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Maternal early life stress is associated with pro-inflammatory processes during pregnancy

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Abstract

Early life stress (ELS) is common in the United States and worldwide, and contributes to the development of psychopathology in individuals with these experiences and their offspring. A growing body of research suggests that early life stress may contribute to adverse health partly through modulation of immune (and particularly inflammatory) responses. Therefore, increased maternal prenatal inflammation has been proposed as a mechanistic pathway by which the observed cross-generational effects of parental early life stress on child neuropsychiatric outcomes may be exerted. We examined associations between early life stress and molecular markers of inflammation (specifically pro-inflammatory gene expression and receptor-mediated transcription factor activity) and a commonly studied circulating marker of inflammation (C-Reactive Protein) in a diverse group of women in or near their third trimester of pregnancy, covarying for age,

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2022.10.012.

race/ethnicity, BMI, concurrent infection, concurrent perceived stress, and per capita household income. Mothers who experienced higher levels of early life stress had significantly increased pro-inflammatory (NF-κB) and decreased anti-viral (IRF) transcription factor activity. Transcripts that were up or down regulated in mothers with high ELS were preferentially derived from both CD16+ and CD16− monocytes. Early life stress was not associated with elevated CRP. Taken together, these findings provide preliminary evidence for an association between ELS and a pro-inflammatory transcriptional phenotype during pregnancy that may serve as a mechanistic pathway for cross-generational transmission of the effects of early life stress on mental and physical health.

Keywords

Early life stress; Inflammation; Pregnancy; Cross-generational transmission of adversity; Conserved transcriptional response to adversity; C-Reactive Protein

1. Introduction

Half of children in the United States and worldwide experience at least one type of early life stress (ELS) in the form of trauma, abuse, neglect or institutional care (Kessler et al., 2010; McLaughlin et al., 2012). These early experiences have lasting health effects. ELS is implicated in 30% of adult mental health diagnoses, and is linked to risk for cognitive decline, cancer, diabetes, and cardiovascular disease, as well as a 20-year decrease in life expectancy (Kessler et al., 2010; Brown et al., 2009; Friedman et al., 2015; Murphy et al., 2017). Additionally, the impact of ELS in one generation may extend into the next. For example, children of parents with ELS exposure have an increased prevalence of internalizing and externalizing psychopathology, developmental disorders (e.g. autism), behavioral challenges (e.g. conduct disorder), and generally poor physical health (Jovanovic et al., 2011; Marr et al., 2018; Rijlaarsdam et al., 2014; Roberts et al., 2014; Roberts et al., 2013). Importantly, children of parents who experienced ELS are at substantially increased risk for these negative health outcomes even if they grew up in different environments from their parents (Jovanovic et al., 2011; Marr et al., 2018; Rijlaarsdam et al., 2014; Roberts et al., 2014; Roberts et al., 2013; Buss et al., 2017).

One way that ELS is thought to contribute to adverse health in individuals and their children is via the immune system. ELS has been consistently associated with increased chronic inflammation through adulthood, which in turn confers risk for cardiovascular and autoimmune diseases, psychiatric illness, obesity, and diabetes, among others (Bilbo and Schwarz, 2009; Slavich, 2015). Pro-inflammatory phenotypes may impact not only the health of individuals who have experienced ELS, but the health of their offspring as well. Maternal prenatal inflammation has been proposed as a pathway for the observed cross-generational effects of parental ELS on child neuropsychiatric outcomes (Buss et al., 2017; Brown and Meyer, 2018). Given that pregnancy initiates comprehensive changes to maternal immune function in general, and inflammation in particular, characterizing the effects of ELS on inflammatory processes during pregnancy merits its own investigation (Challis et al., 2009; Gillespie et al., 2019). However, very little work has probed how

ELS interacts with maternal-placental-fetal gestational inflammatory biology. The current study seeks to explore ELS effects on inflammatory processes during pregnancy, leveraging both circulating markers of inflammation (C Reactive Protein; CRP) and measures of pro-inflammatory gene expression and receptor-mediated transcription factor activity.

1.1. ELS, inflammation, and pregnancy

Three lines of evidence suggest that pregnancy may potentiate pro-inflammatory phenotypes for women exposed to ELS. First, recent meta-analyses and systematic reviews point to small but consistent effects of various forms of ELS on elevated circulating levels of systemic inflammation markers (especially CRP) in adults of childbearing age (Baumeister et al., 2016; Kuhlman et al., 2020). These findings have been replicated in large and diverse samples (Aschbacher et al., 2021; Cicchetti et al., 2015; John-Henderson et al., 2020; Pollitt et al., 2007). Second, concurrent psychosocial stress can potentiate both CRP (Coussons-Read et al., 2007) and inflammatory gene expression during pregnancy (Ross et al., 2019). These phenotypes may in turn impact maternal and child health. Elevated prenatal circulating inflammatory markers and pro-inflammatory gene expression are associated with low birth weight and preterm birth, both predictors of poor long-term child outcomes (Ross et al., 2019; Kuzawa et al., 2017; Romero et al., 2006), and prenatal inflammation also appears to affect early child neurodevelopment (Graham et al., 2018; Rasmussen et al., 2019), psychological outcomes (Graham et al., 2018), and clinical diagnoses (Zerbo et al., 2016). Finally, there have been a handful of studies that have examined circulating inflammatory markers in pregnant ELS-exposed women. These studies have yielded mixed results, with some finding positive links between ELS exposure and inflammatory markers (Mitchell et al., 2018; McCormack et al., 2021), and others not (Aschbacher et al., 2021; Walsh et al., 2016; Hantsoo et al., 2019). These limited findings suggest the ELS pro-inflammatory phenotype persists and may be exacerbated during pregnancy, but additional research is sorely needed, including replication with other non-circulating measures of inflammatory processes.

In recent years, research evaluating long-term consequences of ELS on immunity has shifted from focusing exclusively on circulating systemic markers of inflammation like CRP to also examining complementary measures of cell-level gene expression and receptor-mediated transcription factor activity (Gillespie et al., 2019). Fluctuations in gene expression can occur as a result of psychosocial experiences, and have been proposed as a theoretical mechanism for biological embedding of ELS (Gillespie et al., 2019). Notably, just one study to date has probed the relationship between ELS and inflammatory gene expression during pregnancy, and this study focused almost exclusively on genomic activity related to macrophages, without examining transcription factor activity (Aschbacher et al., 2021). While there are multiple lines of work that point to a relationship between ELS and pro-inflammatory activity (e.g. Zajdel et al., 2019), the conserved transcriptional response to adversity (CTRA) is thought to be a particularly sensitive measure of the biological embedding of early life stress (Cole et al., 2012; Kohrt et al., 2016). The CTRA, which is characterized by upregulation of pro-inflammatory gene expression and down-regulation of genes associated with antiviral responses (e.g. Interferon Type I), was initially established as a measure of the impacts of *chronic* stress on pro-inflammatory gene expression (Cole,

2019). However, recent human and animal work has established a similar relationship between *early life* stress and the CTRA across development (Cole et al., 2012; Schwaiger et al., 2016; Spindola et al., 2017), particularly for the pro-inflammatory component of the CTRA (Bower et al., 2020; Marie-Mitchell and Cole, 2021). Transcription factor activity and transcript origin analysis have also been incorporated into several analytic suites as markers of the CTRA (Cole, 2019). In particular, activity of nuclear factor-κB (NF-κB; a pro-inflammatory transcription factor), Interferon Response Factor (IRF; associated with antiviral transcription), and the glucocorticoid receptor (GR) have all been closely associated with psychosocial stress exposures, and with ELS exposures in particular (Bower et al., 2020; Baes et al., 2012; Pace et al., 2012).

To probe how ELS exposure shapes inflammatory processes during pregnancy, the current study examined the relationship between 1) ELS and CRP and 2) ELS and pro-inflammatory gene expression and transcription factor activity (NF-κB) during or just before the third trimester. We hypothesized that mothers with higher levels of ELS would display elevated levels of CRP during the third trimester, as well as elevated pro-inflammatory gene expression and related transcription factor activity. In addition, we predicted that mothers with greater ELS would have lower IRF and GR transcription factor activity, consistent with the CTRA.

2. Methods and materials

2.1. Participants

All analyses were conducted using data from a follow up to the Community Child Health Network, a five-site longitudinal study of low-income Black, Latina, and/or non-Hispanic white women (Dunkel Schetter et al., 2013). Of the original 2,510 women in the Community Child Health Network cohort, 343 at three sites reported a subsequent pregnancy during the original follow-up period and participated in this follow-up study. The present manuscript reports on data collected from all women who agreed to participate in this follow-up study and who provided data for the ELS assessment and the inflammatory markers of interest. As a result, 90 women from three sites (Washington, DC, Lake County, IL, or eastern North Carolina) were included in the CRP analysis. 60 of these 90 women had additional blood spots banked and available for the gene expression analysis. While this data was collected during a scheduled third trimester visit (27+ weeks gestational age), 6 mothers participated in that study visit prior to 27 weeks gestation for convenience. As a result, gestational age for this sample ranged from 22.7 to 40.29 weeks, with a mean gestational age of just over 32 and a half weeks. Approximately half of the women in the final sample identified as Latina (primarily foreign-born, race unknown), a quarter as white, and a quarter as Black, and participants were on average 28–29 years old during the third trimester of pregnancy when data were collected. On average, mothers reported moderate perceived stress relative to population norms (M_{PSS} = 18.29). Additional descriptive information can be found in Table 1 and in the supplement.

2.2. Early life stress

ELS was assessed using an adapted measure that included 3 items from the Adverse Childhood Experiences Questionnaire (ACE) and 5 items from the Risky Families Questionnaire (RFQ) (Felitti et al., 1998; Taylor et al., 2004). The questions drawn from the RFQ were parallel to items on the original ACE and thus the adapted measure approximated the original ACE. The ACE is a 10-item retrospective self-report assessment of ELS, and has been consistently shown across a variety of large samples to predict later physical and mental health outcomes (Brown et al., 2009; Felitti et al., 1998). The Risky Families Questionnaire (Taylor et al., 2004) is adapted from the ACE measure, and assesses the home environment during childhood and adolescence, probing the extent to which participants felt loved and cared for, were exposed to emotional or physical abuse or neglect, or had a household member go to prison, struggle with substance abuse, or experience severe mental illness. Scores on this measure ranged from 0 to 8 and did not include sexual abuse and neglect. All items and scoring information can be found in Supplemental Table 1. To aid interpretation of fold-differences in gene expression, and consistent with prior work suggesting that ACEs exhibit a dose–response relationship with health outcomes (Danese et al., 2009), mothers were divided into high (2+ ACEs reported), mid (1 ACE reported) and low (0 ACEs reported) ELS groups.

2.3. Inflammatory markers

2.3.1. Collection procedure—High-sensitivity CRP and gene expression data were assayed from non-fasting dried blood spots (DBS) collected from women by trained research staff during home visits. Home visits consisted of a structured interview with blood pressure measurements before and after, followed by saliva collection, a third blood pressure measurement, and anthropometric measures (height, weight, BMI, waist and hip circumference). The DBS samples were then collected using sterile contact-activated lancets, and blood drops were caught on standard blood spot collection cards. Samples used for CRP and gene expression analyses were collected on separate cards. This approach is well-validated for both analyses of interest, and is particularly beneficial for large scale, multi-site studies like this one, as it is relatively non-invasive and can be utilized by nonmedical staff (McDade et al., 2016; McDade, 2014). Blood spot collection cards were left to dry for 30 min after initial data collection, and then stored at −30 °C in plastic bags containing desiccant packs.

2.3.2. CRP analyses—Samples were assayed for CRP at ZRT laboratories (Beaverton, OR) using a high-sensitivity enzyme-linked immunosorbent assay (ELISA) protocol created specifically for use with blood spots. The lower limit for CRP detection was 0.1 mg/L. Intra-assay coefficients of variation spanned from 4.77% to 7.73% and inter-assay coefficients of variation ranged from 4.86% to 11.29%. Because CRP levels are often elevated during pregnancy, we did not exclude participants with CRP values greater than 10 mg/L, and instead excluded only participants with CRP values greater or less than three standard deviations from the sample mean, consistent with prior work in a similar Community Child Health Network cohort (Morgan et al., 2020). Third trimester CRP data was therefore excluded for only one mother (CRP = 29.2 mg/L), resulting in a final CRP sample of 89

women (analyses including this mother are reported in the supplement). Raw CRP values were log10 transformed prior to analysis in accordance with standard procedure.

2.3.3. Gene expression analyses—We probed ELS-linked differences in genome-wide transcriptional profiles to test for increased activity of pro-inflammatory transcription factor NF-κB (as part of the conceptual CTRA). We chose NF-κB because it is a key regulator of inflammatory functioning that has been consistently linked to ELS, concurrent stress responses, and normative immune changes in pregnancy (Challis et al., 2009; Bower et al., 2020; Pace et al., 2012; Chen et al., 2011; Li and Verma, 2002), in addition to concurrent psychosocial stress in this cohort (Ross et al., 2019). Consistent with canonical CTRA analyses, we also examined anti-viral (Interferon Response Factor) transcription factor activity and glucocorticoid receptor (GR) as secondary variables of interest. Lastly, as a purely exploratory post-hoc analysis, we evaluated Early Growth Response 1 (EGR1) transcription factor activity, given its association with ELS-induced changes to hypothalamic–pituitaryadrenal axis functioning (which supports stress responses) and theorized role in ELS-driven changes to prenatal biology (Gillespie et al., 2019).

Following the initial storage at −30 °C described above, samples intended for gene expression analysis were stored at −80 °C and then analyzed at the UCLA Social Genomics Core Laboratory for RNA extraction in accordance with previously reported procedures (Ross et al., 2019). RNA samples were converted to cDNA libraries using the QuantSeq 3′ mRNA-Seq Library Prep Kit FWD for Illumina (a sensitive assay well suited for analysis of DBS data, as it is reliable even for somewhat degraded samples) and sequenced using an Illumina HiSeq4000 instrument in the UCLA Neuroscience Genomics Core Laboratory, following manufacturer guidelines. Although DBS samples typically do not yield enough RNA for pre-assay quantification of RNA integrity, we applied standard endpoint quality controls to ensure data quality (McDade et al., 2016). All samples analyzed met the requisite quality assurance thresholds for DBS RNAseq samples (>10 million single-strand 65-nucleotide reads per sample, >90 % of reads aligning to the reference human genome, and a correlogram average profile ≥0.80).

2.4. Statistical analyses

The relationship between ELS and log-transformed third-trimester CRP was analyzed using multiple regression in SPSS. This analysis controlled for age, race/ethnicity, body mass index (BMI), infection status, per capita household income, and concurrent perceived stress, measured using the Perceived Stress Scale (Cohen, 1988). Additional information about covariates is included in the supplement.

Consistent with standard approaches for targeted hypothesis testing in genome-wide transcriptional profiles (Ross et al., 2019; Cole et al., 2003; Cole et al., 2005; Miller et al., 2008; Fredrickson et al., 2013), gene expression values were normalized to reflect gene transcripts per million total transcripts (TPM), floored at 1 TPM. These values were then log2 transformed, and transcripts that varied by <0.5 log2 units across individuals were excluded from analyses. Genes that showed a twofold difference in average expression between women with high early life stress exposure (2 + ACEs) and low exposure (0

ACEs) were analyzed using a 2-sample variant of the Transcription Element Listening System (TELiS; Cole et al., 2005). This analysis quantified activity of NF-κB, IRF, and glucocorticoid receptor (GR) transcription factor-binding motifs (TFBMs) within the promoters of the differentially expressed genes (using TFBMs from the TRANSFAC database), using values averaged across nine technical specifications using combinations of promoters of different lengths (−300, −600, −1000, and + 200 bp, respectively), and TFBM detection stringency (MatSim.80, 0.90, 0.95). To adjust for correlation across genes, statistical testing for all analyses utilized standard errors produced using bootstrap resampling of linear model residual vectors. This analysis also controlled for age, race/ethnicity, BMI, concurrent infection, per capita household income, and concurrent perceived stress.

3. Results

3.1. Sample characteristics

The present sample was a racially and ethnically diverse group (majority Latina) of women from primarily low-income backgrounds. Demographic information for participants included in the CRP and CTRA analyses are both reported in Table 1. Women included in both the gene expression and CRP analyses reported an average of approximately 1.3 adverse childhood experiences (range: 0–8), with roughly 40% of women reporting 0 ACEs (low ACE group) and 30% reporting 2 or more (high ACE group). This ACE prevalence is consistent with previously reported national averages (McLaughlin et al., 2012).

3.2. Early life stress exposure and CRP

The 89 women in the larger sample had average CRP of 7.17 mg/L (sd = 4.63), with 69 (78%) of CRP values consistent with elevated risk for cardiovascular disease (>3 mg/L). Third trimester CRP levels did not differ between women with high (2+ ACEs) or low (0 ACEs) reported ELS, controlling for age, race/ethnicity, BMI, infection, concurrent perceived stress, and per capita household income ($\beta = 0.153$, $t = 1.038$, $p = 0.305$). This finding held when this analysis was repeated including the mother with a CRP of 29.2 mg/L (see Supplement). BMI was significantly associated with third-trimester CRP values in this sample ($\beta = 0.457$, $t = 3.274$, $p = 0.002$), consistent with previous work.

3.3. Early life stress exposure and gene expression

Women with higher levels of ELS (2+ ACEs) had 303 gene transcripts showing a greater than 2-fold difference in third trimester blood samples relative to women with low ELS exposure (0 ACEs). Analyses of these gene transcripts were indicative of increased activity of pro-inflammatory transcription factor NF-κB (log ratio of TFBMs in promoters of up- vs down-regulated genes = 0.827, $p = 0.043$) in mothers with high ELS (Fig. 1). Additionally, these analyses indicated decreased activity of anti-viral transcription factor IRF (ratio of TFBMs in promoters of down- vs up-regulated genes = −0.753, $p = 0.048$). We found no evidence of decreased glucocorticoid receptor activity (log ratio of TFBMs in promoters of down- vs up-regulated genes = −0.061, $p = 0.736$). Post-hoc unadjusted analyses and a secondary analysis showing BMI is positively associated with NF-κB are reported in the Supplement. Lastly, our exploratory analyses did not reveal increased EGR1 transcription

factor activity (log ratio of TFBMs in promoters of up- vs down-regulated genes = −0.363, p = 0.437).

As visualized in Fig. 2, transcript origin analyses suggested gene transcripts that were up-regulated in mothers with higher levels of ELS (relative to mothers with low ELS) were preferentially derived from both immature/pro-inflammatory CD16− "classical" monocytes and mature CD16+ "non-classical/trophic" monocytes (mean diagnosticity score: 0.191 ± 0.055, $p < 0.001$; 0.106 ± 0.034, $p = 0.001$, respectively). Similarly, gene transcripts that were down-regulated in mothers with high levels of ELS were likewise derived predominately from both CD16− and CD16 + monocytes (0.115 ± 0.058, $p = 0.024$; 0.172 ± 0.036, $p < 0.001$, respectively).

4. Discussion

This study sought to evaluate the effects of early life stress exposures on complementary genomic and circulating measures of inflammation in women in their third trimester, as an initial empirical exploration of the effects of early life stress on pro-inflammatory gene expression during pregnancy. There was no relationship between ELS and third-trimester CRP. However, we found that mothers with higher levels of ELS exposure displayed elevated pro-inflammatory and reduced anti-viral transcription factor activity. This transcriptional phenotype may serve as a mechanistic pathway linking ELS exposure to prenatal maternal and child mental and physical health outcomes (Buss et al., 2017; Gillespie et al., 2019).

Our results are consistent with studies of the conserved transcriptional response to adversity in non-pregnant adults exposed to ELS, and may indicate that the pro-inflammatory phenotype observed following ELS persists during pregnancy. Furthermore, these findings implicate a possible mechanistic pathway for the well-established relationship between ELS exposure and indices of perinatal outcomes (e.g., preterm birth). We did not find the hypothesized association between ELS and CRP in our sample (n = 89), further contributing to mixed reported findings in smaller samples (Aschbacher et al., 2021; Mitchell et al., 2018). Of note, systemic circulating markers of inflammation can derive from outside the circulating immune cell pool (e.g., from adipose tissue), and CRP in particular is strongly associated with BMI in the broader literature and in our sample (where 70% of participants were overweight or obese during the pre/inter-pregnancy interval), possibly complicating the use of this marker during pregnancy.

Pregnancy is a unique biological period characterized by immense psychosocial, physiological, and neurobiological change (Davis and Narayan, 2020). This developmental period programs later mental and physical health outcomes for both mothers and children (Buss et al., 2017; Glynn et al., 2018). Thus, understanding how this biological transition is shaped by stress processes is critical for supporting healthy maternal and child development (Dunkel Schetter, 2011). Pregnancy may also be a critical period for the intergenerational transmission of early adversity, as it is a point of maximal biological transfer between mothers and infants and a time of unique biological and psychological susceptibility to stress phenotypes. Given the interest in these issues, it is notable that so little work has specifically

probed mechanistic pathways. Importantly, one recent study found that only adversity during early life or pregnancy (but not total life adversity) impacted a macrophage-focused measure of pro-inflammatory and anti-viral gene expression during pregnancy (Aschbacher et al., 2021). Integrated with recent work in our sample that suggests that concurrent stress during pregnancy (but not preconception stress) was associated with elevated pro-inflammatory gene expression (Ross et al., 2019), our finding that early life stress is linked to increased pro-inflammatory gene expression during pregnancy provides additional evidence for the potentially unique importance of experiences during early life and pregnancy. Prior work has suggested that other periods of biopsychosocial transition such as puberty can serve as windows of opportunity – or alternatively of risk – following early life adversity (Gunnar et al., 2019; Méndez Leal and Silvers, 2021). Similarly, pregnancy may be a particularly vulnerable period during which large scale changes in biological processes potentiate later maternal physical and mental health outcomes, but also potentially provide an optimal intervention opportunity (Davis and Narayan, 2020).

The current study has several limitations. First, although our CRP sample is slightly larger than those in previous reported work and this study has the added contribution of examining pro-inflammatory sequelae of ELS in a diverse, low-income sample of women historically underrepresented in participant pools in the field, both our CRP and gene expression analyses would benefit from greater power. Second, measures of gene expression and circulating systemic inflammation in this study relied on banked dried blood spots, which provide somewhat noisier transcriptome profiles than those assayed from traditional venipuncture samples (McDade et al., 2016). However, use of this less-invasive sampling approach facilitates community-based data collection in large, underrepresented samples like the original cohort for this study, and the detection of the pro-inflammatory profile in this context is indicative of the strength of the signal of interest. Additionally, given the sample size and sampling technique, this study focused on a suite of a-priori genomic hypotheses – future, hypothesis-free work in larger samples may identify additional correlates of ELS. Lastly, there is relatively little variability in ELS exposure in our sample (although ELS prevalence in our sample is consistent with the national average), and this ELS measure does not provide granular information on type or severity of ELS exposure.

Our findings pose important outstanding questions. Future work in larger studies with more comprehensive ELS assessments will permit further examination of the potentially differential effects of threat and deprivation, as has been observed in studies of ELS-associated changes to circulating inflammatory markers in non-pregnant adults and psychological outcomes during pregnancy (Coelho et al., 2014; Merrick et al., 2020). Recent evidence suggests that it may also be important to examine positive childhood experiences in order to fully characterize links between early experiences and psychosocial health during pregnancy (Merrick et al., 2020).

Ongoing research should examine changes in inflammation across pregnancy. To date, there has been no longitudinal evaluation of pro-inflammatory gene expression or associated transcription factor activity during pregnancy, and longitudinal patterns of circulating inflammation across pregnancy vary by marker measured (Christian and Porter, 2014; Ross et al., 2016; Ferguson et al., 2014; Stewart et al., 2007; Ross et al., 2022). Preliminary

evidence suggests that maternal CRP normatively peaks during the first trimester and then decreases over the course of pregnancy, particularly in mothers with high BMI (Christian and Porter, 2014). However, as these studies assess changes across timepoints that broadly correspond with trimesters, there is little information on how these fluctuations occur over the course of gestation (including in the gestational age range included in our sample). Given that the present study only examines cross-sectional measures of inflammation at a single point during pregnancy, future work might seek to test individual trajectories of ELS-linked inflammation to examine normative changes in inflammation across gestation and assess whether the observed ELS-associated differences in inflammatory processes present prior to pregnancy or are enhanced or reduced during gestation. Continued work on the consequences of ELS on prenatal health would benefit from longitudinal, mechanism-focused assessments: Specifically, it would be valuable to build on recent work (Ross et al., 2022) to characterize inflammatory markers from pre-conception through pregnancy and the postpartum period. This would provide insight into possible pregnancy-induced changes in ELS-associated pro-inflammatory biology (e.g. selective reactivation), with important implications for maternal and child physical and mental health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data will be made available on request.

Abbreviations:

ELS	Early life stress
CRP	C-Reactive Protein
CTRA	Conserverd transcriptional response to adversity
NF-κB	Nuclear Factor-κB
IRF	Interferon Response Factor
GR	glucocorticoid receptor
EGR1	Early Growth Response Factor 1

References

Aschbacher K, Hagan M, Steine IM, Rivera L, Cole S, Baccarella A, et al. , 2021. Adversity in early life and pregnancy are immunologically distinct from total life adversity: macrophage-associated phenotypes in women exposed to interpersonal violence. Transl. Psychiatry 11, 1–9. [PubMed: 33414379]

Baes CVW, de Tofoli SM, C, Martins CMS, Juruena MF, 2012. Assessment of the hypothalamic–pituitary–adrenal axis activity: glucocorticoid receptor and mineralocorticoid receptor function in depression with early life stress – a systematic review. Acta Neuropsychiatrica 24, 4–15. [PubMed: 28183380]

Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V, 2016. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α [no. 5]. Mol. Psychiatry 21, 642–649. [PubMed: 26033244]

Bilbo SD, Schwarz JM, 2009. Early-life programming of later-life brain and behavior: a critical role for the immune system. Front. Behav. Neurosci 3 10.3389/neuro.08.014.2009.

Bower JE, Kuhlman KR, Ganz PA, Irwin MR, Crespi CM, Cole SW, 2020. Childhood maltreatment and monocyte gene expression among women with breast cancer. Brain Behav. Immun. 88, 396–402. [PubMed: 32247915]

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, 389–396. [PubMed: 19840693]

Brown AS, Meyer U, 2018. Maternal immune activation and neuropsychiatric illness: a translational research perspective. AJP 175, 1073–1083.

Buss C, Entringer S, Moog NK, Toepfer P, Fair DA, Simhan HN, et al. , 2017. Intergenerational transmission of maternal childhood maltreatment exposure: implications for Fetal brain development. J. Am. Acad. Child Adolesc. Psychiatry 56, 373–382. [PubMed: 28433086]

Challis JR, Lockwood CJ, Myatt L, Norman JE, Strauss JF, Petraglia F, 2009. Inflammation and pregnancy. Reprod. Sci. 16, 206–215. [PubMed: 19208789]

Chen E, Miller GE, Kobor MS, Cole SW, 2011. Maternal warmth buffers the effects of low early-life socioeconomic status on pro-inflammatory signaling in adulthood [no. 7]. Mol. Psychiatry 16, 729–737. [PubMed: 20479762]

Christian LM, Porter K, 2014. Longitudinal changes in serum proinflammatory markers across pregnancy and postpartum: effects of maternal body mass index. Cytokine 70, 134–140. [PubMed: 25082648]

Cicchetti D, Handley ED, Rogosch FA, 2015. Child maltreatment, inflammation, and internalizing symptoms: Investigating the roles of C-reactive protein, gene variation, and neuroendocrine regulation. Dev. Psychopathol. 27, 553–566. [PubMed: 25997771]

Coelho R, Viola TW, Walss-Bass C, Brietzke E, Grassi-Oliveira R, 2014. Childhood maltreatment and inflammatory markers: a systematic review. Acta Psychiatr. Scand. 129, 180–192. [PubMed: 24205846]

Cohen S (1988): Perceived stress in a probability sample of the United States. The Social Psychology of Health. Thousand Oaks, CA, US: Sage Publications, Inc, pp 31–67.

Cole SW, 2019. The conserved transcriptional response to adversity. Curr. Opin. Behav. Sci. 28, 31–37. [PubMed: 31592179]

Cole SW, Galic Z, Zack JA, 2003. Controlling false-negative errors in microarray differential expression analysis: a PRIM approach. Bioinformatics 19, 1808–1816. [PubMed: 14512352]

Cole SW, Yan W, Galic Z, Arevalo J, Zack JA, 2005. Expression-based monitoring of transcription factor activity: the TELiS database. Bioinformatics 21, 803–810. [PubMed: 15374858]

Cole SW, Conti G, Arevalo JMG, Ruggiero AM, Heckman JJ, Suomi SJ, 2012. Transcriptional modulation of the developing immune system by early life social adversity. PNAS 109, 20578–20583. [PubMed: 23184974]

Coussons-Read ME, Okun ML, Nettles CD, 2007. Psychosocial stress increases inflammatory markers and alters cytokine production across pregnancy. Brain Behav. Immun. 21, 343–350. [PubMed: 17029703]

Danese A, Moffitt TE, Harrington H, Milne BJ, Polanczyk G, Pariante CM, et al. , 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, 1135–1143. [PubMed: 19996051]

Davis EP, Narayan AJ, 2020. Pregnancy as a period of risk, adaptation, and resilience for mothers and infants. Dev. Psychopathol. 32, 1625–1639. [PubMed: 33427164]

Dunkel Schetter C, 2011. Psychological science on pregnancy: stress processes, biopsychosocial models, and emerging research issues. Annu. Rev. Psychol. 62, 531–558. [PubMed: 21126184]

Dunkel Schetter C, Schafer P, Lanzi RG, Clark-Kauffman E, Raju TNK, Hillemeier MM, 2013. Shedding light on the mechanisms underlying health disparities through community participatory methods: the stress pathway. Perspect. Psychol. Sci. 8, 613–633. [PubMed: 26173227]

Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. , 1998. 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, 245–258. [PubMed: 9635069]

Ferguson KK, McElrath TF, Chen Y-H, Mukherjee B, Meeker JD, 2014. Longitudinal profiling of inflammatory cytokines and C-reactive protein during uncomplicated and preterm pregnancy. Am. J. Reprod. Immunol. 72, 326–336. [PubMed: 24807462]

Fredrickson BL, Grewen KM, Coffey KA, Algoe SB, Firestine AM, Arevalo JMG, et al. , 2013. A functional genomic perspective on human well-being. PNAS 110, 13684–13689. [PubMed: 23898182]

Friedman EM, Karlamangla AS, Gruenewald T, Koretz B, Seeman TE, 2015. Early life adversity and adult biological risk profiles. Psychosom. Med. 77, 176–185. [PubMed: 25650548]

Gillespie SL, Cole SW, Christian LM, 2019. Early adversity and the regulation of gene expression: implications for prenatal health. Curr. Opin. Behav. Sci. 28, 111–118. [PubMed: 31815157]

Glynn LM, Howland MA, Fox M, 2018. Maternal programming: application of a developmental psychopathology perspective. Dev. Psychopathol. 30, 905–919. [PubMed: 30068423]

Graham AM, Rasmussen JM, Rudolph MD, Heim CM, Gilmore JH, Styner M, et al. , 2018. Maternal systemic interleukin-6 during pregnancy is associated with newborn amygdala phenotypes and subsequent behavior at 2 years of age. Biol. Psychiatry 83, 109–119. [PubMed: 28754515]

Gunnar MR, DePasquale CE, Reid BM, Donzella B, 2019. Pubertal stress recalibration reverses the effects of early life stress in postinstitutionalized children. PNAS 116, 23984–23988. [PubMed: 31712449]

Hantsoo L, JaŠarević E, Criniti S, McGeehan B, Tanes C, Sammel MD, et al. , 2019. Childhood adversity impact on gut microbiota and inflammatory response to stress during pregnancy. Brain Behav. Immun. 75, 240–250. [PubMed: 30399404]

John-Henderson NA, Henderson-Matthews B, Ollinger SR, Racine J, Gordon MR, Higgins AA, et al. , 2020. Adverse childhood experiences and immune system inflammation in adults residing on the blackfeet reservation: the moderating role of sense of belonging to the community. Ann. Behav. Med. 54, 87–93. [PubMed: 31282543]

Jovanovic T, Smith A, Kamkwalala A, Poole J, Samples T, Norrholm SD, et al. , 2011. Physiological markers of anxiety are increased in children of abused mothers. J. Child Psychol. Psychiatry 52, 844–852. [PubMed: 21501167]

Kessler RC, McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, et al. , 2010. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. Br. J. Psychiatry 197, 378–385. [PubMed: 21037215]

Kohrt BA, Worthman CM, Adhikari RP, Luitel NP, Arevalo JMG, Ma J, et al. , 2016. Psychological resilience and the gene regulatory impact of posttraumatic stress in Nepali child soldiers. PNAS 113, 8156–8161. [PubMed: 27402736]

Kuhlman KR, Horn SR, Chiang JJ, Bower JE, 2020. Early life adversity exposure and circulating markers of inflammation in children and adolescents: a systematic review and meta-analysis. Brain Behav. Immun. 86, 30–42. [PubMed: 30999015]

Kuzawa CW, Fried RL, Borja JB, McDade TW, 2017. Maternal pregnancy C-reactive protein predicts offspring birth size and body composition in metropolitan Cebu, Philippines. J. Dev. Origins Health Dis. 8, 674–681.

Li Q, Verma IM, 2002. NF-κB regulation in the immune system [no. 10]. Nat. Rev. Immunol. 2, 725–734. [PubMed: 12360211]

Marie-Mitchell A, Cole SW (2021). Adverse childhood experiences and transcriptional response in school-age children. Dev. Psychopathol. 1–7.

Marr M, Graham AM, Feczko E, Thomas E, Sturgeon D, Schifsky E, et al. , 2018. 3.20 The trajectory of maternal prenatal stress is associated with newborn amygdala functional connectivity and infant negative affect development over the first two years of life. J. Am. Acad. Child Adolesc. Psychiatry 57, S188.

McCormack C, Lauriola V, Feng T, Lee S, Spann M, Mitchell A, et al. , 2021. Maternal childhood adversity and inflammation during pregnancy: Interactions with diet quality and depressive symptoms. Brain Behav. Immun. 91, 172–180. [PubMed: 33031919]

McDade TW, 2014. Development and validation of assay protocols for use with dried blood spot samples. Am. J. Hum. Biol. 26, 1–9. [PubMed: 24130128]

McDade TW, Ross MK, Fried LR, Arevalo JMG, Ma J, Miller GE, Cole SW, 2016. Genome-wide profiling of RNA from dried blood spots: convergence with bioinformatic results derived from whole venous blood and peripheral blood mononuclear cells. Biodemogr. Soc. Biol. 62, 182–197.

McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, Kessler RC, 2012. Childhood adversities and first onset of psychiatric disorders in a national sample of US adolescents. Arch. Gen. Psychiatry 69, 1151–1160. [PubMed: 23117636]

Méndez Leal AS, Silvers JA, 2021. Neurobiological markers of resilience to early-life adversity during adolescence. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 6, 238–247. [PubMed: 33067165]

Merrick JS, Narayan AJ, Atzl VM, Harris WW, Lieberman AF, 2020. Type versus timing of adverse and benevolent childhood experiences for pregnant women's psychological and reproductive health. Child. Youth Services Rev. 114, 105056.

Miller GE, Chen E, Sze J, Marin T, Arevalo JMG, Doll R, et al. , 2008. A functional genomic fingerprint of chronic stress in humans: blunted glucocorticoid and increased NF-κB signaling. Biol. Psychiatry 64, 266–272. [PubMed: 18440494]

Mitchell AM, Porter K, Christian LM, 2018. Examination of the role of obesity in the association between childhood trauma and inflammation during pregnancy. Health Psychol. 37, 114–124. [PubMed: 28967771]

Morgan JE, Lee SS, Mahrer NE, Guardino CM, Davis EP, Shalowitz MU, et al. , 2020. Prenatal maternal C-reactive protein prospectively predicts child executive functioning at ages 4–6 years. Dev. Psychobiol. 62, 1111–1123. [PubMed: 32441781]

Murphy M, Cohn D, Loria A, 2017. Developmental origins of cardiovascular disease: impact of early life stress in humans and rodents. Neurosci. Biobehav. Rev. 74, 453–465. [PubMed: 27450581]

Pace TWW, Wingenfeld K, Schmidt I, Meinlschmidt G, Hellhammer DH, Heim CM, 2012. Increased peripheral NF-κB pathway activity in women with childhood abuse-related posttraumatic stress disorder. Brain Behav. Immun. 26, 13–17. [PubMed: 21801830]

Pollitt RA, Kaufman JS, Rose KM, Diez-Roux AV, Zeng D, Heiss G, 2007. Early-life and adult socioeconomic status and inflammatory risk markers in adulthood. Eur. J. Epidemiol. 22, 55–66. [PubMed: 17225957]

Rasmussen JM, Graham AM, Entringer S, Gilmore JH, Styner M, Fair DA, et al. , 2019. Maternal Interleukin-6 concentration during pregnancy is associated with variation in frontolimbic white matter and cognitive development in early life. NeuroImage 185, 825–835. [PubMed: 29654875]

Rijlaarsdam J, Stevens GWJM, Jansen PW, Ringoot AP, Jaddoe VWV, Hofman A, et al. , 2014. Maternal childhood maltreatment and offspring emotional and behavioral problems: maternal and paternal mechanisms of risk transmission. Child Maltreat 19, 67–78. [PubMed: 24642695]

Roberts AL, Lyall K, Rich-Edwards JW, Ascherio A, Weisskopf MG, 2013. Association of maternal exposure to childhood abuse with elevated risk for autism in offspring. JAMA Psychiatry 70, 508–515. [PubMed: 23553149]

Roberts AL, Galea S, Austin SB, Corliss HL, Williams MA, Koenen KC, 2014. Women's experience of abuse in childhood and their children's smoking and overweight. Am. J. Prev. Med. 46, 249–258. [PubMed: 24512863]

Romero R, Espinoza J, Gonçalves LF, Kusanovic JP, Friel LA, Nien JK, 2006. Inflammation in preterm and term labour and delivery. Semin. Fetal Neonatal Med. 11, 317–326. [PubMed: 16839830]

Ross KM, Miller G, Culhane J, Grobman W, Simhan HN, Wadhwa PD, et al. , 2016. Patterns of peripheral cytokine expression during pregnancy in two cohorts and associations with inflammatory markers in cord blood. Am. J. Reprod. Immunol. 76, 406–414. [PubMed: 27615067]

Ross KM, Cole SW, Carroll JE, Dunkel Schetter C, 2019. Elevated pro-inflammatory gene expression in the third trimester of pregnancy in mothers who experienced stressful life events. Brain Behav. Immun. 76, 97–103. [PubMed: 30447280]

Ross KM, Carroll JE, Schetter CD, Hobel C, Cole SW, 2019. Pro-inflammatory immune cell gene expression during the third trimester of pregnancy is associated with shorter gestational length and lower birthweight. Am. J. Reprod. Immunol. 82, e13190. [PubMed: 31529581]

Ross KM, Dunkel Schetter C, Carroll JE, Mancuso RA, Breen EC, Okun ML, et al. , 2022. Inflammatory and immune marker trajectories from pregnancy to one-year post-birth. Cytokine 149, 155758. [PubMed: 34773858]

Schwaiger M, Grinberg M, Moser D, Zang JCS, Heinrichs M, Hengstler JG, et al. , 2016. Altered stress-induced regulation of genes in monocytes in adults with a history of childhood adversity. Neuropsychopharmacol 41, 2530–2540.

Slavich GM, 2015. Understanding inflammation, its regulation, and relevance for health: a top scientific and public priority. Brain Behav. Immun. 45, 13–14. [PubMed: 25449576]

Spindola LM, Pan PM, Moretti PN, Ota VK, Santoro ML, Cogo-Moreira H, et al. , 2017. Gene expression in blood of children and adolescents: mediation between childhood maltreatment and major depressive disorder. J. Psychiatr. Res. 92, 24–30. [PubMed: 28384542]

Stewart FM, Freeman DJ, Ramsay JE, Greer IA, Caslake M, Ferrell WR, 2007. Longitudinal assessment of maternal endothelial function and markers of inflammation and placental function throughout pregnancy in lean and obese mothers. J. Clin. Endocrinol. Metab. 92, 969–975. [PubMed: 17192290]

Taylor SE, Lerner JS, Sage RM, Lehman BJ, Seeman TE, 2004. Early environment, emotions, responses to stress, and health. J. Pers. 72, 1365–1394. [PubMed: 15509286]

Walsh K, Basu A, Werner E, Lee S, Feng T, Osborne LM, et al. , 2016. Associations among child abuse, depression, and interleukin 6 in pregnant adolescents. Psychosom. Med. 78, 920–930. [PubMed: 27187846]

Zajdel J, Zager A, Blomqvist A, Engblom D, Shionoya K, 2019. Acute maternal separation potentiates the gene expression and corticosterone response induced by inflammation. Brain Behav. Immun. 77, 141–149. [PubMed: 30590109]

Zerbo O, Traglia M, Yoshida C, Heuer LS, Ashwood P, Delorenze GN, et al. , 2016. Maternal mid-pregnancy C-reactive protein and risk of autism spectrum disorders: the early markers for autism study [no. 4]. Transl. Psychiatry 6, e783. [PubMed: 27093065]

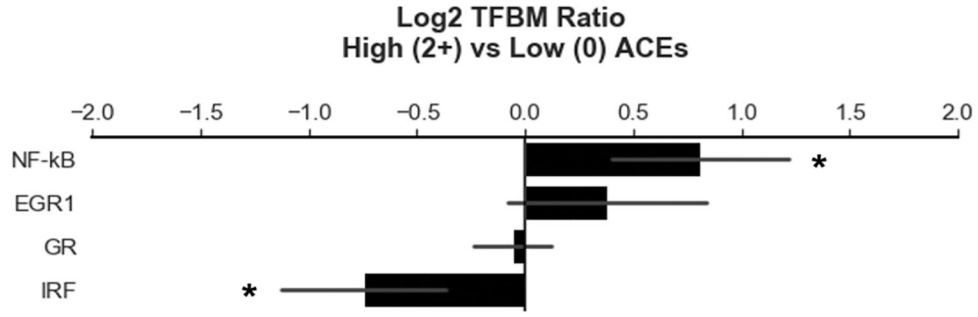

Fig. 1.

Bioinformatic analysis suggests increased pro-inflammatory (NF-κB) and decreased anti-viral (IRF) transcription factor activity in mothers with high levels of ELS. Data shown are log2-transformed ratios of transcription factor-binding motifs (TFBMs) for pro-inflammatory and anti-viral transcription factors in the promoters of the 303 genes that showed a greater than 2-fold difference in expression in PBMCs between mothers with high ELS (2 + ACEs) or low ELS (0 ACEs). *$p < 0.05$. Abbreviations: Interferon Response Factor (IRF); nuclear factor-κB (NF-κB); glucocorticoid receptor (GR); Early Growth Response 1 (EGR1).

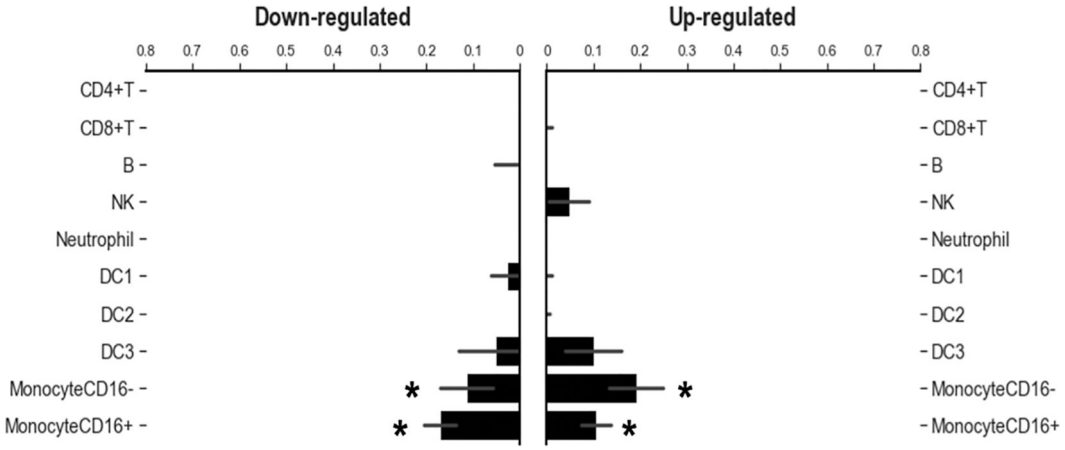

Fig. 2.

Results of transcript origin analyses indicate that both transcripts that were up-regulated in mothers with high vs low ELS and transcripts that were down-regulated in mothers with high ELS vs low ELS were preferentially derived from monocytes.

Table 1

Participant characteristics.

	Gene expression (N = 60)	CRP (N = 89)
Age (years)	28.25 (5.73); 19–39	29.19 (5.69); 19–44
Gestational Age (weeks)	32.59 (3.99); 22.7–40.29	32.75 (3.87); 22.71–40.29
Household Per Capita Income	$16,361 ($20,722)	$14, 550 ($18,367)
Race/Ethnicity		
Black	12 (20%)	16 (18%)
Latina	32 (53%)	48 (53%)
white	16 (27%)	25 (29%)
Education		
Less than high school	15 (25%)	22 (24%)
High school, GED, etc.	23 (38%)	37 (42%)
Some college	7 (12%)	10 (11%)
4 year degree or more	14 (23%)	19 (21%)
Other or unknown	1 (2%)	1 (1%)
ACEs	1.33 (1.75)	1.36 (1.75)
Perceived Stress	18.20 (6.27)	17.91 (5.97)
Concurrent BMI (Third Trimester)	32.15 (5.87)	32.36 (6.53)
Pre (Inter)-Pregnancy BMI	29.69 (8.10)	28.88 (6.02)
	*N = 54	*N = 30
Pre (Inter)-Pregnancy BMI Category	1 (1.85%)	0%
Underweight	15 (27.78%)	7 (23.33%)
Healthy Weight	16 (29.63 %)	10 (33.33%)
Overweight	22 (40.74%)	13 (43.33%)
Obese	*N = 54	*N = 30
Parity	2.62 (0.74)	2.68 (0.74)