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Sex specific associations between prenatal negative life events and birth outcomes

Maria José Rosa[a], **Farida Nentin**[b], **Michelle Bosquet Enlow**[c], **Michele R. Hacker**[d,e], **Nastasia Pollas**[f], **Brent Coull**[g], **Rosalind J. Wright**[a,h,i]

[a]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount, Sinai, New York, NY, USA

[b]Department of Obstetrics, Gynecology and Reproductive Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[c]Department of Psychiatry, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA

[d]Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, KS3, Boston, MA 02215, USA

[e]Department of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School, Boston, MA, USA

[f]Mount Sinai, New York, NY

[g]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[h]Institute for Exposomic Research, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[i]Kravis Children's Hospital, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Abstract

Maternal psychosocial stress can negatively impact gestational length and development of the fetus. These effects may be sex-specific but have not been extensively studied. The objective of this study was to examine the associations between prenatal maternal stress and birth outcomes and whether effects are modified by sex. Prenatal maternal stress was indexed by a maternal negative life events (NLE) score ascertained in 527 urban mothers; a higher NLE score indicates greater stress. Birth outcomes included gestational age, preterm birth (<37 weeks), and birthweight for gestational age z-scores. Modified Poisson regression and linear models were used to evaluate associations of prenatal NLE scores with birth outcomes. Sex differences were assessed by inclusion of an interaction term for sex by NLE score and in sex-stratified analyses. In analyses adjusted for maternal age, education, race/ethnicity, and pre-pregnancy body mass index (BMI), increasing prenatal stress was associated with shortened gestational age (days) (β=−0.63, [95% CI −1.20, −0.06]). This effect was sex specific, with increasing prenatal stress associated with

Corresponding Author: Maria José Rosa, One Gustave L. Levy Place, Box 1057, New York, NY 10029, USA. Telephone: +1 (212) 241-7027; Fax: +1 (212) 212-996-0407; maria.rosa@mssm.edu.

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shortened gestational age, as well as increased risk of preterm birth, in male infants (β=−1.35 [95% CI −2.17,−0.54] and RR=1.18 [95% CI 0.99, 1.42] respectively) but not female infants (β =0.15 [95%CI −0.63, 0.94] and RR=0.85, [95%CI 0.65, 1.11] respectively). Prenatal stress was not associated with birthweight z-scores. Our results support the importance of psychosocial stress as a programming factor that may have sex-specific effects for adverse fetal outcomes. Understanding sex-specific effects of prenatal stress on birth outcomes may inform prevention strategies.

Lay summary:

Higher stress experienced by mothers in prgnancy was associated with shorter length of pregnancy and the effect was stronger in male infants when compared to female infants.

Keywords

prenatal stress; preterm birth; sex-differences; shortened gestational age; birthweight; birth cohort

Introduction

Environmental insults during the prenatal period may lead to alterations in maturation of multiple organ systems impacting fetal developmental trajectories (Wells et al., 2009). Research has focused on identifying and understanding these potential insults and their associations with adverse pregnancy outcomes, including low birthweight (LBW, ≤2500 grams), preterm birth (PTB, gestational age <37 weeks), and shortened gestational age, which are important predictors of health later in life(Ansari et al., 2017; Ask et al., 2018; Leps, Carson, & Quigley, 2018). There are also well-documented disparities in these outcomes by socioeconomic status (Blumenshine, Egerter, Barclay, Cubbin, & Braveman, 2010) and race/ethnicity (Mutambudzi, Meyer, Reisine, & Warren, 2017). Therefore, identifying risk factors that may be differentially distributed based on these factors remains a focus of research.

Previous studies have identified prenatal maternal stress, which varies across different racial and ethnic groups and socioeconomic status (Grobman et al., 2016), as a potential risk factor for adverse birth outcomes (Dunkel Schetter and Tanner, 2012), including LBW(Nkansah-Amankra, Luchok, Hussey, Watkins, & Liu, 2010), PTB (Hedegaard, Henriksen, Secher, Hatch, & Sabroe, 1996; Khashan et al., 2009a), and shortened gestational age (Hedegaard, et al., 1996). In an analysis of 1.35 million births in Denmark, prenatal exposure to severe life events was associated with increased of risk of PTB (Khashan, et al., 2009a). A recent meta-analysis of 88 prospective studies reported a moderate association between maternal stress and pregnancy outcomes, with effects moderated by the type of stress assessment, inclusion of high-risk populations, and study location (Bussieres et al., 2015). Psychosocial stress exposure during pregnancy leads to the activation of systems involved in the regulation of inflammatory processes (i.e., hypothalamic-pituitary-adrenocortical [HPA] axis, autonomic nervous system) and alterations in innate and adaptive immune responses; which may influence the health and development of the exposed fetus (Hobel, 2004; Hobel, Goldstein, & Barrett, 2008; Tollenaar, Beijers, Jansen, Riksen-Walraven, & de Weerth, 2011).

The effects of prenatal stress on birth outcomes have also been shown to vary by offspring sex (Doyle et al., 2015; Van den Bergh et al., 2017). There is evidence to suggest that sex-specific effects may arise through differential placental effects and fetal sex hormones (Clifton, 2010; A. R. Howerton et al., 2014). For example, prenatal socioeconomic adversity was linked to sex-specific changes in methylation of 11β-hydroxysteroid dehydrogenase type 2 in placental tissue (Appleton et al., 2013). Stress has also been linked to sex-specific differences in methylation of the glucocorticoid receptor gene which helps HPA-axis functioning (Ostlund et al., 2016). Most epidemiological research into sex-specific effects of stress on birth outcomes has focused on changes to the male-to-female birth ratio, usually greater than 1.0, but has been shown to decrease under stressful circumstances, including periods of deprivation (Zilko, 2010) and natural disasters (Suzuki, Yamagata, Kawado, & Hashimoto, 2016; Torche and Kleinhaus, 2012). Few studies have examined sex differences in associations between prenatal stress and other birth outcomes;most studies have focused on natural disasters and conflict as the stress exposure reporting higher risk of PTB and LBW (Torche and Kleinhaus, 2012; Wainstock, Shoham-Vardi, Glasser, Anteby, & Lerner-Geva, 2015) in females, lower birthweight in males (Suzuki, et al., 2016), and no evidence of sex differences in gestational duration (Suzuki, et al., 2016).

Given that maternal stress may be modified by intervention and has enormous implications for adverse birth outcomes that are linked to costly chronic disease throughout the life course, focusing on lower income, ethnically-diverse US samples that are more greatly burdened by adverse birth outcomes (Borrell, Rodriguez-Alvarez, Savitz, & Baquero, 2016; Lorch and Enlow, 2016) has important public health implications. Furthermore, understanding the role of sex in these associations can help elucidate potential underlying mechanisms. We hypothesized that higher prenatal stress would be associated with greater risk of adverse fetal outcomes and that the effect would be modified by fetal sex in an established multi-racial/ethnic population-based birth cohort.

Methods

PRogramming of Intergenerational Stress Mechanisms (PRISM) study:

The PRISM study is a prospective pregnancy cohort of mother-child dyads originally designed to study how perinatal stress influences child health and developmental outcomes. English- and Spanish-speaking women who were ≥18 years of age receiving prenatal care at the Beth Israel Deaconess Medical Center and the East Boston Neighborhood Health Center in Boston, MA and the Mount Sinai Hospital in New York City, NY were enrolled at 25.4 ± 7.0 weeks gestation from March 2011 to August 2014. Those who reported ≥ 7 alcoholic drinks/week prior to or any alcohol after pregnancy recognition were excluded. The relevant institutions' human studies committees approved procedures, and mothers provided written consent in their primary language. Of those eligible, 548 agreed to participate (69.4%); 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 to ascertain stress and relevant covariates used in these analyses. Of the 548 participants, the following data were missing (n=3 for maternal age, n=12 for pre-pregnancy BMI, n=1 for mother's race/ethnicity and n=3 for maternal education). Two participants

withdrew from the study. Therefore, the current analyses included 527 women with complete data on prenatal stress exposures and covariates who delivered a live born infant.

Prenatal stress: negative life events

Prenatal maternal stress was measured using the Crisis in Family Systems-Revised (CRISYS-R) survey, validated in English (Shalowitz, Berry, Rasinski, & Dannhausen-Brun, 1998) and Spanish (Berry, Quinn, Portillo, & Shalowitz, 2006). Mothers were asked to endorse life events experienced in the past six months across 11 domains (e.g., financial, legal, career, relationships, safety in the home, safety in the community, medical issues pertaining to self, medical issues pertaining to others, home issues, authority, and prejudice) and to rate each as positive, negative, or neutral. Stress theory centers around the notion that when humans experience environmental demands that rise to the level of overwhelming their existing coping resources, they experience distress/stress with a concomitant physiological disruption that may impact health (Cohen, Kessler, & Gordon, 1995). Research suggests increased vulnerability when experiencing events across multiple domains, as this circumstance is more likely to overwhelm coping resources; therefore, the number of domains with one or more events endorsed as negative were summed to create a negative life events (NLE) domain score, with higher scores indicating greater stress, as done in prior research (Rosa et al., 2016).

Gestational age and birthweight z-score

Gestational age was calculated based on maternal report of last menstrual period and obstetrical estimates from the first trimester ultrasound examination; if the discrepancy was >2 weeks, obstetrical estimates were used. Preterm birth was defined as gestational age less than 37 weeks.

Birthweight data were extracted from labor and delivery records. Because the traditional approach of using raw birthweight data adjusted for gestational age in a linear regression model may add bias (Oken, Kleinman, Rich-Edwards, & Gillman, 2003), z-scores were used, which allow adjustment for gestational age more precisely and factor in non-linear growth, reducing both bias and residual confounding (Oken, et al., 2003). Sex-specific Fenton birthweight for gestational age z-scores(Fenton and Kim, 2013) were calculated using reference curves derived from a growth curve modeling meta-analysis of preterm birth and previously validated with the World Health Organization (WHO) growth curves for postnatal growth.

Covariates

Previously identified covariates related to birth outcomes were considered. Maternal age and maternal education as an indicator of individual-level socioeconomic status were ascertained by interview. Race/ethnicity was self-identified. First, women were asked if they would consider themselves Hispanic and then were asked to select their race, being allowed to select more than one. Participants were categorized as Black, White Hispanic, White, or Other/Multiracial. If participants were Black and Hispanic they were included in the Black category. Participants' parity, marital status and smoking in pregnancy were ascertained through questionnaire at enrollment. Maternal pre-pregnancy height and weight were

determined via self-report at enrollment; body mass index (BMI) was calculated by dividing weight by height squared (kg/m^2).

Statistical Analysis

We used a modified Poisson regression approach (Zou, 2004) to obtain risk ratios for preterm birth and linear models to evaluate the association of prenatal NLE domain scores with gestational age and birthweight z-scores. Models were adjusted for maternal age, education, race/ethnicity, and pre-pregnancy BMI. Parity, marital status and smoking in pregnancy were also considered as potential covariates. Potential sex differences were examined by including an interaction term for sex by NLE domain score in each model and by stratifying analyses by sex. In the stratified analysis for preterm birth, race was collapsed into 2 mutually exclusive categories White and Non-White Analyses were performed in SAS version 9.4 (Cary, NC) and SPSS version 23 (Chicago, IL). In a sensitivity analysis, the NLE score was also calculated omitting items related to medical issues pertaining to self to mitigate the potential that women endorsing this stressor deliver early because they have medically complicated pregnancies.

Results

Demographic characteristics are shown in Table 1. The majority of women were non-White (74%), and approximately one-third had a high school education or less (37%). The incidence of preterm birth (< 37 weeks) was 8.9%, and 53.7% of infants were male. Table 2 shows the linear and logistic model associations for all birth outcomes. In the sample considered as a whole, the prenatal NLE score was not statistically significantly associated with preterm birth or birthweight z-scores. An increasing NLE score was statistically significantly associated with shortened gestational age β−0.63 95%CI (−1.20, −0.06). Parity, marital status and smoking in pregnancy were not included in final models because results remained virtually unchanged after their inclusion as covariates and they were not independently associated with any of the outcomes.

Full regression models for the main effects are included in the supplement (Tables S1–S3) Results were substantively unchanged in the sensitivity analysis using the NLE score omitting items for medical issues related to self (see supplemental material, table S4). We also report percent endorsement within each negative life domain in supplemental table S8. Table 3 shows results of adjusted models for the association between prenatal NLE domain scores and birth outcomes, stratified by sex and including the p-value for the interaction model. Full regression models for the interaction effects are included in the supplement (Tables S5–S7). Betas are shown for a 1 domain increase in prenatal NLE score. There was a statisticallysignificant sex by prenatal NLE score interaction (p=0.02) for gestational age, with only male infants showing a statistically significant negative association between prenatal NLE score and gestational age β −1.35 95%CI (−2.17,−0.54). There also was a suggestion of a sex by stress interaction for PTB (p=0.06); male infants had higher risk of PTB than female infants.

Discussion

These analyses leverage data from an ethnically-diverse urban US pregnancy cohort to examine the association between cumulative negative life events experienced in pregnancy and infant birth outcomes, including gestational age, preterm birth, and birthweight. In this sample, we found a statistically significant association between experiencing negative life events across an increasing number of life domains and decreased length of gestation. The association remained statistically significant after adjustment for potential confounders including maternal education, race/ethnicity, pre-pregnancy BMI and maternal age. There also was suggestive evidence that the effects of prenatal stress were, as measured by the NLE domain score, more pronounced among male infants for shortened gestation and increased risk of preterm birth. Associations between the NLE domain score and birthweight adjusted for gestational age were not statistically significant when examined in the sample as a whole or by infant sex.

When examining the association between prenatal stress and adverse health outcomes, previous work has utilized different stress constructs, including questionnaires related to perceived stress (e.g., Perceived Stress Scale), anxiety (e.g., State Trait Anxiety Inventory), pregnancy-specific anxiety, stressful life events, exposure to natural or man-made disasters, and maternal cortisol secretion. The studies that have used measures of stressful life events have, for the most part, yielded associations with shortened gestation. In a large study in Denmark, stress during pregnancy was ascertained using the modified Life Events Inventory, and a higher score of events classified as highly stressful during mid to late pregnancy was associated with shortened gestation (Hedegaard, et al., 1996). Dominguez *et. al* reported that stressful life events were associated with shortened gestational age in a group of African American women in the United States (Dominguez, Schetter, Mancuso, Rini, & Hobel, 2005). In a Chinese sample, report of greater perceived stress due to a reported life event during the first or second trimester was associated with increased risk of preterm birth (Zhu, Tao, Hao, Sun, & Jiang, 2010). In a study of women living in California, an increase in perceived stress assessed between two prenatal visits was associated with increased risk of PTB, but there was no statistically significant association between report of major life events and risk of PTB (Glynn, Schetter, Hobel, & Sandman, 2008).

There are several potential mechanisms through which prenatal stress exposure may influence birth outcomes. While glucocorticoids are needed for fetal organ development (C. L. Howerton and Bale, 2012), excess exposure may be detrimental to fetal development (Reynolds, 2013). Increased cortisol production due to stress may lead to increased placental corticotropin-releasing hormone (CRH) (Majzoub and Karalis, 1999) and CRH levels may differentiate term from preterm pregnancies (Mclean, et al., 1995). Exposure to psychosocial stress has been associated with increased inflammation and altered or dysregulated immune and inflammatory activity (Christian, 2012; Ross, et al., 2018), and these alterations during pregnancy have been associated with adverse pregnancy outcomes. For example, higher levels of peripheral pro-inflammatory markers have been reported in women who went on to have preterm labor compared to those who delivered at term (Ferguson, et al., 2014; Gargano, et al., 2008) There is also evidence from animal studies demonstrating associations between stress in pregnancy and adverse birth outcomes in offspring. In one study of Wistar

albino rats, exposure to psychological stress in pregnancy, modeled as physical restraint, was associated with increased rates of LBW and PTB when compared to the control group (Govindaraj, Shanmuganathan, & Rajan, 2017). Rodent studies have demonstrated the vulnerability of the fetus to prenatal stress; cortisol and acetyl-corticotropin hormones were found to be elevated in the hypothalami of the fetuses after their mothers experienced stress in pregnancy(Kofman, 2002; Sapolsky, 2000).

Studies examining sex-specific effects of prenatal stress on birth outcomes are sparser. The few epidemiological studies that have examined the effects of stress on birth outcomes by sex have produced mixed results. Wainstock and colleagues reported that stress, conceptualized as exposure to rocket alarms, was mostly associated with higher odds of PTB and LBW in females as compared to males (Wainstock, et al., 2015). Women in Chile who experienced a major earthquake early in pregnancy were reported as having shorter pregnancies and were at higher risk for delivering preterm; the effect was markedly stronger in females than males (Torche and Kleinhaus, 2012). While there was a reported decrease in ratio of male-to-female live births after the Great East Japan Earthquake, the authors reported no statistically significant differences in gestational duration for either males or females when comparing extremely affected regions to moderately or slightly affected regions (Suzuki, et al., 2016). In our study, the association between higher prenatal NLE domain scores and shortened gestation was stronger in male than female infants, suggesting that male fetuses were more vulnerable to maternal prenatal stress. The difference in findings across studies may be due to the varied methods used to measure stress. It also is possible that greater levels of maternal distress like those experienced during disasters or armed conflict result in the culling of male pregnancies (Trivers and Willard, 1973) while female pregnancies survive but with shortened gestations.

There are mechanistic data to support increased vulnerability to prenatal stress in male offspring when compared to female offspring(Sandman, Glynn, & Davis, 2013). A posited mechanism through which these differences may arise is sex-specific placental responsiveness to prenatal maternal stress and fetal sex hormones (Del Giudice et al., 2018; Mueller and Bale, 2008). *In utero* stress may also be more detrimental to male fetuses due to reduced activity and/or sensitivity of placental 11β-hydroxysteroid dehydrogenase type 2, leading to increased fetal glucocorticoid exposure, differential DNA methylation in the placenta (Appleton, et al., 2013), or enhanced vulnerability to stress-induced oxidation *in utero* (Minghetti, Greco, Zanardo, & Suppiej, 2013; Stark, Hodyl, Wright, & Clifton, 2011). Conversely, sex-specific differences in the relationship between fetal and placental glucocorticoid responses may have protective effects on females (Appleton, et al., 2013). While females may be more adaptive in response to stress and adverse events experienced during the prenatal period, there is also data suggesting that they may still suffer the effects of these exposures including increased fearful and reactive behavior and that these effects may last into preadolescence(Sandman, et al., 2013). Therefore, the continued follow-up of this population would be important in order to continue assessing the long term effects of prenatal stress exposure.

Strengths of our study include the prospective design, assessment of stress in pregnancy using a well-validated measure of negative life events that allows women to identify whether

the experience was negative, inclusion of ethnically-diverse populations and our ability to adjust for important confounders. We also acknowledge some limitations. We measured negative life events experienced in the past 6 months during the pregnancy rather than more definitively assessing timing of events; thus, we are unable to examine whether sex-specific effects could be further modified by timing of exposure as other data suggest (Glynn, Wadhwa, Dunkel-Schetter, Chicz-DeMet, & Sandman, 2001; Van den Bergh, et al., 2017). For approximately 30% of the participants, the negative life event scores would include the preconception period (questionnaire administered before 24 weeks). There is some evidence suggesting that stress during the preconception may be associated with increased risk of preterm birth, lower birthweight and higher risk of SGA (Khashan et al., 2009b; Khashan et al., 2008; Witt, Wisk, Cheng, Hampton, & Hagen, 2012). While we can't disentangle the timing effects of preconception from prenatal period we would in general expect to see a similar association. We do not have data on previous PTB, an important predictor of future PTB, in our participants. The rate of PTB in our participants is lower than the rates reported nationwide in the United States (Martin, Hamilton, Osterman, Driscoll, & Mathews, 2017) and we acknowledge that people who agree to participate in the study may be healthier than the general US population.

Studies that include biomarkers to more definitively assess underlying mechanisms that may contribute to sex-specific effects, including measurement of hormones related to the HPA and hypothalamic-pituitary-gonadal (HPG) axes (cortisol and sex steroids) as well as epigenetics in maternal, placental and cord blood DNA are needed. We also cannot rule out potential residual confounding due to unmeasured host and environmental factors that may affect birth outcomes.

This study adds to a growing literature underscoring the need to consider prenatal psychosocial stress as an important programming factor in fetal development and highlights the importance of considering sex-specific effects. Such knowledge can inform prevention and intervention strategies. Future studies should examine the programming of sex differences at varying developmental time points in response to maternal and early life stress to provide further insights into the etiology of adverse fetal outcomes. Future interventions should consider stress reduction modalities in pregnant women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Ansari H, Qorbani M, Rezaei F, Djalalinia S, Asadi M, Miranzadeh S, … Kelishadi R (2017). Association of birth weight with abdominal obesity and weight disorders in children and adolescents: the weight disorder survey of the CASPIAN-IV Study. J Cardiovasc Thorac Res, 9(3), pp. 140–146. doi:10.15171/jcvtr.2017.24 Retrieved from 10.15171/jcvtr.2017.24http://www.ncbi.nlm.nih.gov/pubmed/29118946 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29118946 [PubMed: 29118946]

Appleton AA, Armstrong DA, Lesseur C, Lee J, Padbury JF, Lester BM, & Marsit CJ (2013). Patterning in placental 11-B hydroxysteroid dehydrogenase methylation according to prenatal socioeconomic adversity. PLoS One, 8(9), p e74691. doi:10.1371/journal.pone.0074691 Retrieved from 10.1371/journal.pone.0074691http://www.ncbi.nlm.nih.gov/pubmed/24040322 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24040322 [PubMed: 24040322]

Ask H, Gustavson K, Ystrom E, Havdahl KA, Tesli M, Askeland RB, & Reichborn-Kjennerud T (2018). Association of Gestational Age at Birth With Symptoms of Attention-Deficit/Hyperactivity Disorder in Children. JAMA Pediatr doi:10.1001/jamapediatrics.2018.1315 Retrieved from 10.1001/jamapediatrics.2018.1315http://www.ncbi.nlm.nih.gov/pubmed/29946656 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29946656

Berry CA, Quinn KA, Portillo N, & Shalowitz MU (2006). Reliability and validity of the Spanish Version of the Crisis in Family Systems-Revised. Psychological Reports, 98(1), pp. 123–132. doi:10.2466/pr0.98.1.123-132 Retrieved from 10.2466/pr0.98.1.123-132http://www.ncbi.nlm.nih.gov/pubmed/16673963 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16673963 [PubMed: 16673963]

Blumenshine P, Egerter S, Barclay CJ, Cubbin C, & Braveman PA (2010). Socioeconomic disparities in adverse birth outcomes: a systematic review. American Journal of Preventive Medicine, 39(3), pp. 263–272. doi:10.1016/j.amepre.2010.05.012 Retrieved from 10.1016/j.amepre.2010.05.012http://www.ncbi.nlm.nih.gov/pubmed/20709259 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20709259 [PubMed: 20709259]

Borrell LN, Rodriguez-Alvarez E, Savitz DA, & Baquero MC (2016). Parental Race/Ethnicity and Adverse Birth Outcomes in New York City: 2000–2010. American Journal of Public Health, 106(8), pp. 1491–1497. doi:10.2105/AJPH.2016.303242 Retrieved from 10.2105/AJPH.2016.303242http://www.ncbi.nlm.nih.gov/pubmed/27310345 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/27310345 [PubMed: 27310345]

Bussieres EL, Tarabulsy GM, Pearson J, Tessier R, Forest JC, & Giguere Y (2015). Maternal prenatal stress and infant birth weight and gestational age: A meta-analysis of prospective studies. Developmental Review, 36, pp. 179–199. doi:10.1016/j.dr.2015.04.001 Retrieved from <Go to ISI>://WOS:000355784100008

Christian LM (2012). Psychoneuroimmunology in pregnancy: immune pathways linking stress with maternal health, adverse birth outcomes, and fetal development. Neurosci Biobehav Rev, 36(1), pp. 350–361. doi:10.1016/j.neubiorev.2011.07.005 Retrieved from 10.1016/j.neubiorev.2011.07.005http://www.ncbi.nlm.nih.gov/pubmed/21787802 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21787802 [PubMed: 21787802]

Clifton VL (2010). Sex and the Human Placenta: Mediating Differential Strategies of Fetal Growth and Survival. Placenta, 31, pp. S33–S39. doi:10.1016/j.placenta.2009.11.010 Retrieved from <Go to ISI>://WOS:000275707000006 [PubMed: 20004469]

Cohen S, Kessler RC, & Gordon LU (1995). Strategies for measuring stress in studies of psychiatric and physical disorders Measuring stress: A guide for health and social scientists. (pp. 3–26). New York, NY, US: Oxford University Press.

Del Giudice M, Barrett ES, Belsky J, Hartman S, Martel MM, Sangenstedt S, & Kuzawa CW (2018). Individual differences in developmental plasticity: A role for early androgens? Psychoneuroendocrinology, 90, pp. 165–173. doi:10.1016/j.psyneuen.2018.02.025 Retrieved from 10.1016/j.psyneuen.2018.02.025http://www.ncbi.nlm.nih.gov/pubmed/29500952 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29500952 [PubMed: 29500952]

Dominguez TP, Schetter CD, Mancuso R, Rini CM, & Hobel C (2005). Stress in African American Pregnancies: Testing the roles of various stress concepts in prediction of birth outcomes. Annals of

Behavioral Medicine, 29(1), pp. 12–21. doi:10.1207/s15324796abm2901_3 Retrieved from <Go to ISI>://WOS:000226620000002 [PubMed: 15677296]

Doyle C, Werner E, Feng TS, Lee S, Altemus M, Isler JR, & Monk C (2015). Pregnancy distress gets under fetal skin: Maternal ambulatory assessment & sex differences in prenatal development. Developmental Psychobiology, 57(5), pp. 607–625. doi:10.1002/dev.21317 Retrieved from <Go to ISI>://WOS:000356691900007 [PubMed: 25945698]

Dunkel Schetter C, & Tanner L (2012). Anxiety, depression and stress in pregnancy: implications for mothers, children, research, and practice. Curr Opin Psychiatry, 25(2), pp. 141–148. doi:10.1097/YCO.0b013e3283503680 Retrieved from 10.1097/YCO.0b013e3283503680http://www.ncbi.nlm.nih.gov/pubmed/22262028 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22262028 [PubMed: 22262028]

Fenton TR, & Kim JH (2013). A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr, 13, p 59. doi:10.1186/1471-2431-13-59 Retrieved from 10.1186/1471-2431-13-59http://www.ncbi.nlm.nih.gov/pubmed/23601190 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23601190 [PubMed: 23601190]

Ferguson KK, McElrath TF, Chen YH, Mukherjee B, & Meeker JD (2014). Longitudinal Profiling of Inflammatory Cytokines and C-reactive Protein during Uncomplicated and Preterm Pregnancy. American Journal of Reproductive Immunology, 72(3), pp. 326–336. doi:10.1111/aji.12265 Retrieved from <Go to ISI>://WOS:000340530100009 [PubMed: 24807462]

Gargano JW, Holzman C, Senagore P, Thorsen P, Skogstrand K, Hougaard DM, … Chung H (2008). Mid-pregnancy circulating cytokine levels, histologic chorioamnionitis and spontaneous preterm birth. Journal of Reproductive Immunology, 79(1), pp. 100–110. doi:10.1016/j.jri.2008.08.006 Retrieved from <Go to ISI>://WOS:000260989000014 [PubMed: 18814919]

Glynn LM, Schetter CD, Hobel CJ, & Sandman CA (2008). Pattern of perceived stress and anxiety in pregnancy predicts preterm birth. Health Psychology, 27(1), pp. 43–51. doi:10.1037/0278-6133.27.1.43 Retrieved from 10.1037/0278-6133.27.1.43http://www.ncbi.nlm.nih.gov/pubmed/18230013 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18230013 [PubMed: 18230013]

Glynn LM, Wadhwa PD, Dunkel-Schetter C, Chicz-DeMet A, & Sandman CA (2001). When stress happens matters: Effects of earthquake timing on stress responsivity in pregnancy. Am J Obstet Gynecol, 184(4), pp. 637–642. doi:DOI 10.1067/mob.2001.111066 Retrieved from <Go to ISI>://WOS:000167841300019 [PubMed: 11262465]

Govindaraj S, Shanmuganathan A, & Rajan R (2017). Maternal psychological stress-induced developmental disability, neonatal mortality and stillbirth in the offspring of Wistar albino rats. PLoS One, 12(2), p e0171089. doi:10.1371/journal.pone.0171089 Retrieved from 10.1371/journal.pone.0171089http://www.ncbi.nlm.nih.gov/pubmed/28222133 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/28222133 [PubMed: 28222133]

Grobman WA, Parker C, Wadhwa PD, Willinger M, Simhan H, Silver B, … C, E. K. S. N. I. (2016). Racial/Ethnic Disparities in Measures of Self-reported Psychosocial States and Traits during Pregnancy. American Journal of Perinatology, 33(14), pp. 1426–1432. doi:10.1055/s-0036-1586510 Retrieved from <Go to ISI>://WOS:000388549100014 [PubMed: 27500932]

Hedegaard M, Henriksen TB, Secher NJ, Hatch MC, & Sabroe S (1996). Do stressful life events affect duration of gestation and risk of preterm delivery? Epidemiology, 7(4), pp. 339–345. doi:Doi 10.1097/00001648-199607000-00001 Retrieved from <Go to ISI>://WOS:A1996UT95400003 [PubMed: 8793357]

Hobel CJ (2004). Stress and preterm birth. Clinical Obstetrics and Gynecology, 47(4), pp. 856–880. doi:DOI 10.1097/01.grf.0000142512.38733.8c Retrieved from <Go to ISI>://WOS:000231531000011 [PubMed: 15596939]

Hobel CJ, Goldstein A, & Barrett ES (2008). Psychosocial stress and pregnancy outcome. Clinical Obstetrics and Gynecology, 51(2), pp. 333–348. doi:DOI 10.1097/GRF.0b013e31816f2709 Retrieved from <Go to ISI>://WOS:000256184000015 [PubMed: 18463464]

Howerton AR, Roland AV, Fluharty JM, Marshall A, Chen A, Daniels D, … Bale TL (2014). Sex Differences in Corticotropin-Releasing Factor Receptor-1 Action Within the Dorsal Raphe Nucleus in Stress Responsivity. Biological Psychiatry, 75(11), pp. 873–883. doi:10.1016/

j.biopsych.2013.10.013 Retrieved from <Go to ISI>://WOS:000335902400010 [PubMed: 24289884]

Howerton CL, & Bale TL (2012). Prenatal programing: At the intersection of maternal stress and immune activation. Horm Behav, 62(3), pp. 237–242. doi:10.1016/j.yhbeh.2012.03.007 Retrieved from <Go to ISI>://WOS:000309946300007 [PubMed: 22465455]

Khashan AS, McNamee R, Abel KM, Mortensen PB, Kenny LC, Pedersen MG, … Baker PN (2009a). Rates of preterm birth following antenatal maternal exposure to severe life events: a population-based cohort study. Human Reproduction, 24(2), pp. 429–437. doi:10.1093/humrep/den418 Retrieved from <Go to ISI>://WOS:000262519500023 [PubMed: 19054778]

Khashan AS, McNamee R, Abel KM, Mortensen PB, Kenny LC, Pedersen MG, … Baker PN (2009b). Rates of preterm birth following antenatal maternal exposure to severe life events: a population-based cohort study. Human Reproduction, 24(2), pp. 429–437. doi:10.1093/humrep/den418 Retrieved from 10.1093/humrep/den418http://www.ncbi.nlm.nih.gov/pubmed/19054778 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19054778 [PubMed: 19054778]

Khashan AS, McNamee R, Abel KM, Pedersen MG, Webb RT, Kenny LC, … Baker PN (2008). Reduced infant birthweight consequent upon maternal exposure to severe life events. Psychosomatic Medicine, 70(6), pp. 688–694. doi:10.1097/PSY.0b013e318177940d Retrieved from <Go to ISI>://WOS:000257827100009 [PubMed: 18606728]

Kofman O (2002). The role of prenatal stress in the etiology of developmental behavioural disorders. Neuroscience and Biobehavioral Reviews, 26(4), pp. 457–470. doi:Pii S0149–7634(02)00015–5 Doi 10.1016/S0149–7634(02)00015–5 Retrieved from <Go to ISI>://WOS:000178191300004 [PubMed: 12204192]

Leps C, Carson C, & Quigley MA (2018). Gestational age at birth and wheezing trajectories at 3–11 years. Archives of Disease in Childhood doi:10.1136/archdischild-2017-314541 Retrieved from 10.1136/archdischild-2017-314541http://www.ncbi.nlm.nih.gov/pubmed/29860226 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29860226

Lorch SA, & Enlow E (2016). The role of social determinants in explaining racial/ethnic disparities in perinatal outcomes. Pediatric Research, 79(1–2), pp. 141–147. doi:10.1038/pr.2015.199 Retrieved from 10.1038/pr.2015.199http://www.ncbi.nlm.nih.gov/pubmed/26466077 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/26466077 [PubMed: 26466077]

Majzoub JA, & Karalis KP (1999). Placental corticotropin-releasing hormone: Function and regulation. Am J Obstet Gynecol, 180(1), pp. S242–S246. doi:Doi 10.1016/S0002–9378(99)70708–8 Retrieved from <Go to ISI>://WOS:000078224700008 [PubMed: 9914625]

Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, & Mathews TJ (2017). Births: Final data for 2015. National vital statistics report. 66(1)

Mclean M, Bisits A, Davies J, Woods R, Lowry P, & Smith R (1995). A Placental Clock Controlling the Length of Human-Pregnancy. Nature Medicine, 1(5), pp. 460–463. doi:DOI 10.1038/nm0595–460 Retrieved from <Go to ISI>://WOS:A1995RN10000038

Minghetti L, Greco A, Zanardo V, & Suppiej A (2013). Early-life sex-dependent vulnerability to oxidative stress: the natural twining model. Journal of Maternal-Fetal & Neonatal Medicine, 26(3), pp. 259–262. doi:10.3109/14767058.2012.733751 Retrieved from <Go to ISI>://WOS:000313681200010 [PubMed: 23020682]

Mueller BR, & Bale TL (2008). Sex-specific programming of offspring emotionality after stress early in pregnancy. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. Journal Neuroscience, 28(36), pp. 9055–9065. doi:10.1523/JNEUROSCI.1424-08.2008 Retrieved from 10.1523/JNEUROSCI.1424-08.2008http://www.ncbi.nlm.nih.gov/pubmed/18768700 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18768700 [PubMed: 18768700]

Mutambudzi M, Meyer JD, Reisine S, & Warren N (2017). A review of recent literature on materialist and psychosocial models for racial and ethnic disparities in birth outcomes in the US, 2000–2014. Ethn Health, 22(3), pp. 311–332. doi:10.1080/13557858.2016.1247150 Retrieved from 10.1080/13557858.2016.1247150http://www.ncbi.nlm.nih.gov/pubmed/27852109 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/27852109 [PubMed: 27852109]

Nkansah-Amankra S, Luchok KJ, Hussey JR, Watkins K, & Liu X (2010). Effects of maternal stress on low birth weight and preterm birth outcomes across neighborhoods of South Carolina, 2000–2003. Matern Child Health J, 14(2), pp. 215–226. doi:10.1007/s10995-009-0447-4 Retrieved from

10.1007/s10995-009-0447-4http://www.ncbi.nlm.nih.gov/pubmed/19184386 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19184386 [PubMed: 19184386]

Oken E, Kleinman KP, Rich-Edwards J, & Gillman MW (2003). A nearly continuous measure of birth weight for gestational age using a United States national reference. BMC Pediatr, 3, p 6. doi: 10.1186/1471-2431-3-6 Retrieved from 10.1186/1471-2431-3-6http://www.ncbi.nlm.nih.gov/pubmed/12848901 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12848901 [PubMed: 12848901]

Ostlund BD, Conradt E, Crowell SE, Tyrka AR, Marsit CJ, & Lester BM (2016). Prenatal Stress, Fearfulness, and the Epigenome: Exploratory Analysis of Sex Differences in DNA Methylation of the Glucocorticoid Receptor Gene. Front Behav Neurosci, 10 doi:ARTN 147 10.3389/fnbeh.2016.00147 Retrieved from <Go to ISI>://WOS:000379393200001

Reynolds RM (2013). Glucocorticoid excess and the developmental origins of disease: two decades of testing the hypothesis−−2012 Curt Richter Award Winner. Psychoneuroendocrinology, 38(1), pp. 1–11. doi:10.1016/j.psyneuen.2012.08.012 Retrieved from 10.1016/j.psyneuen.2012.08.012http://www.ncbi.nlm.nih.gov/pubmed/22998948 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22998948 [PubMed: 22998948]

Rosa MJ, Just AC, Tamayo YOM, Schnaas L, Svensson K, Wright RO, … Wright RJ (2016). Prenatal and postnatal stress and wheeze in Mexican children: Sex-specific differences. Ann Allergy Asthma Immunol doi:10.1016/j.anai.2015.12.025 Retrieved from 10.1016/j.anai.2015.12.025http://www.ncbi.nlm.nih.gov/pubmed/26822280 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/26822280

Ross KM, Cole SW, Carroll JE, & Dunkel Schetter C (2018). Elevated pro-inflammatory gene expression in the third trimester of pregnancy in mothers who experienced stressful life events. Brain Behav Immun doi:10.1016/j.bbi.2018.11.009 Retrieved from 10.1016/j.bbi.2018.11.009http://www.ncbi.nlm.nih.gov/pubmed/30447280 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30447280

Sandman CA, Glynn LM, & Davis EP (2013). Is there a viability-vulnerability tradeoff? Sex differences in fetal programming. Journal of Psychosomatic Research, 75(4), pp. 327–335. doi: 10.1016/j.jpsychores.2013.07.009 Retrieved from <Go to ISI>://WOS:000325838400006 [PubMed: 24119938]

Sapolsky RM (2000). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Archives of General Psychiatry, 57(10), pp. 925–935. doi:DOI 10.1001/archpsyc.57.10.925 Retrieved from <Go to ISI>://WOS:000089650300001 [PubMed: 11015810]

Shalowitz MU, Berry CA, Rasinski KA, & Dannhausen-Brun CA (1998). A new measure of contemporary life stress: development, validation, and reliability of the CRISYS. Health Services Research, 33(5 Pt 1), pp. 1381–1402. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9865225 [PubMed: 9865225]

Stark MJ, Hodyl NA, Wright IM, & Clifton VL (2011). Influence of sex and glucocorticoid exposure on preterm placental pro-oxidant-antioxidant balance. Placenta, 32(11), pp. 865–870. doi:10.1016/j.placenta.2011.08.010 Retrieved from 10.1016/j.placenta.2011.08.010http://www.ncbi.nlm.nih.gov/pubmed/21903264 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21903264 [PubMed: 21903264]

Suzuki K, Yamagata Z, Kawado M, & Hashimoto S (2016). Effects of the Great East Japan Earthquake on Secondary Sex Ratio and Perinatal Outcomes. J Epidemiol, 26(2), pp. 76–83. doi:10.2188/jea.JE20150055 Retrieved from 10.2188/jea.JE20150055http://www.ncbi.nlm.nih.gov/pubmed/26639751 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/26639751 [PubMed: 26639751]

Tollenaar MS, Beijers R, Jansen J, Riksen-Walraven JMA, & de Weerth C (2011). Maternal prenatal stress and cortisol reactivity to stressors in human infants. Stress-the International Journal on the Biology of Stress, 14(1), pp. 53–65. doi:10.3109/10253890.2010.499485 Retrieved from <Go to ISI>://WOS:000285422400007

Torche F, & Kleinhaus K (2012). Prenatal stress, gestational age and secondary sex ratio: the sex-specific effects of exposure to a natural disaster in early pregnancy. Human Reproduction, 27(2), pp. 558–567. doi:10.1093/humrep/der390 Retrieved from 10.1093/humrep/der390http://www.ncbi.nlm.nih.gov/pubmed/22157912 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22157912 [PubMed: 22157912]

Trivers RL, & Willard DE (1973). Natural selection of parental ability to vary the sex ratio of offspring. Science, 179(4068), pp. 90–92. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/4682135 [PubMed: 4682135]

Van den Bergh BRH, van den Heuvel MI, Lahti M, Braeken M, de Rooij SR, Entringer S, … Schwab M (2017). Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. Neurosci Biobehav Rev doi:10.1016/j.neubiorev.2017.07.003 Retrieved from 10.1016/j.neubiorev.2017.07.003http://www.ncbi.nlm.nih.gov/pubmed/28757456 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/28757456

Wadhwa PD, Garite TJ, Porto M, Glynn L, Chicz-DeMet A, Dunkel-Schetter C, & Sandman CA (2004). Placental corticotropin-releasing hormone (CRH), spontaneous preterm birth, and fetal growth restriction: A prospective investigation. Am J Obstet Gynecol, 191(4), pp. 1063–1069. doi:10.1016/j.ajog.2004.06.070 Retrieved from <Go to ISI>://WOS:000224812100004 [PubMed: 15507922]

Wainstock T, Shoham-Vardi I, Glasser S, Anteby E, & Lerner-Geva L (2015). Fetal sex modifies effects of prenatal stress exposure and adverse birth outcomes. Stress-the International Journal on the Biology of Stress, 18(1), pp. 49–56. doi:10.3109/10253890.2014.974153 Retrieved from 10.3109/10253890.2014.974153http://www.ncbi.nlm.nih.gov/pubmed/25319674 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/25319674

Wells PG, McCallum GP, Chen CS, Henderson JT, Lee CJ, Perstin J, … Wong AW (2009). Oxidative stress in developmental origins of disease: teratogenesis, neurodevelopmental deficits, and cancer. Toxicological Sciences, 108(1), pp. 4–18. doi:10.1093/toxsci/kfn263 Retrieved from 10.1093/toxsci/kfn263http://www.ncbi.nlm.nih.gov/pubmed/19126598 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19126598 [PubMed: 19126598]

Witt WP, Wisk LE, Cheng ER, Hampton JM, & Hagen EW (2012). Preconception mental health predicts pregnancy complications and adverse birth outcomes: a national population-based study. Matern Child Health J, 16(7), pp. 1525–1541. doi:10.1007/s10995-011-0916-4 Retrieved from 10.1007/s10995-011-0916-4http://www.ncbi.nlm.nih.gov/pubmed/22124801 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22124801 [PubMed: 22124801]

Zhu P, Tao F, Hao J, Sun Y, & Jiang X (2010). Prenatal life events stress: implications for preterm birth and infant birthweight. Am J Obstet Gynecol, 203(1), pp. 34 e31–38. doi:10.1016/j.ajog.2010.02.023 Retrieved from 10.1016/j.ajog.2010.02.023http://www.ncbi.nlm.nih.gov/pubmed/20417475 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20417475 [PubMed: 20417475]

Zilko CE (2010). Economic contraction and birth outcomes: an integrative review. Hum Reprod Update, 16(4), pp. 445–458. doi:10.1093/humupd/dmp059 Retrieved from 10.1093/humupd/dmp059http://www.ncbi.nlm.nih.gov/pubmed/20085917 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20085917 [PubMed: 20085917]

Zou GY (2004). A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol, 159(7), pp. 702–706. doi:10.1093/aje/kwh090 Retrieved from <Go to ISI>://WOS:000220484900009 [PubMed: 15033648]

Table 1.

Descriptive characteristics of PRISM sample (N=527)

Maternal age at delivery, median (IQR)	30.2 (25.2, 34.6)
Maternal pre-pregnancy BMI, median (IQR)	24.4 (21.9, 29.8)
Race/Ethnicity, n (%)	
White, Hispanic	180 (34.2)
Black	191 (36.2)
White, non-Hispanic	125 (23.7)
Other/multi-racial	31 (5.9)
Education, n (%)	
≤ High school	195 (37.0)
> High school	332 (63.0)
Parity, n (%)	
Nulliparous	211 (40)
Parous	313 (60)
Missing	3
Marital Status, n (%)	
Married or living with partner	386 (73.2)
Single, divorced, separated or widowed	141 (26.8)
Maternal smoking in pregnancy, n (%)	87 (16.5)
Missing	1
Child sex, n (%)	
Male	282 (53.5)
Female	245 (46.3)
Negative life event (NLE) domain score, median (IQR) *	2 (1, 3)
Gestational age (days), mean (SD)	273 (12.8)
Birthweight for gestational age z-score, mean (SD) †	−0.20 (0.90)
Preterm birth (<37 weeks), n (%)	47 (8.9)

Abbreviations: IQR, interquartile range; BMI, body mass index; SD: standard deviation.

*Assessed using Crisis in Family Systems-Revised (CRISYS-R) survey; multi-item survey summarized into a continuous score.

†Sex-specific Fenton birthweight for gestational age z-scores calculated using reference curves derived from growth curve modeling meta-analysis

Table 2.

Adjusted regression models assessing the relationship between prenatal stress and gestational age, preterm birth, and birthweight z-score[*] (N=527)

	Estimates (95%CI)	*P*-value
Gestational age (days)	−0.63 (−1.20, −0.06)	0.03
Preterm birth (<37 weeks) (RR)	1.01 (0.88, 1.17)	0.85
Birthweight for gestational age z-score[†]	−0.01 (−0.05, 0.04)	0.79

β shown for gestational age and birthweight z-scores. β represents the change in gestational age in days or birthweight z-score per 1 domain increase in the prenatal NLE score. Risk ratio shown for preterm birth.

[*] All models adjusted for child sex, maternal age, education, race/ethnicity, and pre-pregnancy BMI.

[†] Sex-specific Fenton birthweight for gestational age z-scores calculated using reference curves derived from growth curve modeling meta-analysis

Table 3.

Adjusted regression models assessing the relationship between prenatal NLE domain score and birth outcomes stratified by infant sex*

	Male Infants N=282	Female Infants N=245	P-value interaction
	Estimates (95% CI)	**Estimates (95% CI)**	
Gestational age	−1.35 (−2.17,−0.54)	0.15 (−0.63, 0.94)	0.02
Preterm birth (< 37 weeks)	1.18 (0.99, 1.42)	0.85 (0.65, 1.11)	0.06
Birthweight for gestational age z-score†	−0.02 (−0.08, 0.037)	0.02 (−0.04, 0.072)	0.26

β shown for gestational age and birthweight z-scores. β represents the change in gestational age in days or birthweight z-score per 1 domain increase in the prenatal NLE score. RR shown for preterm birth.

*All models adjusted for maternal age, education, race/ethnicity, and pre-pregnancy BMI.

†Sex-specific Fenton birthweight for gestational age z-scores calculated using reference curves derived from growth curve modeling meta-analysis