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The Impact of Early and Recent Life Stress on Trajectories of Inflammatory Biomarkers in a Diverse Sample of Adolescents

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Abstract

Elevated inflammatory activity is one possible pathway through which exposure to childhood adversity engenders risk for physical and psychiatric illnesses. Limited research has investigated the compounding effects of childhood and adolescent stress exposure on changes in circulating levels of inflammatory biomarkers. This study assessed whether childhood adversity interacted with chronic or acute stress during adolescence to affect the temporal trajectories of five inflammatory biomarkers across at least three blood draws in a diverse sample of adolescents (N = 134; observations = 462). Using multilevel modeling, the interaction of childhood adversity, time, and within-person variance of acute stressors significantly predicted trajectories of higher interleukin-10 levels, controlling for demographics, medication use, and body mass index. Adolescents with high levels of childhood adversity who were exposed to a higher frequency of acute stressors compared to their own average rate of stress exposure consistently had higher levels of IL-10 as they got older, but those with average and below frequency of acute stressors had decreasing trajectories of log IL-10 as they matured. The results demonstrate how events early in life shape biological responses to the adolescent environment. This study also highlights the importance of developmental timing on the body's enhanced reactivity to acute and sustained stressors following childhood adversity.

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Author Contributions All authors contributed to the study design. Data collection was performed by M. M. Kautz, B. A. McArthur, D. P. Moriarity, and L. B. Alloy. M. M. Kautz performed the data analysis and interpretation under the supervision of D. P. Moriarity and J. Klugman. C. L. Coe conducted the inflammation assays. L.Y. Abramson and L.B. Alloy wrote the funding grant. M. M. Kautz drafted the manuscript, and all authors edited the manuscript.

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Compliance with Ethical Standards

Ethical Approval All procedures performed in the study were in accordance with the ethical standards of the institution and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board of Temple University.

Informed Consent Informed consent was obtained from all individual participants and the legal guardians included in the study.

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Keywords

Childhood adversity; Inflammation; Stressful life events; Adolescence

Introduction

Childhood adversity is a risk factor for many negative mental and physical health outcomes (Taylor, 2010). High physical and psychological stress during childhood has been linked to an increased risk for experiencing psychological disorders (e.g., depression, anxiety, substance use, psychosis) and chronic physical health problems during adulthood (e.g., respiratory disease, diabetes, cancer, and heart disease) (Danese et al., 2009; Hughes et al., 2017; Norman et al., 2012; Varese et al., 2012). Similar to adults, youth who have experienced high levels of adversity early in life are at greater risk for developing psychological and behavioral problems (Benjet et al., 2010; Keiley et al., 2001; Moran et al., 2004). Recent work has more specifically implicated inflammatory physiology as a key conduit for the influence of stress on later illness, but most prior research has examined the influence of early or recent stressors separately and assessed inflammatory physiology only once. This study examines how the combination of childhood adversity and recent stressful life events synergistically influence trajectories of inflammatory biomarkers across adolescence.

Childhood Adversity and Inflammation

Childhood adversity (e.g., maltreatment, family discord, and poverty) has been associated consistently with an elevated inflammatory phenotype across adolescence and adulthood in both cross-sectional and longitudinal studies. A meta-analysis found that adults exposed to childhood trauma had elevated baseline levels of C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor-alpha (TNF-α) in community and clinical samples (Baumeister et al., 2016). Additionally, a recent meta-analysis of eight studies with adolescent samples found a positive association between early life adversity and CRP (Kuhlman et al., 2020). In prospectively assessed adolescent samples, higher levels of childhood adversity have been associated with higher CRP levels from a single assessment (Baldwin et al., 2018; Boch & Ford, 2015). When inflammation has been measured repeatedly during adolescence, higher cumulative childhood adversity predicted elevated levels of CRP across time (Copeland et al., 2014; Slopen et al., 2013).

Cumulative Effects of Childhood and Recent Life Stress on Inflammation

The *early-life stress sensitization model* may account for the relationship between childhood and adolescent stressors and elevated inflammatory biomarkers. This model hypothesizes that childhood adverse events have an independent effect on biological stress reactivity and, additionally, amplify biological reactions to subsequently experienced stressors (Hostinar et al., 2015). Fully testing this model would require measuring the effect of childhood adversity on inflammatory responses during early development and then examining the independent and interactive effects of recent stressful life events on inflammatory trajectories across adolescence and adulthood. Support for this model would be reflected

in a compounding and summative effect of childhood adversity and recent stress continuing to increase the synthesis and release of inflammatory proteins to stress exposures over time. The model suggests that reducing stressor exposure as early as possible could lessen the effects of elevated low-grade inflammation on the neural architecture of youth, and therefore, prevent the progression to psychopathology and altered cognitive functioning in later development (Kautz, 2021).

Although no study has fully tested this model due to the challenges of longitudinal assessments over many years, recent work supports aspects of the early-life stress sensitization model in adult samples (Carpenter et al., 2010; Gouin et al., 2012; Simons et al., 2019; c.f. Hostinar et al., 2015; Lin et al., 2016). Three studies also have provided support for this model in adolescent samples. Among female adolescents assessed four times over 1.5 years, those raised in a harsh environment, who also experienced recent stressors over the last six months, had leukocytes that released more IL-6 following in vitro stimulation with bacterial endotoxin (Miller & Chen, 2010). Across four timepoints over two years, children with asthma who experienced chronic family stress during childhood and acute stressful events during the prior three months had cells that released more IL-4, IL-5, and interferon-gamma following in vitro stimulation (Marin et al., 2009). Although these studies utilized repeat assessments of recent stress exposure and inflammation, they did not examine prior adverse events and it is not known whether this pattern of sensitization would persist into adolescence for those with more exposure to childhood adversity.

Across an average of five timepoints over 2.5 years, adolescent girls with a history of childhood adversity were found to have elevated IL-6 release following in vitro stimulation of their cells with lipopolysaccharide from bacteria (Ehrlich et al., 2016). Although recent stressful life events were not assessed in this study, it supported the conceptual view that early stress exposure primes the immune system for more pronounced responses to subsequent life stressors. However, although the Ehrlich et al. (2016) study and our current analysis both examine the biological embedding model of early adversity, there are key differences in the hypotheses being tested, the methodology, and analytic approaches. The present study attempts to test the early-life stress sensitization model more systematically and, thereby, to fill a gap in the literature. The influence of childhood adversity was determined along with a prospective assessment of stressful life events –both acute and chronic– and circulating levels of multiple inflammatory proteins across at least three time points in a diverse sample of adolescents.

Differentiation of Chronic and Acute Stressors' Influence on the Immune System

Both acute physical and psychological stressors activate the release of stress response hormones (i.e., adrenocorticotropic hormone, cortisol, norepinephrine, and epinephrine) that prepare the body to respond adaptively to potential threats and stimulate the release of pro- and anti-inflammatory cytokines (e.g., IL-6, IL-8, TNF-α, and IL-10) into peripheral blood (McEwen & McEwen, 2017). Typically, this systematic cascade shuts off when the stressful event ends. However, when stressors are present for a prolonged time and become chronic, this same cascade can begin to deplete and exhaust the body's resources (i.e. glucocorticoid resistance) and alter physiological regulation, leading to an increased risk for long-term

negative health outcomes (McEwen & McEwen, 2017). Most prior research on the influence of stressful life events on inflammatory physiology has not distinguished between the longterm effects of acute and chronic stressful experiences leading to a lack of knowledge about the distinct health implications (Rohleder, 2019). Based on the current literature, a rapid elevation of circulating pro- and anti-inflammatory cytokines, such as IL-6, TNF-α, and IL-10, would be expected to occur in response to an acute stressor (Marsland et al., 2017). In contrast to the transient changes following acute stressors, systemic low-grade elevations in inflammatory biomarkers, such as IL-6, TNF-α, and CRP, have been found to be potentiated by experiences of prolonged stressors (Rohleder, 2019). Given these distinctly different patterns of inflammatory responses to acute and chronic stressors, we hypothesized that the duration of event exposure (i.e., acute or chronic) would interact with childhood adversity in different ways.

The Present Study

The current study examined whether there is a synergistic effect between childhood adversity and recent stressful life events on the trajectories of inflammatory biomarkers in a sample of racial and socioeconomically diverse adolescents. The primary aims were to examine the combined effect of childhood adversity and chronic or acute recent stressful events on several commonly measured inflammatory biomarkers across adolescence. Based on prior evidence supporting portions of the early-life stress sensitization model, we hypothesized that adolescents with more exposure to childhood adversity and larger within-person changes in chronic stressors, as well as more short-term stress (in the past two weeks), would have elevated levels of four pro- and one anti-inflammatory biomarkers. An exploratory aim of this project was to identify how the strength of the association with childhood adversity and recent stressful experiences would vary across the longitudinal trajectories of these peripheral inflammatory biomarkers. However, because there is still limited research directly comparing the longitudinal trajectories of multiple inflammatory markers in adolescent samples, this question was considered as an exploratory subaim.

Method

Participants and Procedures

The participants were a subset of individuals in a multi-wave, prospective, longitudinal study of the development of depression in adolescence that began recruiting in 2008 and concluded data collection in 2018. Participants were recruited through school mailings and follow-up phone calls over four years from public and private middle schools or ads in local newspapers in an urban area. Participants' demographics and experiences of childhood adversity prior to enrollment in the study were reported by primary female caregivers at baseline. Chronic and acute stressful life events were assessed approximately every six months and inflammatory biomarker levels were assessed approximately annually through venipuncture depending on participant availability. Potentially confounding variables, such as medications that may affect inflammatory response, time of day when the blood draw was completed, and time since last meal were recorded at each blood draw, and participants' height and weight were measured to allow calculation of body mass index (BMI) at each

blood draw. See Fig. S1 in the Supplemental Materials for a timeline of data collection procedures.

Adolescents were included in Project ACE if they were 12 to 14 years old at recruitment, they self-identified as Caucasian or white, African American or black, or biracial, and if their mother/primary female caregiver was willing to participate. Exclusion criteria included an inability to read or speak English well enough to complete project assessments or the presence of a severe cognitive or learning disability, cognitive impairment, psychotic disorder, developmental disorder, or any other psychiatric or medical problem that would prevent the adolescents or their caregivers from completing the study. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki, the study design was reviewed and approved by the Institutional Review Board of Temple University, and informed consent was completed prior to participation.

Of the full Project ACE sample at baseline (N = 642), 315 participants gave consent to participate in the supplementary blood draw protocol. To be included in this analytic sample, participants must have completed at least three blood draws (n = 178) during their participation in Project ACE, as three observations per participant was the threshold for estimating a trajectory. Attrition analyses using linear probability models examining the chances of having completed at least three blood draws revealed that being black or biracial slightly increased the probability of completing three blood draws ($B = 0.09$, $SE = 0.04$, $t = 2.24$, $p = 0.025$). Childhood adversity score, gender, and socioeconomic status did not significantly affect the likelihood of completing three blood draws. Blood draw timepoints were excluded from this analytic sample if at the time of the blood draw, the participant reported having diabetes, a blood clotting disease, or a serious autoimmune disease, leaving a sample of 168 participants. Additionally, data from blood draw timepoints were not included in the analysis if a participant had a CRP level > 10 mg/L on that day (Landry et al., 2017; Pearson, 2003) to account for the possible presence of current illness, reducing the sample to 155.

Furthermore, participants were excluded (full list-wise deletion) from this analytic sample if the participants did not complete at least one life events interview prior to each of their blood draws (n = 12) or they were missing inflammatory marker data (n = 1), SES information (n = 3), or BMI and medication information (n = 2). Three participants were excluded from this analysis because the participant's age at the time of the adverse childhood event was missing from > 50% of adverse events reported by the mother. After accounting for inclusion/exclusion criteria and missing data, the final analytic sample was n = 134 with 462 observations (58 participants completed only three blood draws, 36 completed four blood draws, 27 completed five blood draws, and 13 completed six blood draws). An examination of excluded participants was conducted to determine whether the analytic sample of 134 adolescents differed significantly from the full Project ACE sample at baseline (N = 642). The analytic sample was representative of the full ACE sample with respect to gender, racial, and SES composition ($\chi^2(1) = 0.04$, $p = 0.834$; $\chi^2(6) = 8.87$, $p = 0.181$; $\chi^2(1) = 0.45$, $p = 0.502$, respectively).

Assessments

Childhood Adversity—To assess childhood adversity, at baseline, mothers completed the Children's Life Events Scale (CLES; Crossfield et al., 2002), which is a checklist of 50 moderate to major adverse events that the adolescent may have experienced from birth until time of enrollment. Four trained objective raters determined if an event met criteria as a moderate or major adverse event ($\kappa = 0.83$; Shapero et al., 2015). The mothers' reports were used because the adolescent may have been too young to recall some of these events. CLES items include events in the following six domains: family difficulties, deaths of close family or friends, negative emotional feedback (e.g., bullying by peers), achievement failures, maltreatment (sexual, physical, emotional), and developmental delays or struggles. For each item the mother reported, she also provided the adolescent's age at the time of the event. For this analysis, major adverse events (e.g., physical/sexual abuse, neglect, or death of loved one) were weighted as two points and moderate events were weighted as one point in a weighted total childhood adversity score, summing across all subscales (Shapero et al., 2015). The total score of childhood adverse events was Z-standardized across individuals.

Stressful Life Events—Adolescents completed the 63-item Adolescent Life Events Questionnaire (ALEQ; Hankin & Abramson, 2002), assessing a broad range of stressors in familial, social, relationship, appearance, and school/achievement domains during the previous six months. Following completion of the ALEQ, adolescents completed the Life Events Interview (LEI; (Safford et al., 2007), which generated detailed information about events endorsed on the ALEQ and when they occurred. LEI interviewers were blind to participants' diagnoses, depressive symptoms, childhood adversity, and inflammatory biomarker levels. The LEI uses manualized, event-specific definitions to maintain consistency, and a priori probes were provided to each interviewer to help them determine whether reported events met criteria for a chronic or acute life event (Safford et al., 2007). When making this determination, first, each interviewer compared the participant's reported experience to the a priori criteria to decide if it matched the definition of one of the pre-determined chronic or acute events listed in the LEI manual; See Supplementary Table S1 for the category and frequency of each event. Each event not meeting definitional criteria was excluded to reduce subjective reporting biases. Second, if an event was objectively determined by the LEI interview to be an acute event, the interviewer would examine the timing and frequency of the event to ensure that all events categorized as acute did not happen more than once per week for five weeks nor twice per month for six months. If this was the case, then the acute event was designated as a chronic event for this analysis. Strong reliability and validity previously have been established for the ALEQ (Abela et al., 2011; Hankin & Abramson, 2002) and the LEI (Francis-Raniere et al., 2006; Safford et al., 2007) in community and clinical samples of adolescents.

For this study, the number of acute and chronic stressful events that occurred between each blood draw were summed separately. Additionally, because the acquisition of baseline information occurred before the first blood draw, the number of stressful life events that occurred between baseline and the first blood draw were summed to calculate stressful life event scores prior to the first blood draw. For these analyses, only the acute stressful events that occurred in the two weeks prior to each blood draw were summed to create an

"acute 2-week stressors" score. This score represents events that have been categorically and temporally identified as "acute". Both types of stressful event scores (i.e., acute and chronic) were Z-standardized across observations and then personcentered to measure the within-person changes in stressful events that occurred across time. The between-person variance also was isolated by calculating the mean of stressful event scores across all time points for each individual. The isolated within-person variance examines changes in stress exposure over time, whereas the isolated between-person effect is used to compare differences between the participants' overall average levels of stress exposure (Falkenström et al., 2017). In this analysis, all stressful event scores vary within an individual across time. Additionally, the number of LEI interviews that each participant completed prior to their first blood draw and between each blood draw was included in the analysis to control for any variations in the recall of events due to repeated measurement.

Inflammatory Biomarkers—Blood was obtained annually at regularly scheduled lab visits and timed for the late afternoon to control for diurnal variation in inflammatory physiology. Samples were collected via antecubital venipuncture by a certified phlebotomist (BD Vacutainer, Ref: 362788). The blood samples settled at room temperature for at least 20 min, then were centrifuged and stored in an ultracold –80 °C freezer until thawed on the day of assay. IL-6, IL-8, IL-10, and TNF-α were quantified by multi-cytokine array, and high-sensitivity CRP (hs-CRP) was determined in a singleplex assay, using an electrochemiluminescence platform and a QuickPlex SQ 120 imager for quantification of both cytokines and CRP (Meso Scale Discovery, Rockville, MD). Each specimen was assayed in duplicate, with intra-assay coefficients of variation between 1.94 – 4.38%, and values referenced to a standard curve generated from 7 calibrators with known concentrations. The lower limit of cytokine detection (LLOD) was 0.1 pg/mL, with a large dynamic range up to 2000 pg/mL. After running the diluted plasma so that detection of CRP corresponded to the standard curve, the values were converted to mg/L units and were calculated down to 0.1 mg/L to be consistent with the units used in the clinical literature (Breen et al., 2011). Cytokine and CRP data were log-transformed (value × 100) to normalize the distribution of values, which successfully brought these variables into an acceptable range of skewness. Diagnostic evaluations, including Q-Q plots and Shapiro–Wilk tests, comparing the observation-level and person-level residuals of the models with and without the transformations applied to the inflammatory variables indicated that the log-transformed residuals deviated less from a normal distribution and were retained in the final analyses.

Other Potential Confounds—Demographic variables were assessed by self-report at baseline and the participant's age was measured at each blood draw. A dichotomous variable was created to indicate if a participant was taking medication that may have affected inflammation levels at a given blood draw, including medications for asthma, ADHD, SSRIs, SNRIs, mood stabilizers, antipsychotics, anti-convulsants, birth control, NSAIDs, acne medication, painkillers, and inflammation-related steroids. BMI and the medication variable were person-centered to account for within-person changes in these variables across time. The participant's age at each blood draw was person-mean-centered to isolate the within-person changes in time (i.e., aging effects).

Statistical Analysis

Multilevel modeling was used to investigate whether the combination of childhood adversity and within-person changes in the frequency of acute and chronic stressful events predict trajectories of inflammation, controlling for demographics and other variables that may influence inflammatory biomarkers. All analyses were performed in R version 3.5.1 (Team, 2013) and multilevel models were estimated using the lmer4 package (Bates et al., 2015). Multilevel modeling was used for these analyses, rather than traditional regression techniques, because the multiple stressful event and inflammatory biomarker observations were clustered within individuals, and if this nesting was not accounted for, the probability of committing a Type I error would increase and less efficient coefficients would be estimated.

One multilevel model predicting each inflammatory marker was conducted to test the main effects of childhood adversity, chronic or recent acute stressful life events, and passage of time on the trajectories of inflammation (i.e., five models in total). Models were estimated using restricted maximum likelihood. All analyses accounted for the effects of person-centered BMI, person-centered use of inflammation-affecting medications, being female, being Black or Biracial, SES determined by free school lunch status, age at baseline, and the number of Life Event Interviews completed between each blood draw. Adding the random slope for time since baseline did not significantly improve model fit (i.e., reduced deviance) for the CRP, IL-6, and IL-10 inflammatory biomarkers; there were no substantial differences between the outcomes of the IL-8 and TNF-α models with and without the inclusion of the random slope. To facilitate comparability between models, all models did not include this random slope. Following the models examining main effects, five identical models were estimated that included the three-way interaction between childhood adversity, time since baseline, and stressful life events and all component two-way interactions.

When probing the effects of any significant interactions, time since baseline was considered the focal predictor and childhood adversity and stressful events were considered the moderators. Models with significant interactions were probed at the mean and ± 1 standard deviation from the mean of the moderators. To assess conditional effects, each simple slope was compared to zero. Post hoc pairwise contrasts also were conducted to test the difference in the prediction of particularly high levels of biomarkers (+ 1 standard deviation from the mean) in association with within-person changes in stressful events. The Tukey method for comparing a family of three estimates (low, moderate, and high childhood adversity) was used for each of these models and an adjusted *p*-value was reported.

Results

Initial Analyses

Table 1 presents the means and standard deviations for demographic variables, childhood adversity, the frequency of recent stressful life events, inflammatory biomarker levels, and control variables along with bivariate correlations. Childhood adversity was positively associated with all biomarker indicators of inflammation, supporting the hypothesis that it is a driver of an elevated inflammatory phenotype across time. Chronic and acute stressful

life events were correlated positively with log IL-10 and negatively correlated with Time. Time also was negatively correlated with IL-10, IL-8, and TNF-α indicating that on average these markers declined as adolescents aged. Furthermore, BMI, number of LEI interviews between blood draws, gender, SES, and race also all were correlated significantly with at least one inflammatory marker, supporting their inclusion as control variables in the analyses; See Supplementary Table S3 for further details on participant characteristics. Notably, childhood adversity was not correlated with recent stressful life events, indicating that participants who experienced more frequent childhood adversity did not necessarily experience more frequent recent stressful events during adolescence. The frequency of each type of childhood adverse event and chronic and acute recent stressful life events are provided in the Supplementary Materials (Tables S1−S2).

Main Effects of Childhood Adversity, Stressful Life Events, and Time

The unconditional main effects of childhood adversity and within-person changes in chronic and acute stressful life events on levels of inflammation were explored. As can be seen in Models 4 and 7 in Table 2, adolescents with more childhood adversity had elevated trajectories of log IL-6 and IL-10, controlling for all specified covariates. In addition, adolescents with higher average chronic stressful event scores across all time points had elevated trajectories of log IL-10 when compared to other adolescents with less exposure to stress (see Table 2, Model 7). As supported in the correlation matrix, increased age was associated with decreasing trajectories of IL-10, IL-8, and TNF-α, controlling for all specified covariates.

Examining the Interactive Role of Childhood Adversity and Stressful Life Events Across Time—None of the three-way interactions between childhood adversity, time since baseline, and chronic stressful events predicted trajectories of inflammatory markers (as documented in Table 2, Models 2, 5, 8, 11, and 14). The three-way interaction between childhood adversity, time since baseline, and acute stressful events was found to significantly predict trajectories of log IL-10 when holding all other variables constant (B = 0.03, SE = 0.01, p = 0.006; as detailed in Table 2, Models 9).

To further probe the conditional effects of the interaction, the simple slopes of within-person variance of time on log IL-10 were estimated at low, moderate, and high levels of childhood adversity and the within-person variance of acute stressors (see Fig. 1). Adolescents with high childhood adversity who were exposed to a higher frequency of acute stressors compared to their own average rate of stress exposure consistently had higher levels of IL-10 as they got older (i.e., a flat slope across time; B = −0.01, SE = 0.02, t = −0.40, p = 0.688). Adolescents with high childhood adversity exposure who experienced an average and below average frequency of acute stressors had decreasing trajectories of log IL-10 as they matured (B = −0.03, SE = 0.01, t = −2.87, p = 0.005, B = −0.05, SE = 0.06, t = −3.60, p < 0.001, respectively). Adolescents with moderate levels of childhood adversity who experienced a high and average frequency of acute stressors also had declining trajectories of log IL-10 with age (B = −0.02, SE = 0.01, t = −1.99, p = 0.047, B = −0.02, SE = 0.01, t = −2.64, p = 0.009, respectively). For adolescents with low levels of childhood adversity and a high frequency of acute stressors compared to their own average rate of stress exposure, there

also was a significant decline in the trajectory of log IL-10 as they got older ($B = -0.04$, $SE = 0.02$, $t = -2.43$, $p = 0.016$). Post hoc pairwise contrasts of log IL-10 indicated that later in development, adolescents who experienced relatively more frequent acute stressors and high childhood adversity had 1.20 pg/mL more IL-10 in their blood ($SE = 0.05$, $t = 3.40$, adjusted $p = 0.002$) compared to those with low levels of childhood adversity.

Discussion

This study used a detailed assessment of adversity and life stress from birth through adolescence to investigate the compounding effect of these experiences for predicting the levels of several inflammatory biomarkers in circulation. Consistent with prior literature, more frequent childhood adverse events were associated independently with higher levels of IL-6 and IL-10 across time, regardless of the types of recent stressful events experienced. These findings concur with prior evidence indicating that childhood adversity has a strong independent role in modulating inflammatory physiology across development. However, we did not find consistent support for the independent association of within-person changes in chronic or acute stressors on these inflammatory indices. Although adolescents who on average had more frequent acute stress exposure across adolescence had trajectories of increasing log IL-10, rather than the more typical decline with age.

Counter to our a priori hypothesis, trajectories of these individual immune proteins were not specifically predicted by the combination of childhood adversity, chronic stressors, and time in adolescents across development. However, consistent with our hypothesis, across time, only those adolescents with both more childhood adversity and relatively more frequent acute stressors had consistently higher levels of IL-10 as indicated by the flat stable slopes across time (Fig. 1, right panel). These results indicate that trajectories of these cytokines may remain consistently elevated in response to more recently experienced acute stressors; however, this particular pattern of association was not found with the compound effect of childhood adversity and chronic stress exposures. Considered together, the findings suggest an exaggerated inflammatory response to short-term stressors may function according to the *early-life stress sensitization model,* but only later in development (Carpenter et al., 2010; Gouin et al., 2012; Miller & Chen, 2010; Simons et al., 2019). There also may be an “incubation” effect of time on the sensitization of the inflammatory system to the combined effect of childhood adversity and acute stressors. If additional research supports this model, then efforts should be made to focus on the early identification of secondary stress exposure following childhood adversity to limit the pathophysiological effects of dysregulated cytokines and reduce potential effects on brain development and risk for subsequent psychopathology (Burke Harris et al., 2017; Kautz, 2021).

Although a comprehensive understanding of all mechanisms and processes associated with biological stress reactivity is still emerging, it is important to consider how inflammation levels may be “transducing” life experiences of chronic and acute stress exposure to initiate physiological dysregulation. Human and animal models previously have found distinct associations between elevated IL-10 levels and acute stressors, possibly as a result of effect on intracellular patterns of gene activation and transcription, which would affect synthesis and release of proteins into circulation (Hodes et al., 2014; Miller et al., 2002). Immunology

literature has found that IL-10 is a regulatory cytokine that influences the activity of many immune cells, including T-cells (Ng et al., 2013). Our findings support the potential explanation that a sustained IL-10 regulatory response is a more sensitive indicator of the reaction to acute stressors possibly due to is regulatory function within the immune system, whereas none of the pro-inflammatory markers appeared to remain elevated over time as a reaction to the experience of prolonged chronic stress. Although it should be noted that the collection of blood was not necessarily on the same day as the recent stressful event, and thus, not an immediate measure of cytokine responses to stressors. Overall, when focusing on the temporal trajectory over years, the findings indicate that individual inflammatory markers may have different patterns of response to stress exposure across adolescence. Future studies examining this dynamic period of development in the life course thus would benefit from the use of multi-cytokine arrays rather than assaying just one biomarker (Felger & Miller, 2020).

For example, a finding unique to IL-10 in this study is that, for lower childhood adversity exposure, IL-10 was elevated for adolescents experiencing a relatively higher frequency of acute stress whereas IL-10 was lower for those experiencing relatively lower frequency of acute stress exposure (Fig. 1, left panel). Although this pattern is consistent with our hypotheses, it only held *closer* in time to the first baseline assessment. Contrary to our a priori hypotheses, this relationship reversed later in development for those with lower experiences of childhood adversity. It is possible that for adolescents with lower childhood adversity, and thus, less adversity-related biological priming, there were rising levels of IL-10 in circulation across all conditions of acute stress exposure. IL-10 levels also may be influenced by the hormonal changes during puberty, especially rising levels of reproductive hormones like estrogen in pubescent females. In addition, pubertal timing may be a factor to consider; latestage (i.e., more advanced) puberty has been associated with both more interpersonal stressors and lower levels of certain immune markers, which could contribute to our findings of lower IL-10 levels for those with low childhood adversity but high acute stress exposure *only* further in time from the baseline assessment (Jiang et al., 2021; Stumper et al., 2020). To test this hypothesis more systematically, more longitudinal studies examining how trajectories of adolescent inflammatory markers are influenced by childhood adversity, recent stress exposure, and pubertal development are needed.

Clinical Implications and Limitations

Two clinical implications of the synergistic effect between childhood and recent stressors should be addressed in future research. First, there is growing evidence that adverse events during childhood may lead to structural changes in key brain regions and alterations in neurocircuitry that can influence the immune system and compromise emotional and cognitive functions (Lupien et al., 2009). Future examination of these neural and behavioral changes is needed to fully understand the compound effect of childhood adversity and recent stressors on peripheral physiology. Second, it is also important to consider the frequent observation of elevated inflammatory activity, specifically CRP, IL-6, and IL-10, in individuals who have a history of childhood adversity and are currently depressed (Danese et al., 2011; de Punder et al., 2018; Miller & Cole, 2012; Moreira et al., 2018). Our results suggest that there are both antecedent events in early childhood as well as the transitional

period during adolescence that may contribute to these observed effects of depression in adulthood (Hankin et al., 1998). There are many translational implications of the *early-life stress sensitization model* for both clinical practice and public policy.

Notwithstanding the unique aspects of our study design and analysis, several limitations should be acknowledged. One caveat is that childhood adversity was based on maternal retrospective report when the adolescent was age 12–14 years of age. Although considered to be a reliable method for assessing a history of childhood adversity, future analyses would benefit from inclusion of a personal report from the young participant. Prospective analyses would potentially be possible but that would require a very long follow-up period to capture later experiences and physiology across adolescence. Although a model involving association precludes a definitive establishment of causality, one strength of this study was the use of our prospective interview-based account of stressful life events across adolescence and employing objectively defined measures and categories of acute and chronic stressors to standardize the quantification of events across time and person. Another strength for generalizing the results was the focus on a racially and socioeconomically diverse sample, which included both females and males. The potential influence of these demographic factors was considered in the modeling by the inclusion of covariates, although we did not specifically test for differences in developmental trajectories based on these factors, which we did previously (Stumper et al., 2020). Although the current study excluded participants with developmental disorders, future work should seek to diversify the sample in that regard as well. Finally, an important strength was the examination of multiple inflammatory biomarkers across different time points, enabling us to distinguish the specific sensitivity of IL-10 levels as a novel biomarker for research on adolescence.

Conclusion

Through an examination of longitudinal trajectories of inflammatory biomarkers, this study demonstrates that childhood adversity can sensitize specific inflammatory markers in distinctive ways in response to past and recent stress experiences. The findings indicate that childhood adversity can enhance the body's reactivity to subsequent stressful events, potentially increasing the susceptibility to later psychological and physical illness. This analysis extends our knowledge on the synergistic effect of childhood and adolescent stress exposure on circulating levels of inflammatory biomarkers, illuminating the long-term impact of early-life events on pathways of biological risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

The data that support the findings of this study are available from the corresponding author, LBA, upon reasonable request.

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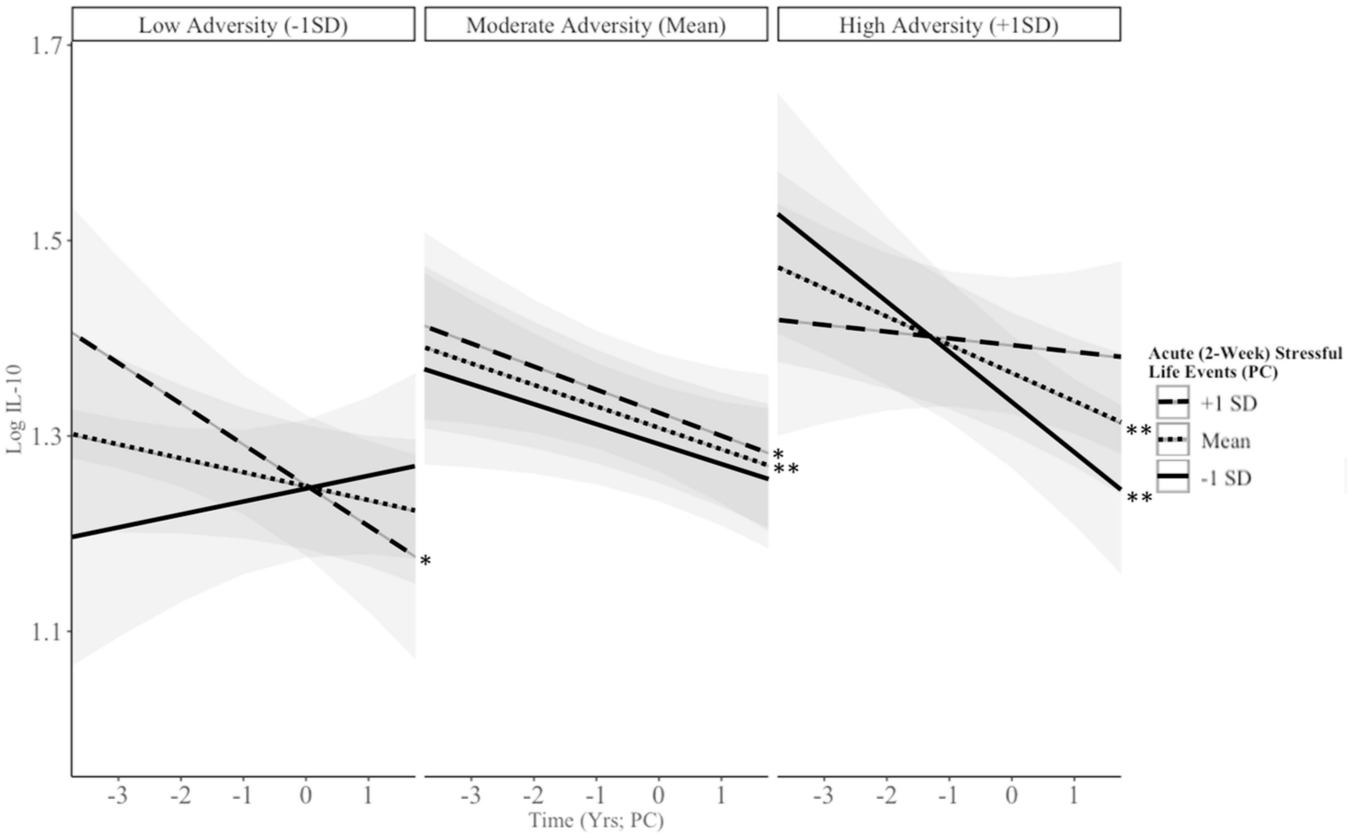

Fig. 1.

Log IL-10 as a function of time and childhood adversity faceted by acute stressful life events in the past two-weeks. Displays $\hat{y}$ for each combination of x and moderator level; Childhood Adversity = Children's Life Events Scale; IL = interleukin; PC = Person-centered variables. *****$p < 0.05$; ******$p < 0.01$ (Indicators reflect a slope that is different from zero)

Table 1

Means, standard deviations, and correlations

Variable	Format	M/N	SD/ %	1	2(a)	2(b)	3(a)	3(b)	4	5	6	7	8	9	10	11	12	13	14	15
1. Total Childhood Adversity	*Raw*	10.80	4.67																	
	Z	0.04	0.97																	
2. Chronic LEs	*Raw*	11.10	19.24																	
	Z-PC (a)	0.00	0.81	−0.00																
	Z-M (b)	−0.00	0.59	−0.01	0.00															
3. Acute (2-week) LEs	*Raw*	0.63	1.27																	
	Z-PC (a)	0.00	0.83	−0.00	0.07	0.00														
	Z-M (b)	0.00	0.56	0.08	0.00	0.23**	0.00													
4. CRP	*Raw*																			
	Log	1.78	0.61	0.11*	−0.04	−0.05	0.00	−0.08												
5.IL-6	*Raw*																			
	Log	1.49	0.30	0.17**	0.07	−0.04	−0.00	0.01	0.46**											
6. TNF-α	*Raw*																			
	Log	2.13	0.13	0.10*	0.04	0.00	0.05	0.11*	0.10*	0.19**										
7.IL-10	*Raw*																			
	Log	1.29	0.25	0.20**	0.10*	0.17**	0.11*	0.13**	0.15**	0.17**	0.48**									
8.IL-8	*Raw*																			
	Log	2.55	0.28	0.09*	0.03	−0.01	0.04	0.11*	−0.03	0.05	0.27**	0.24**								
9.BMI	*Raw*	24.27	6.20																	
	PC	0.00	2.19	0.00	−0.13**	0.00	−0.11*	−0.00	0.20**	0.10*	−0.00	−0.07	−0.04							
10. Meds Affecting Inflam. (Utilized)	*Raw*	0.23	0.42																	
	PC	0.00	0.28	−0.00	−0.13**	0.00	−0.05	0.00	0.07	0.05	0.03	−0.01	0.01	0.16**						
11. Time (Yrs)	*Raw*	17.80	1.79																	

Variable	Format	M/N	SD/ %	1	2(a)	2(b)	3(a)	3(b)	4	5	6	7	8	9	10	11	12	13	14	15
	PC	0.00	1.34	−0.00	−0.36**	0.00	−0.23**	−0.00	0.15**	0.02	−0.14**	−0.17**	−0.12**	0.45**	0.13**					
12. Number of LEIs		2.18	1.26	−0.03	0.46**	0.06	0.09*	0.00	−0.02	0.07	0.07	0.16**	−0.03	−0.24**	−0.06	−0.40**				
13. Gender (Female)		70	52.24	0.05	−0.00	0.11*	−0.00	0.01	0.11*	0.22**	−0.07	0.03	−0.07	0.00	0.00	−0.00	−0.02			
14. Race (Non-White)		81	60.45	−0.03	−0.00	−0.21**	−0.00	0.03	−0.03	0.05	−0.20**	−0.14**	−0.12*	0.00	0.00	0.00	−0.01	0.04		
15. SES (Yes, Free Lunch)		64	47.76	0.03	−0.00	−0.14**	0.00	0.03	0.04	0.12*	−0.08	0.01	−0.00	−0.00	0.00	−0.00	−0.01	0.11*	0.44**	
16. Age at Baseline		13.11	1.00	0.08	0.00	−0.09	−0.00	−0.03	0.09	0.01	−0.12**	−0.19**	−0.07	0.00	0.00	−0.00	−0.12**	0.07	0.21**	0.05

Pearson correlations coefficients are displayed. M and SD are used to represent mean and standard deviation, respectively

Z=Z-standardized variable, *PC*=Person-centered variablesl, *LEs*=Life Events Total Score, *BD*=Blood draw, *BMI*=Body mass index, *IL*=interleukin, *TNF-α*=tumor necrosis factor-alpha,

LEIs=Life Event Interviews, *SES*=socioeconomic status

* $p < 0.05$

** $p < 0.01$

Table 2

ction of Childhood Adversity and Chronic and Acute Stressful Life Events Predicts Trajectory of Inflammatory Biomarkers

	Dependent variable:														
	Log CRP			Log IL-6			LogIL-10			Log IL-8			Log TNF-α		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
ood Adversity [Z]	0.06 (0.04)	0.07 (0.05)	0.06 (0.04)	0.04* (0.02)	0.04* (0.02)	0.04* (0.02)	0.06*** (0.02)	0.05** (0.02)	0.06*** (0.02)	0.02 (0.02)	0.02 (0.02)	0.02 (0.02)	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)
Years-PC]	0.04* (0.02)	0.04* (0.02	0.04* (0.02)	0.00 (0.01)	0.00 (0.01)	0.00 (0.01)	−0.02** (0.01)	−0.02** (0.01)	−0.02** (0.01)	−0.03** (0.01)	−0.03** (0.01)	−0.03** (0.01)	−0.02*** (0.01)	−0.02*** (0.01)	−0.02*** (0.01)
ic LEs [Z-PC]	0.01 (0.03)	0.00 (0.03)	0.01 (0.03)	0.03 (0.02)	0.01 (0.02)	0.03 (0.02)	0.01 (0.01)	0.01 (0.02)	0.01 (0.01)	0.01 (0.02)	−0.01 (0.02)	0.01 (0.02)	−0.00 (0.01)	−0.00 (0.01)	−0.00 (0.01)
ic LEs [Z-M]	−0.02 (0.07)	−0.03 (0.07)	−0.02 (0.07)	−0.03 (0.03)	−0.05 (0.03)	−0.03 (0.03)	0.05* (0.02)	0.05 (0.03)	0.05* (0.02)	−0.03 (0.03)	−0.05 (0.03)	−0.03 (0.03)	−0.01 (0.01)	−0.01 (0.02)	−0.01 (0.01)
2-Week LEs [Z-PC]	0.03 (0.02)	0.03 (0.02)	0.03 (0.03)	0.00 (0.01)	0.00 (0.01)	0.01 (0.02)	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.01 (0.02)	0.01 (0.02)	−0.00 (0.02)	0.00 (0.01)	0.00 (0.01)	0.01 (0.01)
2-Week LEs [Z-M]	−0.08 (0.08)	−0.08 (0.08)	−0.07 (0.08)	0.00 (0.03)	0.01 (0.04)	0.02 (0.04)	0.04 (0.03)	0.04 (0.03)	0.04 (0.03)	0.06 (0.03)	0.06* (0.03)	0.05 (0.03)	0.02 (0.02)	0.02 (0.02)	0.03 (0.02)
ood Adversity [Z] X Time [PC]		−0.02 (0.02)	−0.02 (0.01)		0.00 (0.01)	−0.00 (0.01)		−0.01 (0.01)	−0.01 (0.01)		−0.01 (0.01)	−0.01 (0.01)		0.00 (0.00)	−0.00 (0.00)
ood Adversity [Z] X Chronic LEs]		0.05 (0.04)			0.02 (0.02)			−0.01 (0.02)			−0.00 (0.02)			0.00 (0.01)	
ic LEs [Z-PC] X Time [PC]		−0.01 (0.03)			−0.03 (0.02)			−0.01 (0.01)			−0.03 (0.02)			0.00 (0.01)	
ood Adversity [Z] X Chronic LEs] X Time [PC]		0.03 >(0.04)			0.01 (0.02)			−0.01 (0.02)			−0.00 (0.02)			−0.00 (0.01)	
ood Adversity [Z] X Acute 2-LEs [Z-PC]			0.01 (0.03)			0.01 (0.02)			0.02 (0.01)			−0.01 (0.02)			−0.00 (0.01)
2-Week LEs [Z-PC] X Time [PC]			0.01 (0.02)			0.02 (0.01)			−0.00 (0.01)			−0.01 (0.01)			0.01 (0.01)
ood Adversity [Z] X Acute 2-LEs [Z-PC] X Time [PC]			0.01 (0.03)			0.02 (0.01)			0.03** (0.01)			−0.00 (0.01)			0.01 (0.01)
nt	1.09* (0.54)	1.10* (0.54)	1.10* (0.54)	1.50*** (0.25)	1.49*** (0.25)	1.53*** (0.25)	1.84*** (0.19)	1.84*** (0.19)	1.84*** (0.19)	2.89*** (0.21)	2.88*** (0.21)	2.88*** (0.21)	2.34*** (0.11)	2.34*** (0.11)	2.35*** (0.11)
vations	462	462	462	462	462	462	462	462	462	462	462	462	462	462	462

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			Dependent variable:													
			Log CRP			Log IL-6			LogIL-10			Log IL-8			Log TNF- α	
			(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
	0.08	0.09	0.09			0.10	0.11	0.11	0.16	0.16	0.17	0.07	0.07	0.07	0.09	0.10	0.10
nal)																	
m	*Variance*	*Components*															
s																	
scent,	0.18*	0.18*			0.18*	0.03*	0.03*	0.03*	0.02*	0.02*	0.02*	0.01*	0.01*	0.01*	0.01*	0.01*	0.01*
vation	0.17	0.17			0.17	0.05	0.05	0.05	0.04	0.04	0.04	0.06	0.06	0.06	0.01	0.01	0.01
σ^2																	

ardized coefficients are presented with standard errors in parentheses from multilevel model regressions. All analyses controlled for Body Mass Index (Person-centered), Medications Affecting nation (Person-centered), Gender (Female), Race (Non-White), Socioeconomic Status (Yes Free Lunch), Age at Baseline, and Number of Life Event Interviews. The numbers (1) through (10) at the e table refers to statistical models 1 – 10

leukin, *TNF-α*=tumor necrosis factor-alpha, Z=Z-Standardized variable, *PC*=Person-centered variables, *LEs*=Life Events Total Score

5;

01;

.001 (according to profile confidence interval for τ^2_{00} and according to deviance test for τ^2_{11})