HHS Public Access

Author manuscript

J Pediatr. Author manuscript; available in PMC 2019 December 01.

Published in final edited form as:

J Pediatr. 2018 December ; 203: 301–308. doi:10.1016/j.jpeds.2018.07.069.

Maternal Lifetime Trauma and Birthweight: Effect Modification by *in utero* Cortisol and Child Sex

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Abstract

Objectives: To evaluate associations between maternal lifetime traumatic stress and offspring birthweight and examine modifying effects of third trimester cortisol and fetal sex.

Study design: Analyses included 314 mother-infant dyads from an ethnically mixed pregnancy cohort. Maternal lifetime trauma was reported via the Life Stressor Checklist-Revised (LSC-R). Fenton birthweight for gestational age z-scores (BWGA-z) were calculated. A 3-cm scalp-nearest maternal hair segment collected at birth was assayed to reflect cumulative third trimester cortisol secretion. Multivariable regression was used to investigate associations between maternal lifetime trauma and BWGA-z and examine 2-and 3-way interactions with cortisol and fetal sex. Because subjects with low or high cortisol levels could represent susceptible populations, varying coefficient models that relax the linearity assumption on cortisol level were used to assess modification of maternal lifetime trauma associations with BWGA-z as a function of cortisol.

Results: Women were primarily minorities (41% Hispanic, 26% black) with ≤12 years education (63%); 63% reported ≥1 traumatic event. Prenatal cortisol modified the association between

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maternal lifetime trauma and birthweight. Women with higher lifetime trauma and increased cortisol had significantly lower birthweight infants in males; among males exposed to the 90th percentile of cortisol, a 1-unit increase in trauma score was associated with a 0.19-unit decrease in BWGA-z (95% Confidence Interval [CI] -0.34,-0.04). Associations among females were nonsignificant, regardless of cortisol level.

Conclusions: These findings underscore the need to consider complex interactions among maternal trauma, disrupted *in utero* cortisol production, and fetal sex to fully elucidate intergenerational effects of maternal lifetime trauma.

Size at birth is a determinant of lifelong function, health and disease[1, 2]. Minority women and those of disadvantaged socio-economic status (SES) are more likely to have low birthweight infants[3, 4]. Moreover, birthweight disparities parallel the distribution of associations between disparities in SES and adverse outcomes over the lifecourse[5, 6]. Identifying modifiable factors influencing birthweight can inform interventions to reduce health disparities over the lifespan.

A variety of maternal stressors have been examined in relation to birthweight with findings varying across studies[6–17]. The majority of studies considered stress in the prenatal or immediate preconception period with some[11–13, 15, 18, 19] but not all[8, 9, 20] showing associations with reduced birthweight. Notably, the limited number of studies that consider a woman's lifetime stress consistently support associations with lower birthweight[6, 7], and effects persist when accounting for stress in pregnancy[7]. Our group[21] and others[22] demonstrate high rates of trauma exposure in lower income, ethnic minority women of childbearing age. Trauma can result in altered psychophysiological states that persist years after an event which, when carried into pregnancy, can impact the developing fetus[23].

Although mechanisms remain unclear, hypothalamic-pituitary-adrenal (HPA) axis functioning and consequent maternal cortisol production play a key role. The placenta modulates fetal effects via 11-β-hydroxysteroid dehydrogenase-type 2 (11β-HSD2) activity[24]. Chronic stress downregulates 11β-HSD2, increasing placental permeability to cortisol[25]. Levels of 11β-HSD2 decrease late in pregnancy; thus the fetus can be more vulnerable in the third trimester[26]. Chronic traumatic stress disrupts other regulatory systems including autonomic nervous system (ANS) and immune functioning, which interact with cortisol *in utero* to influence fetal development[27, 28]. Thus, maternal trauma history and altered cortisol in pregnancy may have joint effects on fetal programming. Fetal sex can also modify stress effects[29], with evidence of complex associations among stress, cortisol, and fetal sex and increased susceptibility of males to effects of *in utero* stress [30, 31].

In the current study, we examined associations between maternal lifetime traumatic stress and infant birthweight, modifying effects of third trimester maternal cortisol levels, and differences by fetal sex. We hypothesized that infants born to women with higher lifetime trauma who also had disrupted cortisol production *in utero* would have lower birthweight and that males would be more susceptible to intrauterine effects of maternal lifetime trauma.

Methods

Pregnant women receiving prenatal care were recruited from Beth Israel Deaconess Medical Center and the East Boston Neighborhood Health Center in Boston, MA from March 2011 - December 2013 and the Mount Sinai Hospital in New York City, NY from April 2013 - July 2014. Eligibility criteria included English- or Spanish-speaking, ≥18 years of age and single gestation pregnancy. Exclusion criteria included maternal intake of ≥7 alcoholic drinks/week prior to or any alcohol after pregnancy recognition, as usage at or above these thresholds have been associated with increased risk of a number of child outcomes[32, 33]; and congenital abnormalities or chronic child health conditions (eg, severe neurodevelopmental delays) that would impact participation. The relevant institutions' human studies committees approved procedures and mothers provided written consent in their primary language. Trained research staff approached women in participating prenatal clinics on select clinic days. Of those approached and eligible, N=548 agreed to participate (69.4%); women were enrolled at an average of 25.44 ± 7.0 weeks' gestation (25 weeks and 3 days ± 7 weeks) and participants and non-participants did not differ on race/ethnicity, education or income. Within 2 weeks of enrollment, mothers completed standardized surveys via in-person interviews. Funding was later obtained to collect hair at delivery; all women who had not delivered (n=359) agreed to hair sampling; 45 were excluded due to insufficient hair length, shift work, exogenous steroid use in the past 6 months, or multiple gestation, leaving a final sample of 314 for the present analysis. Those included in the present analysis did not significantly differ from the sample as a whole based on mean maternal age, race, education level, prenatal smoking, pre-pregnancy body mass index (BMI), or child sex. All questionnaire measures were administered in a face-to-face interview in a private setting by trained research staff.

Main Exposure

Maternal lifetime trauma exposure:

Mothers completed the 30-item Life Stressor Checklist-Revised (LSC-R) to report exposure to potentially traumatic events (e.g., accident or natural disaster, death of someone close, childhood maltreatment, interpersonal violence, sexual assault) over the life course. To classify an event as traumatic, mothers were asked whether there was concern that they or someone else was at risk of death or serious injury in association with the event [34]; positive responses were summed to create a lifetime trauma score. The LSC-R was administered by trained research staff via face-to-face interview and has been used in diverse populations with demonstrated test-retest reliability and validity[35].

Outcome

Birthweight:

Birthweight was extracted from delivery records. Gestational age was determined by reported last menstrual period (LMP) and compared with obstetrical estimates from the first trimester ultrasound; if the discrepancy was >2 weeks, obstetrical estimates were used[36].

Sex-specific Fenton birthweight for gestational age z-scores (BWGA-z) were derived[37]. Z-scores factor in non-linear growth, which reduces bias and residual confounding[38].

Effect Modifiers

Cortisol:

Most studies of prenatal HPA axis functioning consider salivary or serum cortisol obtained at discrete time points reflecting cortisol secretion over hours or days[39]. Hair provides an integrated measure reflecting cortisol levels over weeks to months[40]. Hair cortisol levels demonstrate expected increases over pregnancy and correlate with salivary cortisol measures and chronic stress[4142]. Hair was collected from mothers within 1 week of delivery. A 3 to 9 cm long by 3 mm diameter hair segment (~50 strands) was collected close to the scalp at the posterior vertex[43] and stored at room temperature until shipment for analysis using a published protocol (Kirschbaum laboratory, Dresden, Germany)[44]. Based on an average monthly hair growth of ~1 cm, a 3 cm scalp-nearest hair segment was assayed to reflect cumulative maternal third trimester cortisol secretion. Cortisol was quantified using enzyme-linked immunosorbent assay (ELISA) (n=137) (CLIA, IBL-Hamburg, Germany; sensitivity 0.16 ng/ml, inter-assay coefficient of variance 5–7%) or liquid chromatograph-mass spectrometry (LC-MS/MS)(n=177) (sensitivity 0.1 pg/mg, inter-assay variability 3.7–8.8%)[44]; immunoassay results were converted into standard LC-MS/MS equivalents as previously described[45]. Cortisol levels were not impacted by chemical treatment in the past year, use of gels, oils or sprays on the day of collection, or mode of delivery; thus these factors were not considered further in analyses.

Fetal Sex:

Sex was determined from birth records.

Covariates

Factors associated with stress and birthweight were considered as confounders including maternal age, education (≤12 years vs >12 years), race/ethnicity (White, black and Hispanic), and body mass index (BMI). BMI was calculated from maternal self-reported pre-pregnancy weight and height as weight (kg) divided by height (m) squared. There is previously demonstrated reliability of self-reported anthropometric measures[46].

Statistical analyses

Analyses proceeded in several steps. We first examined the distribution of covariates in the sample overall and by fetal sex. We calculated descriptive statistics and examined differences by sex using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Hair cortisol was natural log-transformed to reduce skewness and we calculated z-scores for analyses; we report the raw scale (pg/mg) for comparison with prior studies.

We used linear regression to examine the association between maternal lifetime trauma exposure and BWGA-z, adjusting for confounders. The main model adjusted for fetal sex, third trimester hair cortisol (hereafter referred to as prenatal cortisol), maternal age, race/

ethnicity and pre-pregnancy BMI. Subsequent models examined two-way interactions between maternal lifetime trauma and sex and prenatal cortisol. The final model included a three-way interaction between maternal lifetime trauma, prenatal cortisol and fetal sex.

We assessed modification of maternal lifetime trauma associations with BWGA-z by prenatal cortisol using varying coefficient models. These models are similar to a linear regression model, but no longer assume a linear effect of cortisol because stress and disrupted reactivity of the HPA axis can result in either elevated or reduced cortisol levels[47] and both elevated and blunted cortisol production have been associated with low birthweight[48, 49]. Thus, cortisol is entered into the model as an unspecified, potentially nonlinear, smooth function that is estimated from the data both in the main effect of cortisol and the *cortisol x trauma* interaction. The resulting model allows the association of trauma and birthweight to vary as a potentially nonlinear function of cortisol. The varying coefficient model takes the form $BWGA\text{-}z_i = \beta_0 + \beta_1 LSCR_i + \beta_2(c_i) + \beta_3(c_i)\, LSCR_i + \beta_4 x_i + \varepsilon_i$, where $\beta_2(c_i)$ is the main, potentially nonlinear smooth association between birthweight z-score and prenatal cortisol level when $LSCR_i=0$; $\beta_3(c_i)$ is the association between maternal lifetime trauma exposure and BWGA-z for a subject having cortisol level c_i; and x_i is a vector containing the additional covariates. Figures were created to present estimates and corresponding confidence intervals for $\beta_1 + \beta_3(c)$ the association of maternal lifetime trauma with BWGA-z, as a function of prenatal cortisol level c. To examine effect modification by fetal sex, we stratified the above model by fetal sex.

Results

Descriptive Data

Table 1 shows sample characteristics overall and by fetal sex. Women were primarily minorities (41.1% Hispanic, 26.4% Black) and the majority reported ≤12 years education (63.1%); 197 (62.7%) reported one or more traumatic events in their lifetime. There were no significant differences by sex for maternal age, race/ethnicity, education, pre-pregnancy BMI, or maternal lifetime trauma score. Median prenatal hair cortisol was 6.65 pg/mg (Intraquartile Range (IQR) 2.8–22.9) with higher levels in mothers of male vs. female infants.

Maternal lifetime trauma and BWGA-z scores: Main effects

In multivariable regression models adjusted for child's sex and maternal age, race/ethnicity, education, BMI and hair cortisol, there was no significant main effect of maternal lifetime trauma on BWGA-z; sex and prenatal cortisol were not independently associated with BWGA-z.

Effect modification by third trimester hair cortisol and child's sex

To investigate whether the association between maternal lifetime trauma and BWGA-z varied by sex or prenatal cortisol level, we examined two-way interactions for maternal lifetime trauma with 1) prenatal cortisol and 2) fetal sex. The interaction term for *maternal lifetime trauma x prenatal cortisol* was marginally significant ($P = .058$), and the interaction term for *maternal lifetime trauma x sex* was not significant (P=0.91). In the model including

a three-way interaction for *maternal lifetime trauma x prenatal cortisol x sex*, the main effect of trauma was essentially unchanged; however, we observed a statistically significant three-way interaction (P=0.02).

To demonstrate variations in the association between maternal lifetime trauma and BWGA-z across prenatal cortisol levels and by sex, we calculated predicted effect estimates of trauma on BWGA-z based on results of the linear regression models incorporating interactions between maternal lifetime trauma, prenatal cortisol, and sex. We considered the following four conditions to highlight associations at the upper and lower levels of prenatal cortisol level: 1) boys exposed to prenatal cortisol at the 10th percentile, 2) boys exposed to prenatal cortisol at the 90th percentile, 3) girls exposed to prenatal cortisol at the 10th percentile, and 4) girls exposed to prenatal cortisol at the 90th percentile. We emphasize that this model was fit using the original continuous cortisol measures, and these percentiles are chosen for interpreting the magnitudes of the *trauma x cortisol* interaction terms. These results are presented in Figure 1. Among males exposed to prenatal cortisol at the 90th percentile (i.e., 74.03 pg/mg), a 1-unit increase in maternal trauma score was associated with a 0.19-unit decrease (95% CI -0.34,-0.04) in BWGA-z, and among those exposed to prenatal cortisol at the 10th percentile (i.e., 1.14 pg/mg), a 1-unit increase in trauma score was associated with a 0.14-unit increase (95% CI 0.03,0.26) in BWGA-z. We found no association between maternal trauma score and BWGA-z in females regardless of prenatal cortisol levels.

Effect modification by hair cortisol: Varying coefficient models

We further examined the *trauma x cortisol* interactions on birthweight using varying coefficient models to allow for nonlinear trends in the BWGA – trauma associations across the range of cortisol levels. To present the findings, we use graphical displays to present the estimated associations between maternal lifetime trauma and infant birthweight along a continuum of cortisol levels. Figure 2, A presents estimates of the change in BWGA-z associated with a one-unit increase in maternal trauma exposure at each value of prenatal cortisol exposure. Models were adjusted for fetal sex and maternal age, education, race/ethnicity, and pre-pregnancy BMI. The association between maternal lifetime trauma and infant BWGA-z varied by prenatal cortisol level. Among infants exposed to the highest levels of prenatal cortisol, maternal trauma exposure was inversely associated with BWGA-z. In contrast, among infants exposed to lower prenatal cortisol, maternal trauma was associated with higher BWGA-z. Results were statistically significant at the upper and lower levels of prenatal cortisol as evidenced by the 95% confidence intervals (CI) (represented by dotted bands) not containing zero. In the overall sample, the interaction term for the multivariable-adjusted regression model was marginally significant (P=0.058, Table 2).

Figure 2, B and C present sex-stratified estimates of associations between maternal trauma and BWGA-z as a smooth function of prenatal cortisol, adjusted for maternal age, race/ethnicity, and pre-pregnancy BMI. Findings among males were similar to findings in the overall sample: in males exposed to higher prenatal cortisol, maternal lifetime trauma was inversely associated with BWGA-z, and among those with lower cortisol exposure, maternal trauma was positively associated with BWGA-z. The dotted lines (representing 95% CI) indicate that associations at the extremes of prenatal cortisol are statistically significant. In

females, the association between maternal trauma and BWGA-z was not statistically significant regardless of prenatal cortisol (Figure 2, C).

Discussion

These analyses did not demonstrate an independent relationship between increased maternal lifetime trauma and birth weight adjusted for gestational age. Rather, higher maternal lifetime trauma exposure was associated with offspring birthweight adjusted for gestational age only after considering modifying effects of *in utero* cortisol levels. Specifically, children born to mothers with higher lifetime trauma exposure and higher third trimester cortisol levels had significantly lower birthweight, and children born to mothers with higher lifetime trauma exposure and lower third trimester cortisol had significantly higher birthweight. Finally, only males were vulnerable to the joint effects of maternal trauma exposure and higher cortisol late in pregnancy.

The present study builds on a growing body of literature demonstrating that trauma occurring over a mother's lifetime can contribute to adverse pregnancy outcomes[50]. Such findings are of public health significance given epidemiological data showing high rates of trauma exposure among pregnant women and women of childbearing age, particularly for lower-income, racial/ethnic minority samples[21, 51]. A majority of women in this racially/ethnically mixed, lower income pregnancy cohort experienced one or more traumatic events in their lifetime; this prevalence is consistent with other reports in samples of similar sociodemographics[21, 51].

Several lines of prior evidence can inform why those women with a history of trauma exposure who secreted higher levels of cortisol in late pregnancy were most likely to have lower birthweight infants. Trauma exposure can result in altered psychophysiological states, including abnormal reactivity of the HPA axis with alterations persisting years after an event. Therefore, women exposed to trauma can enter pregnancy with disrupted physiological states (e.g., aberrant HPA axis reactivity, enhanced inflammation)[52] that in turn influence fetal programming. Another recent study found that maternal trauma history was only associated with lower birthweight and preterm delivery when prenatal maternal psychological dysfunction was considered[23]. Specifically, associations between increased anxiety late in pregnancy and lower birthweight were significantly stronger in women with a trauma history. Although the study did not examine potential underlying mechanisms, mood disorders in pregnancy can be associated with disrupted stress responsivity and reactivity (e.g., HPA, ANS disruption) and increased fetal exposure to cortisol[53].

Elevated maternal prenatal cortisol production has been associated with reduced birthweight in prior studies. Bolten et al reported that higher prenatal cortisol levels were associated with smaller size at birth, independent of maternal perceived stress[54]. Valladares et al linked partner violence during pregnancy to high salivary cortisol levels, which in turn were associated with reduced birthweight[55].

We observed sex-specific effects, as associations between maternal lifetime trauma exposure, elevated prenatal cortisol and birthweight were evident in males but not females.

For example, in terms of birthweight in grams among males who were born at gestational age 39 weeks (the mean and median of the sample included in the analysis), among those exposed to prenatal cortisol at the 90th percentile, a 1-unit increase in maternal trauma score corresponds to an 88 gram decrease in birthweight and among those exposed to prenatal cortisol at the 10th percentile, a 1-unit increase in maternal trauma score corresponds to a 65 gram increase in birthweight. Fetal sex may impact the association between maternal psychosocial stress and birthweight given reported differences in fetal growth as well as maternal HPA axis activity by fetal sex[56]. Our results are consistent with literature showing that males are more susceptible to effects of *in utero* stress and stress correlates on fetal growth[31, 57]. For example, Thayer et al found that elevated maternal cortisol levels assessed prior to conception disproportionately impacted fetal growth in boys.[31] Bublitz et al showed that lower maternal SES was associated with altered maternal cortisol production and lower birthweight in male infants.[58]

Future studies are needed to elucidate mechanisms underlying these associations. Recently, epigenetic programming has been receiving increasing attention in this context. Maternal stress influences placental permeability to cortisol through altered production of 11β-HDS2 with evidence that chronic stress and prenatal mood disorders are associated with downregulation of 11β-HDS2 and increased placental permeability to cortisol[49]. Changes in epigenetic regulation of both 11β-HDS2[59] and the glucocorticoid receptor[60] may play a role and also show sex-specific effects[61, 62].

This study has a number of strengths, including the racially/ethnically mixed, lower income, higher risk sample, the consideration of effects of maternal trauma on birthweight using a lifecourse framework, and use of hair cortisol as an integrated measure of maternal cortisol secretion in the third trimester to consider interactions between trauma and HPA axis disruption in pregnancy. Our measure of hair cortisol demonstrated expected increases across pregnancy, which is consistent with the literature to date[40, 41], and correlations between trimester-specific cortisol levels were high and ranged from 0.89–0.96. First and second trimester cortisol levels were available for a smaller sample of the study population (given differences in hair length at delivery); we replicated analyses using first and second trimester cortisol levels and the overall inferences were unchanged. Our analyses focused on third trimester maternal hair cortisol levels given that the developing fetus may be particularly vulnerable late in pregnancy to elevated cortisol[63]. Birthweight was considered as a continuous measure, rather than low/extremely low birthweight, which is important as lower birthweight in the normal range has been associated with adverse health outcomes[49].

There are also some limitations which will be important to consider in future studies. Maternal lifetime trauma exposure was obtained by self-report via the LSC-R. However, the LSC-R is a reliable measure of lifetime trauma exposure, with data suggesting possible under-reporting of trauma exposure which would lead to an underestimate of association[64]. The LSC-R was collected prior to birth and is thus unlikely to have been reported differentially by birthweight. In addition, we obtained funding to measure hair cortisol 6 months after study initiation and had to exclude women recruited prior to cortisol assessment.

This study underscores the need to consider complex interactions among maternal trauma, biomarkers of disrupted stress reactivity *in utero,* and fetal sex in order to more fully elucidate the intergenerational effects of maternal trauma on offspring health and development. These findings also highlight the importance of taking a lifecourse approach which hypothesizes that a woman's life experiences prior to pregnancy can shape the development of the fetus and pregnancy outcomes as well as elucidating the etiology of perinatal health disparities[65, 66]. Early identification of women at elevated risk of having lower birthweight babies can help reduce adverse maternal-child outcomes. Identifying a prior history of trauma and providing interventions, for example treatment for associated mood disturbances[67], could lead to improved perinatal outcomes that have lifelong implications for health.

Acknowledgments

Data collection was supported by the National Institutes of Health (NIH) (R01HL095606 [to R.W. and M.E.] and R21HD00359 [to R.W.]). Phenotyping and biostatistical support was funded by the NIH (P30 ES023515 and P30 ES000002). K.B. received research support from the NIH (K99ES024116 and R00ES024116). The other authors declare no conflicts of interest.

Abbreviations:

SES	Socio-economic status
11β-HSD2	11-β-hydroxysteroid dehydrogenase-type 2
ANS	Autonomic nervous system
LSC-R	Life Stressor Checklist-Revised
LMP	Last menstrual period
BWGA-z	Birthweight for gestational age z-scores
ELISA	Enzyme-linked immunosorbent assay
LC-MS/MS	Liquid chromatograph-mass spectrometry
BMI	Body mass index
IQR 95%	Intraquartile Range
CI 95%	Confidence Interval
s.e.	Standard error
SD	Standard Deviation

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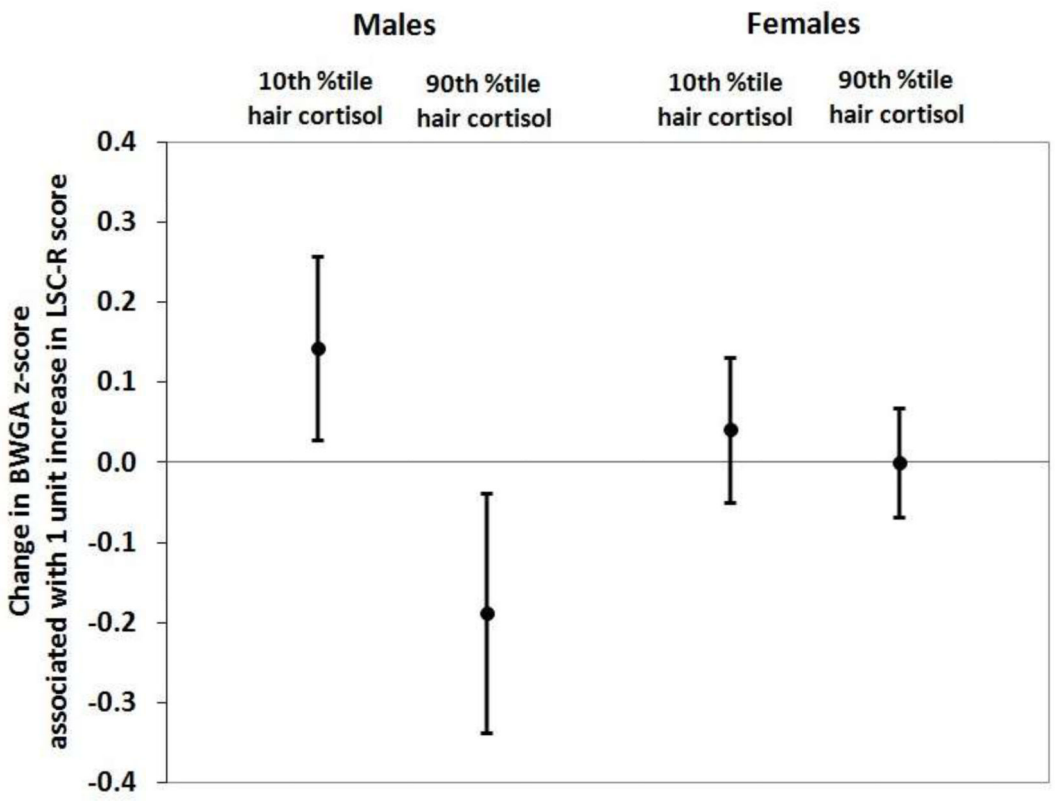

Figure 1. Predicted effect estimates for maternal lifetime trauma exposure on infant birthweight for gestational age z-score (BWGA-z) by prenatal cortisol level and fetal sex

Estimated change in BWGA z-scores (with 95% CI) associated with a one-unit increase in maternal trauma exposure (continuous ratings from the LSC-R). Estimates from multivariableadjusted regression model under the following four conditions: 1) males born to mothers with prenatal hair cortisol level at 10th percentile, 2) males born to mothers with prenatal hair cortisol level at 90th percentile, 3) females born to mothers with prenatal hair cortisol level at 10th percentile, and 4) females born to mothers with prenatal hair cortisol level at 90th percentile. Prenatal cortisol (natural log-transformed z-score) was assessed from maternal hair representing the third trimester of pregnancy. Analyses adjusted for maternal age at enrollment, race/ethnicity, maternal education status, and pre-pregnancy BMI.

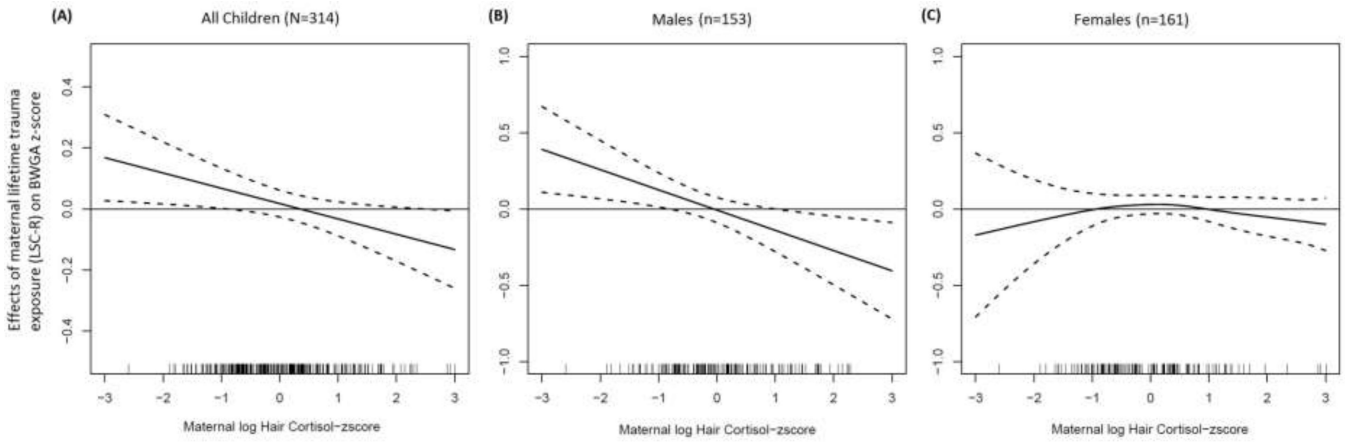

Figure 2. Association between maternal lifetime trauma exposure and infant birthweight for gestational age z-score (BWGA-z): Effect modification by prenatal cortisol overall and by fetal sex.

Change in BWGA-z for a one-unit increase in maternal trauma at each cortisol value estimated as a smooth function of cortisol (solid line) and 95% pointwise confidence intervals (CIs, dashed lines). Areas in which 95% CIs fall above or below zero indicate intervals of cortisol z-score in which there is a significant association between trauma and BWGA-z. (A) overall sample, (B) Male fetal sex, and (C) female fetal sex. Analyses adjusted for (A) fetal sex, maternal age, race/ethnicity, education, and BMI and (B, C) maternal age, race/ethnicity, education, and BMI

Table 1.

PRISM participant characteristics

	All children (N=314)		Male (n=153)		Female (n=161)		*p*-value[a]
Maternal age at enrollment (year; mean, SD [b])	30.0	5.9	29.7	5.7	30.4	6.1	0.28
Race/Ethnicity (n, %)							
White	102	32.5	48	31.4	54	33.5	0.89
Black	83	26.4	42	27.5	41	25.5	
Hispanic	129	41.1	63	41.2	66	41.0	
Maternal education status (n, %)							
≤12 years	198	63.1	103	67.3	95	59.0	0.13
>12 years	116	36.9	50	32.7	66	41.0	
Maternal pre-pregnancy BMI (kg/m^2; median, IQR)	24.4	21.9–29.3	25.1	22.5–30.7	24.0	21.9–28.3	0.09
Maternal lifetime trauma exposure: LSC-R (mean, SD) [c]	1.79	2.33	1.76	1.97	1.81	2.63	0.07
Prenatal cortisol [d]							
Original scale (pg/mg; median, IQR)	6.65	2.8–22.9	9.13	3.8–25.4	5.14	2.1–17.0	<0.01
z-score; ln-transformed (mean, SD) [c]	−0.05	0.97	0.08	0.95	−0.16	0.97	0.02
Fenton birthweight for gestational age z-score (mean, SD)	−0.11	0.90	−0.11	0.99	−0.10	0.80	0.82
Gestational age at birth (weeks; median, IQR)	39.1	38.1–40.1	39.2	38–40.1	39.0	38.4–40.0	0.99

[a] p-value comparing boys and girls (χ^2 test for categorical variables; Wilcoxon rank-sum test for continuous variables)

[b] Standard Deviation (SD)

[c] Maternal lifetime trauma exposures assessed as number of endorsed events meeting DSM-5 Criterion A via the Life Stressor ChecklistRevised (LSC-R).

[d] Maternal third trimester hair cortisol

Table 2.

Multivariable-adjusted regression models[a] examining maternal lifetime trauma exposure (LSC-R) in relation to birthweight for gestational age zscore

	Main Model			Interaction Models								
				Maternal Lifetime Trauma[b] x Fetal Sex Model			Maternal Lifetime Trauma[b] x Cortisol[c] Model			Maternal Lifetime Trauma[b] x Cortisol[c] x Fetal Sex Model		
	beta	s.e.[d]	p	beta	s.e.[d]	p	beta	s.e.[d]	p	beta	s.e.[d]	p
Maternal Lifetime Trauma[b]	0.01	0.02	0.59	0.01	0.03	0.62	0.02	0.02	0.39	0.02	0.03	0.46
Fetal sex (male as referent)	−0.03	0.10	0.75	−0.02	0.13	0.86	−0.05	0.10	0.64	0.04	0.13	0.79
Prenatal cortisol[c]	0.06	0.06	0.25	0.06	0.06	0.26	0.14	0.07	0.04	0.08	0.09	0.41
Interaction terms:												
Maternal Lifetime Trauma x Fetal Sex				−0.01	0.05	0.91				−0.04	0.05	0.43
Maternal Lifetime Trauma x Prenatal Cortisol							−0.04	0.02	0.0 58	−0.02	0.02	0.48
Prenatal Cortisol x Fetal Sex										0.24	0.14	0.09
Maternal Lifetime Trauma x Prenatal Cortisol x Fetal Sex										−0.12	0.05	0.02

[a]Covariates include child's sex, prenatal hair cortisol, maternal age at enrollment, race/ethnicity, maternal educational status, pre-pregnancy BMI

[b]Maternal lifetime trauma exposure assessed as number of endorsed events meeting DSM-5 Criterion A via the Life Stressor Checklist-Revised (LSC-R).

[c]Third-trimester hair cortisol z-score, ln-transformed

J Pediatr. Author manuscript; available in PMC 2019 December 01.