.pone.0045419 [PubMed: 23049799]

Caserta MT, O'Connor TG, Wyman PA, Wang H, Moynihan J, Cross W, … Jin X (2008) The associations between psychosocial stress and the frequency of illness, and innate and adaptive immune function in children. Brain Behav Immun, 22(6), 933–940. doi: S0889–1591(08)00032–9 [pii]10.1016/j.bbi.2008.01.007 [PubMed: 18308510]

Caserta MT, Wyman PA, Wang H, Moynihan J, & O'Connor TG (2011). Associations among depression, perceived self-efficacy, and immune function and health in preadolescent children.

Development and Psychopathology, 23(4), 1139–1147. doi: 10.1017/S0954579411000526 [PubMed: 22018086]

Caspi A, Harrington H, Moffitt TE, Milne BJ, & Poulton R (2006). Socially isolated children 20 years later: risk of cardiovascular disease. Arch Pediatr Adolesc Med, 160(8), 805–811. doi: 160/8/805 [pii]10.1001/archpedi.160.8.805 [PubMed: 16894079]

Chen E, Miller GE, Kobor MS, & Cole SW (2010). Maternal warmth buffers the effects of low early-life socioeconomic status on pro-inflammatory signaling in adulthood. Mol Psychiatry. doi: mp201053 [pii]10.1038/mp.2010.53

Chen M, & Lacey RE (2018). Adverse childhood experiences and adult inflammation: Findings from the 1958 British birth cohort. Brain Behav Immun, 69, 582–590. doi: 10.1016/j.bbi.2018.02.007 [PubMed: 29458198]

Chiang JJ, Bower JE, Almeida DM, Irwin MR, Seeman TE, & Fuligni AJ (2015). Socioeconomic status, daily affective and social experiences, and inflammation during adolescence. Psychosom Med, 77(3), 256–266. doi: 10.1097/PSY.0000000000000160 [PubMed: 25829237]

Cusick SE, & Georgieff MK (2016). The Role of Nutrition in Brain Development: The Golden Opportunity of the "First 1000 Days". J Pediatr, 175, 16–21. doi: 10.1016/j.jpeds.2016.05.013 [PubMed: 27266965]

Danese A, Moffitt TE, Harrington H, Milne BJ, Polanczyk G, Pariante CM, … Caspi A (2009). Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. Arch Pediatr Adolesc Med, 163(12), 1135–1143. doi: 163/12/1135 [pii]10.1001/archpediatrics.2009.214 [PubMed: 19996051]

Derogatis L (2000). Brief Symptom Inventory. Vol. 18. Minneapolis, MN: NCS Pearson.

Dowd JB, Zajacova A, & Aiello AE (2010). Predictors of inflammation in U.S. children aged 3–16 years. Am J Prev Med, 39(4), 314–320. doi: S0749–3797(10)00387–9 [pii]10.1016/j.amepre.2010.05.014 [PubMed: 20837281]

Dube SR, Miller JW, Brown DW, Giles WH, Felitti VJ, Dong M, & Anda RF (2006). Adverse childhood experiences and the association with ever using alcohol and initiating alcohol use during adolescence. J Adolesc Health, 38 (4), 444 e441–410. doi: S1054-139X(05)00298-3 [pii]10.1016/j.jadohealth.2005.06.006 [PubMed: 16549308]

Elwenspoek MMC, Kuehn A, Muller CP, & Turner JD (2017). The effects of early life adversity on the immune system. Psychoneuroendocrinology, 82, 140–154. doi: 10.1016/j.psyneuen.2017.05.012 [PubMed: 28549270]

Essex MJ, Klein MH, Cho E, & Kalin NH (2002). Maternal stress beginning in infancy may sensitize children to later stress exposure: effects on cortisol and behavior. Biol Psychiatry, 52(8), 776–784. doi: S0006322302015536 [pii] [PubMed: 12372649]

Essex MJ, Shirtcliff EA, Burk LR, Ruttle PL, Klein MH, Slattery MJ, … Armstrong JM (2011). Influence of early life stress on later hypothalamic-pituitary-adrenal axis functioning and its covariation with mental health symptoms: a study of the allostatic process from childhood into adolescence. Dev Psychopathol, 23(4), 1039–1058. doi: S0954579411000484 [pii]10.1017/S0954579411000484 [PubMed: 22018080]

Everett BM, Pradhan AD, Solomon DH, Paynter N, Macfadyen J, Zaharris E, … Ridker PM (2013). Rationale and design of the Cardiovascular Inflammation Reduction Trial: a test of the inflammatory hypothesis of atherothrombosis. Am Heart J, 166(2), 199–207 e115. doi: 10.1016/j.ahj.2013.03.018 [PubMed: 23895801]

Fagundes CP, Glaser R, & Kiecolt-Glaser JK (2013). Stressful early life experiences and immune dysregulation across the lifespan. Brain, behavior, and immunity, 27(1), 8–12. doi: 10.1016/j.bbi.2012.06.014

Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, … Marks JS (1998a). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med, 14(4), 245–258. [PubMed: 9635069]

Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, … Marks JS (1998b). Relationship of childhood abuse and household dysfunction to many of the leading causes of death

in adults. The Adverse Childhood Experiences (ACE) Study. American Journal of Preventive Medicine, 14(4), 245–258. doi: S0749379798000178 [pii] [PubMed: 9635069]

Flaherty EG, Thompson R, Dubowitz H, Harvey EM, English DJ, Proctor LJ, & Runyan DK (2013). Adverse childhood experiences and child health in early adolescence. JAMA Pediatr, 167(7), 622–629. doi: 10.1001/jamapediatrics.2013.22 [PubMed: 23645114]

Flaherty EG, Thompson R, Litrownik AJ, Theodore A, English DJ, Black MM, … Dubowitz H (2006). Effect of early childhood adversity on child health. Arch Pediatr Adolesc Med, 160(12), 1232–1238. doi: 160/12/1232 [pii]10.1001/archpedi.160.12.1232 [PubMed: 17146020]

Fox SE, Levitt P, & Nelson CA 3rd. (2010). How the timing and quality of early experiences influence the development of brain architecture. Child Dev, 81(1), 28–40. doi: 10.1111/j.1467-8624.2009.01380.x [PubMed: 20331653]

Fuligni AJ, Telzer EH, Bower J, Irwin MR, Kiang L, & Cole SW (2009). Daily family assistance and inflammation among adolescents from Latin American and European backgrounds. Brain Behav Immun, 23(6), 803–809. doi: S0889–1591(09)00068–3 [pii]10.1016/j.bbi.2009.02.021 [PubMed: 19275931]

Goodman SH, & Gotlib IH (1999). Risk for psychopathology in the children of depressed mothers: a developmental model for understanding mechanisms of transmission. Psychol Rev, 106(3), 458–490. [PubMed: 10467895]

Gustafsson HC, Cox MJ, & the Family Life Project Key, I. (2012). Relations Among Intimate Partner Violence, Maternal Depressive Symptoms, and Maternal Parenting Behaviors. J Marriage Fam, 74(5), 1005–1020. doi: 10.1111/j.1741-3737.2012.01010.x [PubMed: 23869110]

Halligan SL, Herbert J, Goodyer IM, & Murray L (2004). Exposure to postnatal depression predicts elevated cortisol in adolescent offspring. Biological psychiatry, 55(4), 376–381. doi: 10.1016/j.biopsych.2003.09.013 [PubMed: 14960290]

Harrington RA (2017). Targeting Inflammation in Coronary Artery Disease. N Engl J Med, 377(12), 1197–1198. doi: 10.1056/NEJMe1709904 [PubMed: 28844177]

Hibel LC, Granger DA, Blair C, & Cox MJ (2009). Intimate partner violence moderates the association between mother-infant adrenocortical activity across an emotional challenge. J Fam Psychol, 23(5), 615–625. doi: 2009-17949-001 [pii]10.1037/a0016323 [PubMed: 19803598]

Hoelscher DM, Day RS, Kelder SH, & Ward JL (2003). Reproducibility and validity of the secondary level School-Based Nutrition Monitoring student questionnaire. J Am Diet Assoc, 103(2), 186–194. doi: 10.1053/jada.2003.50031S0002822302000354 [pii] [PubMed: 12589324]

Holt S, Buckley H, & Whelan S (2008). The impact of exposure to domestic violence on children and young people: a review of the literature. Child Abuse Negl, 32(8), 797–810. doi: S0145–2134(08)00134–8 [pii]10.1016/j.chiabu.2008.02.004 [PubMed: 18752848]

Hughes K, Bellis MA, Hardcastle KA, Sethi D, Butchart A, Mikton C, … Dunne MP (2017). The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. Lancet Public Health, 2(8), e356–e366. doi: 10.1016/S2468-2667(17)30118-4 [PubMed: 29253477]

Jonker I, Rosmalen JGM, & Schoevers RA (2017). Childhood life events, immune activation and the development of mood and anxiety disorders: the TRAILS study. Transl Psychiatry, 7(5), e1112. doi: 10.1038/tp.2017.62 [PubMed: 28463238]

Korte SM, Koolhaas JM, Wingfield JC, & McEwen BS (2005). The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. Neurosci Biobehav Rev, 29(1), 3–38. doi: S0149–7634(04)00148–4 [pii]10.1016/j.neubiorev.2004.08.009 [PubMed: 15652252]

Kuhlman KR, Chiang JJ, Horn S, & Bower JE (2017). Developmental psychoneuroendocrine and psychoneuroimmune pathways from childhood adversity to disease. Neurosci Biobehav Rev, 80, 166–184. doi: 10.1016/j.neubiorev.2017.05.020 [PubMed: 28577879]

Meyer RJ, Haggerty RJ (1962). Streptococcal infections in families. Pediatrics, 29, 539–549. [PubMed: 14473162]

Miller GE, & Chen E (2010). Harsh family climate in early life presages the emergence of a proinflammatory phenotype in adolescence. Psychol Sci, 21(6), 848–856. doi: 0956797610370161 [pii]10.1177/0956797610370161 [PubMed: 20431047]

O'Connor TG, Moynihan JA, & Caserta MT (2014). Annual Research Review: The neuroinflammation hypothesis for stress and psychopathology in children - developmental psychoneuroimmunology. Journal of child psychology and psychiatry, and allied disciplines, 55(6), 615–631. doi: 10.1111/jcpp.12187

O'Connor TG, Scheible K, Sefair AV, Gilchrist M, Blackmore ER, Winter MA, … Caserta MT (2017). Immune and neuroendocrine correlates of temperament in infancy. Dev Psychopathol, 29(5), 1589–1600. doi: 10.1017/S0954579417001250 [PubMed: 29162168]

O'Connor TG, Wang H, Moynihan JA, Wyman PA, Carnahan J, Lofthus G, … Caserta MT (2015). Observed parent-child relationship quality predicts antibody response to vaccination in children. Brain Behav Immun, 48, 265–273. doi: 10.1016/j.bbi.2015.04.002 [PubMed: 25862953]

Pedersen JM, Mortensen EL, Christensen DS, Rozing M, Brunsgaard H, Meincke RH, … Lund R (2018). Prenatal and early postnatal stress and later life inflammation. Psychoneuroendocrinology, 88, 158–166. doi: 10.1016/j.psyneuen.2017.12.014 [PubMed: 29291495]

Pietras SA, & Goodman E (2013). Socioeconomic status gradients in inflammation in adolescence. Psychosom Med, 75(5), 442–448. doi: 10.1097/PSY.0b013e31828b871a [PubMed: 23533285]

Ramchandani PG, Stein A, O'Connor TG, Heron J, Murray L, & Evans J (2008). Depression in men in the postnatal period and later child psychopathology: a population cohort study. J Am Acad Child Adolesc Psychiatry, 47(4), 390–398. doi: 10.1097/CHI.0b013e31816429c2 [PubMed: 18388761]

Raposa E, Hammen C, Brennan P, & Najman J (2014). The long-term effects of maternal depression: early childhood physical health as a pathway to offspring depression. J Adolesc Health, 54(1), 88–93. doi: 10.1016/j.jadohealth.2013.07.038 [PubMed: 24060574]

Raposa EB, Bower JE, Hammen CL, Najman JM, & Brennan PA (2014). A developmental pathway from early life stress to inflammation: the role of negative health behaviors. Psychol Sci, 25(6), 1268–1274. doi: 10.1177/0956797614530570 [PubMed: 24760142]

Schmeer KK, & Yoon A (2016). Socioeconomic status inequalities in low-grade inflammation during childhood. Arch Dis Child, 101(11), 1043–1047. doi: 10.1136/archdischild-2016-310837 [PubMed: 27371708]

Scott S, Briskman J, & O'Connor TG (2014). Early Prevention of Antisocial Personality: Long-Term Follow-Up of Two Randomized Controlled Trials Comparing Indicated and Selective Approaches. The American journal of psychiatry. doi: 10.1176/appi.ajp.2014.13050697

Slopen N, Kubzansky LD, McLaughlin KA, & Koenen KC (2013). Childhood adversity and inflammatory processes in youth: A prospective study. Psychoneuroendocrinology, 38(2), 188–200. doi: 10.1016/j.psyneuen.2012.05.013 [PubMed: 22727478]

Slopen N, McLaughlin KA, Dunn EC, & Koenen KC (2013). Childhood adversity and cell-mediated immunity in young adulthood: does type and timing matter? Brain Behav Immun, 28, 63–71. doi: 10.1016/j.bbi.2012.10.018 [PubMed: 23108062]

Stein A, Netsi E, Lawrence PJ, Granger C, Kempton C, Craske MG, … Murray L (2018). Mitigating the effect of persistent postnatal depression on child outcomes through an intervention to treat depression and improve parenting: a randomised controlled trial. Lancet Psychiatry, 5(2), 134–144. doi: 10.1016/S2215-0366(18)30006-3 [PubMed: 29413138]

Straus MA, & Douglas EM (2004). A short form of the Revised Conflict Tactics Scales, and typologies for severity and mutuality. Violence Vict, 19(5), 507–520. [PubMed: 15844722]

Strauss MA, & Gelles RJ (1990). Physical violence in American families: Risk factors and adaptations to violence in 8,145 families. New Brunswick, NJ: Transaction.

Suglia SF, Enlow MB, Kullowatz A, & Wright RJ (2009). Maternal intimate partner violence and increased asthma incidence in children: buffering effects of supportive caregiving. Arch Pediatr Adolesc Med, 163(3), 244–250. doi: 10.1001/archpediatrics.2008.555 [PubMed: 19255392]

Taylor SE, Lehman BJ, Kiefe CI, & Seeman TE (2006). Relationship of early life stress and psychological functioning to adult C-reactive protein in the coronary artery risk development in young adults study. Biological psychiatry, 60(8), 819–824. doi: 10.1016/j.biopsych.2006.03.016 [PubMed: 16712805]

Taylor SE, Way BM, & Seeman TE (2011). Early adversity and adult health outcomes. Dev Psychopathol, 23(3), 939–954. doi: 10.1017/S0954579411000411 [PubMed: 21756443]

Towe-Goodman NR, Stifter CA, Mills-Koonce WR, & Granger DA (2012). Interparental aggression and infant patterns of adrenocortical and behavioral stress responses. Developmental Psychobiology, 54(7), 685–699. doi: 10.1002/dev.20618 [PubMed: 22127795]

Vernon-Feagans L, Cox M, & Investigators FLPK (2013). The Family Life Project: An epidemiological and developmental study of young children living in poor rural communities. Monographs of the Society for Research in Child Development, 78(5), 1–150.

Wegman HL, & Stetler C (2009). A meta-analytic review of the effects of childhood abuse on medical outcomes in adulthood. Psychosomatic medicine, 71(8), 805–812. doi: 10.1097/PSY.0b013e3181bb2b46 [PubMed: 19779142]

Wolfson AR, Carskadon MA, Acebo C, Seifer R, Fallone G, Labyak SE, & Martin JL (2003). Evidence for the validity of a sleep habits survey for adolescents. Sleep, 26(2), 213–216. [PubMed: 12683482]

Wood BL, Brown ES, Lehman HK, Khan DA, Lee MJ, & Miller BD (2018). The effects of caregiver depression on childhood asthma: Pathways and mechanisms. Ann Allergy Asthma Immunol, 121(4), 421–427. doi: 10.1016/j.anai.2018.06.031 [PubMed: 29981440]

Highlights

There is now reliable evidence that early stress exposures are associated with behavioral health in children, but the associations with physical health is less clear.

In a large, at-risk sample, we found that caregiver depressive symptoms in early childhood predicted elevated CRP almost a decade later.

The prediction was significant after accounting for multiple covariates such as socio-economic adversity, health behaviors and body mass index.

Table 1.

Demographics of Subsample of FLP Early Adolescents in the Immune Study

	Mean (SD) or % (n)
Family/Parent characteristics	
Race (% African-American)	35.8 (120)
Income < $25,000	60.2 (201)
Educational attainment	
< High school degree	9.9 (33)
High school degree	25.4 (85)
> High school degree	64.7 (216)
Family size	3.6 (1.4)
Child characteristics	
Age (years)	11.0 (.59)
Sex (% female)	44.5 (149)
BMI	20.75 (5.8)
Pubertal status	
Stage 4 or later (boys)	18% (34)
Stage 4 or later (girls)	20% (29)

Table 2.

Bivariate Associations between Early Risk and Inflammatory Markers and Health Behaviors in Early Adolescence

	Early Exposures				Early Adolescence				
	INR	**Depressive Symptoms**	**Family Violence**	**Single**	**CRP**	**IL-6**	**TNF-alpha**	**GRA**	**Obesity**
INR	--	−.11	−.11	−39***	−.02	−.12*	.07	−.01	−.06
Symptoms		--	.52***	.24***	.10+	.02	−.08	−.04	.02
Family violence			--	.16**	.00	.00	−.01	−.06	.01
Ever Single				--	.09	.15**	−.08	−.07	.12*
Adolescence									
CRP					--	.57***	037***	.11	.43***
IL-6						--	.29***	.13*	.29***
TNF-alpha							--	.05	.19**
GRA								--	.13*
Obesity									--

Note. INR = income to needs ration; GRA = glucocorticoid resistance; IL = interleukin; ever single indicates whether the child has spent time in a single-parent household in the first two years. Caregiver Depressive symptoms are from the depression subscale from the BSI measure; family violence is based on the Conflict Tactics Scale. + p<.10,

* p<.05,

** p<.01,

*** p<.01.

Table 3.

Regression Model Predicting CRP from Early Risk Exposures and Current Risk

	B	SE	t
Intercept	3.53	1.91	1.84
Gender (male)	.15	.20	.75
Race (African-American)	−.14	.29	−.48
Early childhood			
Income to Needs ratio	.00	.07	−.05
Family violence	−.39	.18	−2.15*
Depressive symptoms	.05	.02	2.68**
Single-parent household	.08	.25	.32
Early adolescence			
Obesity	1.70	.23	7.30***
Recent illness	.91	.24	3.80***
Depressive symptoms	.00	.01	−.11

Note: Caregiver Depressive symptoms are from the BSI depression subscale collected in early childhood and early adolescence; family violence is based on the Conflict Tactics Scale. Model is also adjusted for exercise and sleep quality in adolescence; variation in temperature in the sample in transit; time of draw; state of residence; household size; and parent education and income in early adolescence.

* p<.05,

** p<.01,

*** p<.01.