Prenatal and postnatal stress and asthma in children: Temporal- and sex-specific associations

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Background: Temporal- and sex-specific effects of perinatal stress have not been examined for childhood asthma.
Objectives: We examined associations between prenatal and/or postnatal stress and children's asthma (n = 765) and effect modification by sex in a prospective cohort study.
Methods: Maternal negative life events were ascertained prenatally and postpartum. Negative life event scores were categorized as 0, 1 to 2, 3 to 4, or 5 or greater to assess exposure-response relationships. We examined effects of prenatal and postnatal stress on children's asthma by age 6 years, modeling each as independent predictors, mutually adjusting for prenatal and postnatal stress, and finally considering interactions between prenatal and postnatal stress. Effect modification by sex was examined in stratified analyses and by fitting interaction terms.
Results: When considering stress in each period independently, among boys, a dose-response relationship was evident for each level increase on the ordinal scale prenatally (odds ratio [OR], 1.38; 95% CI, 1.06-1.79; *P* value for trend = .03) and postnatally (OR, 1.53; 95% CI, 1.16-2.01; *P* value for trend = .001); among girls, only the postnatal trend was significant (OR, 1.60; 95% CI, 1.14-2.22; *P* value for trend = .005). Higher stress in both the prenatal and postnatal periods was associated with increased odds of receiving a diagnosis of asthma in girls (OR, 1.37; 95% CI, 0.98-1.91; $P_{interaction}$ = .07) but not boys (OR, 1.08; 95% CI, 0.82-1.42; $P_{interaction}$ = .61).
Conclusions: Although boys were more vulnerable to stress during the prenatal period, girls were more affected by postnatal stress and cumulative stress across both periods in relation to asthma. Understanding sex and temporal differences in response to early-life stress might provide unique insight into the cause and natural history of asthma. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: *Negative life events, perinatal stress, childhood asthma, sex- and temporal-specific effects*

A growing number of prospective epidemiologic studies demonstrate associations between increased prenatal maternal stress and early asthma phenotypes.[1-5] Although the magnitude of the association varies across studies, likely because of differences in study design, timing of exposure, and the stress measure used, a recent meta-analysis substantiated a significant relationship between prenatal stress and childhood asthma.[6] Similarly, increased postnatal caregiver perceived stress,[7] adverse life events,[1] and persistent depressive symptoms in mothers[8,9] have all been prospectively linked with wheeze and asthma in preschool-aged children. Although studies to date have assessed the effect of either prenatal or postnatal stress exposure, the relative importance of either exposure window is not well understood.

Exposure to psychological stress in critical developmental windows, including pregnancy and early childhood, can result in permanently altered changes in stress-response systems (eg, immune, autonomic, neuroendocrine, and oxidation),[10-12] which are thought to play a role in the programming of respiratory disorders, including asthma.[13-16] The fetus is particularly vulnerable to stress because of immature immune, neuroendocrine, and antioxidant defenses.[17,18] In addition, infants continue to be vulnerable because these systems are still developing and remain highly reactive and labile in response to environmental stressors in early life, particularly in the first 2 years.[19,20]

Pioneering studies performed largely in animals demonstrate that effects of prenatal stress, hormonal correlates, or both on offspring development might be different from those related to postnatal stress[21] and might differ based on the offspring's sex. Sex-specific placental responsiveness to prenatal maternal stress and fetal sex hormones can contribute to differential effects of *in utero* stress on developmental outcomes.[22,23] Potential mechanisms might include differential placental 11β-hydroxysteroid dehydrogenase type 2 activity, sensitivity, or both[24,25]; stress-induced oxidation *in utero*[26]; and/or prenatal stress effects on inflammatory disorders caused by interactions of sex hormones and immune-inflammatory pathways.[27]

Prenatal stress can also result in altered programming of stress-response systems, with enhanced vulnerability to subsequent stressful events such that those exposed in both time periods might be at greatest risk (ie, a "2-hit" model of disease[28]).

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Abbreviations used
BC: Black carbon
BMI: Body mass index
BWGA: Birth weight for gestational age
HPA: Hypothalamic-pituitary-adrenal
HPG: Hypothalamic-pituitary-gonadal
NLE: Negative life event
OR: Odds ratio

Evidence demonstrates that an adverse postnatal environment modulates developmental consequences of prenatal stress in a sex-specific manner as well, with female subjects generally being more adversely affected.[29]

Human studies examining sex-specific effects of early-life stress on childhood asthma are sparse, with conflicting results. An analysis using hospital contact data (n > 400,000) found that prenatal exposure to maternal bereavement (a proxy for maternal prenatal stress) was associated with a faster time to first asthma event between ages 1 and 4 years and having a documented asthma attack at age 7 to 12 years in boys but not girls.[30] A study of 68 children born to mothers exposed prenatally to disaster-related stress (ie, the 1998 Quebec Ice Storm) showed increased physician-diagnosed asthma in girls but not boys.[31] Although these findings suggest differential effects of prenatal stress on asthma development based on fetal sex, the studies were limited by the indirect measurement of prenatal stress and a lack of postnatal stress assessment so that the relative importance of exposure timing could not be examined. Understanding temporal- and sex-specific perinatal stress effects on asthma might help elucidate programming mechanisms and better identify those at heightened risk so that interventions can be applied at the correct life stage to promote optimal development.

In this study we leveraged a prospective pregnancy cohort to examine the relative importance of exposure to prenatal and/or postnatal stress in association with children's asthma onset by age 6 years. Specifically, we first examined the effects of prenatal and postnatal stress in independent models, then mutually adjusted for prenatal/postnatal stress, and finally examined the joint effects of exposure to increased stress in both pregnancy and the first 2 years of life. We also examined whether temporal effects of perinatal stress differed relative to the child's sex. We hypothesized that among boys, increased prenatal stress would be more strongly associated with asthma development, whereas among girls, increased exposure to stress in the postnatal period and/or joint exposure to increased prenatal and postnatal stress would be associated with a greater likelihood of having asthma.

METHODS

Study participants

The Asthma Coalition on Community, Environment, and Social Stress project, a pregnancy cohort designed to examine the effects of perinatal stress and other environmental factors on urban childhood asthma risk, has been described previously.[32] Briefly, English- or Spanish-speaking women receiving prenatal care at 2 Boston hospitals and affiliated community health centers were recruited from August 2002 to September 2009; 989 (78.1%) eligible women approached between 28.4 ± 7.9 weeks' gestation agreed to enroll. Of those enrolled, 955 gave birth to a singleton live born infant and continued follow-up. There were no significant differences for race/ethnicity, education, and income between eligible participants who enrolled compared with those who declined. These analyses include 765 mother-infant dyads with data on prenatal and postnatal stress followed up to age 6 years. Procedures were approved by human studies committees at the Brigham and Women's Hospital and Boston Medical Center; written consent was obtained in the participant's primary language.

Negative life events

Prenatal and postnatal maternal stress were measured by using the Crisis in Family Systems–Revised survey, which was validated in English and Spanish[33,34] and administered within 2 weeks of enrollment and between 12 and 18 months postnatally. Mothers were asked to endorse life events experienced in the past 6 months across 11 domains (eg, 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 we experience environmental demands that rise to the level of overwhelming our existing coping resources, we experience distress/stress with a concomitant physiologic disruption that can affect health.[35,36] Research suggests increased vulnerability when experiencing events across multiple domains because this circumstance is more likely to overwhelm coping resources; therefore domains with 1 or more negative event were summed to create a negative life event (NLE) domain score, with higher scores indicating greater stress.[37]

Asthma onset

Telephone and face-to-face interviews at approximately 3-month intervals for the first 24 months of life and then annually thereafter up to age 6 years were used to determine maternal-reported clinician-diagnosed asthma. Mothers were asked, "Has a doctor or nurse ever said that your child had asthma?" The majority of children received a diagnosis of asthma after age 3 years (78.7%, see Fig E1 in this article's Online Repository at www.jacionline.org).

Covariates

Potential confounders and pathway variables were considered. Questionnaires ascertained maternal age, education, race/ethnicity, atopic history (ever having clinician-diagnosed asthma, eczema, and/or hay fever), prepregnancy height and weight, and child's sex, season of birth, and birth weight. Gestational age was based on reported last menstrual period and obstetric estimates on medical record review.[38] Birth weight for gestational age (BWGA) z scores were calculated based on normative US data.[39] Mothers who reported smoking at baseline, in the third trimester, or both were classified as prenatal smokers; postnatal smoke exposure was documented based on maternal report of smoking and/or whether others smoked in the home at each postpartum interview. Maternal body mass index (BMI) was calculated by dividing weight by height squared (in kilograms per meter squared). An internal validation analysis showed good agreement comparing height and weight measured early in pregnancy (<10 weeks) with self-reported values.[40]

Urban residents experiencing a greater number of NLEs might be more likely to be exposed to other environmental conditions that contribute to asthma expression.[41,42] Prenatal exposure to traffic-related air pollution, specifically black carbon (BC), was estimated by using a validated spatiotemporal land-use regression model that used maternal residential address over the entire pregnancy, as detailed previously.[43] Populations of lower socioeconomic status exposed to higher stress might also be exposed to increased levels of household allergens.[44] Settled dust collected within 2 weeks of enrollment from the mother's bedroom using a standardized protocol[45] was assayed for cockroach allergen (*Blatella germanica*, Bla g 1 and 2) by using an mAb-based ELISA (Indoor Biotechnologies, Charlottesville, Va). Social resources that might influence stress experiences and asthma among residents can also vary by neighborhood characteristics or quality.[41] A measure of neighborhood disadvantage was derived by linking enrollment addresses with aggregated data (census tract) from the 2000 US Census indexed as an average z score for percentages of neighborhood residents who were living below the poverty line, unemployed, non-US citizens, and nonwhite.[46] Higher z scores indicated greater disadvantage.