Prenatal Maternal Stress and Pediatric Asthma Across Development: Adolescent Female-Specific Vulnerability

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Abstract

Prenatal maternal stress (PNMS) is linked to physical sequelae in offspring, including childhood asthma. This study sought to examine the roles of objective and subjective PNMS in the development of asthma at offspring ages 5 and 15. The sample included 815 mother-child dyads from the Mater Misericordiae Mothers' Hospital-University of Queensland Study of Pregnancy. PNMS was measured via retrospective self-report during pregnancy and 3–5 days after birth. Postnatal maternal stress was measured at offspring age 5. Objective PNMS was associated with elevated asthma risk at age 5 (OR = 1.21, 95% CI = 1.00, 1.45, $p = 0.05$), albeit not above concurrent postnatal stress. Sex moderated the association between PNMS and asthma at age 15, controlling for postnatal stress. Sex stratified analyses revealed a positive association between objective PNMS and age 15 asthma in females, but *not* males. Results provide evidence that PNMS may impact asthma outcomes in adolescence.

Summary

Prenatal maternal stress (PNMS) is linked to physical and mental health sequelae in offspring, including childhood asthma. To date, studies linking PNMS to asthma outcomes do not extend into adolescence. This study sought to expand longitudinal findings by examining the roles of objective and subjective PNMS in the development of asthma at offspring ages 5 and 15 years. The sample included 815 mother-child dyads from the Mater Misericordiae Mothers' Hospital-University of Queensland Study of Pregnancy. Objective and subjective PNMS were measured via retrospective self-report both during pregnancy (gestational age: $M = 19.36$ weeks, $SD = 5.80$ weeks) and 3–5 days after birth. Objective and subjective postnatal maternal stress were measured at the offspring age 5 visit. Offspring asthma was measured at ages 5 and 15 years by maternal report. Objective PNMS (stressful live events in the last 6 months of pregnancy) was associated with elevated asthma risk at age 5 years (OR = 1.21, 95% CI = 1.00, 1.45, $p = 0.05$), albeit not above the effects of concurrent maternal stress at offspring age 5. Sex moderated the association between subjective and objective PNMS stress and asthma at age 15 years, even when controlling for maternal stress at offspring age 5. Sex stratified analyses revealed a positive association between objective PNMS and age 15 asthma in females, but *not* males. These results reinforce the importance of examining moderators of the PNMS-asthma relationship, including offspring sex and timing of PNMS, and provide preliminary evidence that PNMS may impact asthma outcomes into adolescence, particularly in females.

Prenatal Maternal Stress And Pediatric Asthma Across Development: Adolescent Female-specific Vulnerability

Accumulating evidence suggests that asthma risk originates as early as the prenatal period[1,2]. Moreover, the last two decades of asthma research have brought unprecedented progress in documenting several perinatal risk factors in the ontogenesis of asthma, ranging from maternal tobacco use [3] and diet in pregnancy[4], to obstetric complications[5] and microbiome disruption[6]. The hypothesized mechanisms

underlying these vulnerabilities include the dysregulation of the developing fetal and infant hypothalamic–pituitary–adrenocortical (HPA) axis and immune system, thought to engender postnatal airway inflammation while hindering airway and lung growth through epigenetic modifications and placental nutrition[7]. Perhaps due to its established associations with these prenatal exposures and physiological mechanisms, prenatal maternal stress (PNMS) has become increasingly central to the narrative of the fetal origins of asthma, as demonstrated by several recent reviews[8–11].

Despite generally well-replicated findings linking PNMS and asthma outcomes, questions persist regarding the operationalization of maternal stress[12]. Definitions of PNMS have encompassed anxiety, depression, bereavement, work-related stress, and stressful life events; measurements have included a variety of self-report questionnaires, population registries, and semi-structured interviews [10]. A multidimensional measure of PNMS has been thought to most reliably capture stress [13]. In the general stress literature, a robust and heavily evidenced framework divides stress into its two fundamental components: the stress exposure and the stress response[14]. This approach is well-established within the neuropsychiatric outcome research of PNMS and has been favored as more comprehensive operationalization of the prenatal stress experience[15]. In some cases, the effects of PNMS on neuropsychiatric child outcomes depend on the type of maternal stress experienced, suggesting critical information may be lost when investigating PNMS as a unidimensional construct[15]. To date, however, the multidimensional PNMS approach has been neglected in the asthma literature, with few studies examining *both* subjective and objective PNMS measures in the context of asthma risk[8].

Timing of maternal stress during pregnancy may impact risk for physical outcomes in offspring, with body system development displaying varying windows of vulnerability to PNMS. Furthermore, PNMS may set the stage for the impact of additional environmental insults, conferring risk for asthma across the lifespan. Postnatal maternal stress may also increase risk of certain maternal behaviors, such as tobacco use, that can alter the household environment and subsequently increase child asthma risk[16]. On the other hand, postnatal maternal stress may be exacerbated by child asthma-risk factors (e.g., poor living conditions, limited access to healthcare) [17]. Despite the documented contributions of postnatal maternal stress in child asthma risk, few PNMS studies explicitly test for the competing impacts of postnatal maternal stress[18]. Thus, the current study seeks to explore potential differential impacts of varying types of PNMS exposures while also examining the competing impacts of maternal stress in the early years of development.

Our knowledge of the relationship between PNMS and asthma risk is further limited by the lack of empirical research on asthma outcomes past early childhood, with only two studies looking as far as early adolescence[12,19]. A Denmark population study of over 750,000 mother-child dyads, the largest study of the prenatal origins of asthma to date, studied children up to age 15 and explored long-term developmental consequences of PNMS. Although PNMS was associated with heightened asthma risk in children ages 0–3 years, the study did not find an association in children aged 4–15 years [19], possibly due to restricted operationalization of PNMS to solely bereavement. On the other hand, a study of dyads

exposed to the 1998 Quebec Ice Storm found that subjective PNMS predicted asthma outcomes in females, but not males, up to age 12[12]. The impact of Project Ice Storm is two-fold, supporting the extended analyses of PNMS into adolescence and underscoring the potential moderating role of biological sex in asthma risk. As such, more research is needed to elucidate the role of PNMS on asthma outcomes into adolescence, utilizing improved operationalization of the PNMS and considering the moderating roles of stress timing and biological sex.

Biological Sex

Biological sex, or sex assigned at birth, may modify how PNMS affects fetal development and subsequent child physical health. Several studies document a significant male bias in fetal mortality, birth complications, and developmental impairments in early childhood [20]. Fetal male viability may be more resource-sensitive and vulnerable to environmental influences than females due to evolutionary bias towards female offspring in adverse conditions [20,21]. Female fetuses are thought to be more likely to survive PNMS, but are hypothesized to suffer more long term consequences via increased stress vulnerability later in development[18]. This theory is supported by preclinical studies indicated that female offspring are more vulnerable to stress in adulthood if exposed to PNMS [22]. Further support is shown by a preliminary study in humans that increased vulnerability of females to prenatal maternal stress persists into adolescence [23].

Age-dependent sex-differences are seen in asthma prevalence. Prior to puberty, males are at an increasingly higher risk than their female counterparts for onset of asthmatic symptomology, early symptom severity, and hospitalization[24]. For some children, almost exclusively male, early asthma symptoms decrease or disappear completely by puberty; yet, following puberty, females are at higher risk of developing new asthma symptoms [25]. Documented in the International Study of Asthma and Allergies in Childhood, asthma prevalence was greater in males ages 6–7 years but greater in females 13–14 years [26].

Current evidence that biological sex impacts the relationship between PNMS and asthma across development are mixed: some studies have demonstrated a stronger relationship between PNMS and asthma in males[18,27–29] while others only in females[12]. Offspring age may account for this variability. Studies demonstrating that males carried a greater susceptibility to PNMS worked with children 6 years and younger. Alternatively, studies with children ages 11 years and older supported a female vulnerability[12]. Animal studies have provided preliminary evidence of this potential PNMS-related *pubertal switch* in asthma outcomes, suggesting that sex-dependent differences in lung development could explain the late onset of stress-induced fetal programming of asthma in females [30]. Cumulatively, these findings highlight the importance of examining the relationship between PNMS and asthma outcomes across development while also considering postnatal sex differences in developmental presentations.

The Current Study

While growing evidence suggests a link between PNMS and offspring asthma, the roles of the type and timing of stress, as well as offspring sex, on outcomes across developmental stages remain unclear. The current study investigates the prospective associations between both objective and subjective PNMS and offspring asthma measured at two time points (childhood and adolescence). Furthermore, we examine how biological sex of the offspring may moderate these relationships. We hypothesized that objective and subjective PNMS measures reported during pregnancy and shortly after birth would predict child asthma at 5 and 15 years of age. Furthermore, we predicted that males would show greater vulnerability to the effects of PNMS on asthma risk at age 5 while females would show greater vulnerability at age 15. Finally, we probed the impact of maternal stress in the postnatal period on the relationship between PNMS and asthma outcomes in offspring. Specifically, we explored whether PNMS has unique predictive effects beyond early life maternal stress in the prediction of child asthma.

Methods

Participants and Procedure

Participants in this study consisted of 815 mothers recruited from the longitudinal Mater Misericordiae Mothers' Hospital-University of Queensland Study of Pregnancy (MUSP). These women gave birth between 1981 and 1984 and participated in a longitudinal cohort study with visits occurring during pregnancy, 3 to 5 days after birth, and when offspring were ages 5 years [31]. These mothers and their offspring participated in a follow-up study when youth were 15 years of age. This particular follow-up study oversampled for mothers experiencing or at high-risk of depression in order to better assess the effects of maternal depression on child development [32]. Women in this sample identified primarily as low to lower-middle class and White (see Table 1).

Prenatal assessments, including questionnaires assessing maternal stress, were conducted at the hospital in conjunction with the mother's first prenatal visit which occurred at an average age of 19.36 weeks gestation (*SD* = 5.80). Postnatal assessments (3–5 days after birth, offspring ages 5 and 15), including questionnaires assessing maternal stress and child health status, were conducted by postgraduate psychology students either in the family homes or locations convenient to the family and children. All participants provided written consent. The research protocol was approved by the institutional review boards of the University of Queensland, University of California, Los Angeles, and Emory University.

Table 1

Demographic characteristics of the sample (N = 815)

	N	%	Mean	SD
Maternal Variables				
Maternal Age at Offspring Birth	815		25.40 years	5.05 years
Maternal Income Level (Per Year)[1]	765	93.9%		
$0-$2,599	12	1.6%		
$2,600-$5,199	42	5.5%		
$5,200-$10,399	200	26.1%		
$10,400-$15,599	298	39%		
$15,600-$20,799	132	17.3%		
$20,800-$25,999	55	6.7%		
$26,000 or more	26	3.4%		
Maternal Education	809			
High School Completion or Less	442	54.6%		
Post High School Education	367	45.4%		
Maternal Stress Measures				
Subjective Reported in Pregnancy	814		11.78	4.39
Subjective Reported at Age 5	813		12.15	4.12
Objective Reported in Pregnancy	812		1.65	1.64
Objective Reported at Birth	808		1.32	1.44
Objective Reported at Age 5	815		1.17	1.28
Offspring Variables				
Gestational Age at Prenatal Visit (weeks)	814		19.36	5.80
Gestational Age at Birth (weeks)	814		39.34	1.73
Child's Race	815			
Caucasian	746	91.5%		
Asian	35	4.3%		
Māori/Pacific Islander	17	2.1%		

	N	%	Mean	SD
Aboriginal	17	2.1%		
Child's Biological Sex	815			
Male	412	50.6%		
Female	403	49.4%		
Child Asthma				
Age 5	815			
Present	46	5.7%		
Absent	755	94.3%		
Age 15	813			
Present	203	25%		
Absent	610	75%		

[1]Maternal income measured in Australian Dollar (AUD) between timeframe of 1981 to 1984.

Prenatal Maternal Stress

Subjective and objective PNMS were reported during pregnancy and shortly after birth. Figure 1 provides a timeline of the administration of all assessment measures. Subjective PNMS was assessed using the Reeder Stress Inventory (RSI)[33]. The RSI is a self-report measure comprised of four questions that assess physiological and psychological reactions to daily life on a five-point Likert scale from Never to All of the Time. The items include: (1) "In general, I am usually tense or nervous"; (2) "There is a great amount of nervous strain connected with my daily activities"; (3) "At the end of the day I am completely exhausted mentally and physically"; and (4) "My daily activities are extremely trying and stressful." The RSI is a well-established measure of subjective stress with strong construct validity [34,35]. The RSI had good reliability in this sample; $\alpha = 0.80$; scores on the prenatal RSI ranged from 5 to 25 with an average of 11.78 ($SD = 4.39$).

Objective PNMS was measured by maternal retrospective report of 9 specific stressful life events within the 6 months prior to assessment. Life events included: death or sickness of a loved one, personal health problems, disagreements with partner and/or loved one, financial problems, major changes in work situation for self-and/or partner, serious problems with housing or accommodation, and personal and/or partner having problems with the law. These life events were originally selected due to stressor severity and common use within the PNMS literature. Scores on the objective stressful life events measure ranged

from 0 to 9 with an average of 1.65 (*SD* = 1.64) for the prenatal study visit and an average of 1.32 (*SD* = 1.44) for the newborn study visit.

Postnatal Maternal Stress

Postnatal maternal subjective stress was measured using the RSI at the age 5 study visit. Scores on the postnatal RSI ranged from 5 to 25 with an average of 12.15 (*SD* = 4.12). Postnatal maternal objective stress was also measured at the age 5 study visit by querying the mothers about whether, in the past year, they had experienced the same 9 life events that they previously reported on during pregnancy and shortly after giving birth. Scores on the postnatal maternal objective stressful life events measure ranged from 0 to 7 with an average of 1.17 (*SD* = 1.28).

Asthma

Presence of asthma in offspring was reported by mothers via questionnaire at the youth ages 5- and 15-year study visits. At age 5, asthma was marked present if the mother answered yes to “has your child had any of these symptoms or conditions continuing longer than three months: Asthma.” At age 15, maternal report of youth asthma over the past 6 months was measured with option choices “Never”, “Sometimes,” and “Always.” Responses were recoded (0 for “Never” and 1 for “Sometimes” and “Always”) and examined dichotomously.

Covariates

Potential covariates were selected based on literature documenting their associations with increased risk for asthma outcomes in offspring. These included gestational age at birth [36], birthweight [37], income during pregnancy [38], mother’s level of education [39], number of cigarettes smoked per day during pregnancy [3], alcohol use during pregnancy [40], maternal history of depression [41], breast-feeding following birth [42], and child’s race [43]. Within this Australian sample, race was categorized as the following: White, Asian, Māori/Pacific Islander, and Aboriginal.

Analytic Plan

All statistical tests were conducted using SPSS statistical package, version 28.0 for Macintosh. All pre- and postnatal maternal stress variables were mean centered to reduce multicollinearity. Preliminary analyses examined bivariate correlations between PNMS, early life maternal stress, asthma outcomes and potential covariates. Missing data was minimal (less than 3%), and all analyses included the full data available for hypothesis testing.

First, separate logistic regressions predicting to each asthma timepoint (ages 5 and 15) from all stress variables were conducted. Second, hierarchical logistic regressions models were conducted to evaluate whether PNMS would remain a significant predictor of child asthma when controlling for early life stress. To assess the independent predictive effect of PNMS, we entered any covariates and maternal postnatal (offspring age 5) stress in the first block and PNMS in the second block. All tests were two-tailed with $p < 0.05$ indicating significance.

Finally, we conducted hierarchical logistic regression analyses to examine the moderating role of sex assigned at birth of the offspring in the relationship between PNMS and offspring asthma outcomes. We entered the main effects of PNMS and child sex entered together in one block, and the interaction of PNMS and child sex entered in the next block. In total, we performed 6 logistic regression analyses. Significant interactions for biological sex and PNMS were probed via sex-stratified analyses. We also performed post-hoc analyses to examine whether significant associations between PNMS and child asthma associations were still evident when adjusting these models for postnatal maternal stress of the same type (i.e., subjective or objective).

Results

Descriptives

Descriptive statistics are presented in Table 1. At age 5, a total of 46 (5.6%) children were reported to have chronic current asthma, with a marginally higher female prevalence (54.4% female). At age 15, asthma symptoms were reported in 203 children (24.9%), 107 of whom were male (52.7%). Of the 46 children reported to have chronic asthma at age 5, 32 continued to show symptoms at age 15 (69.6%). Of the 753 children whose mothers did not report chronic asthma at age 5, 167 (22.2%) were reported to have asthma symptoms at age 15. Bivariate correlations across stress variables are presented in Table 2. All maternal stress variables were significantly correlated with one another ($p < 0.001$ for all correlations). Of the potential covariates explored, only maternal educational status was significantly associated with asthma at age 15 and was therefore included in all analyses examining this outcome (see Table 3). Asthma incidence at ages 5 and 15 years were significantly correlated ($r = 0.26$, $p < 0.001$).

Table 2
Bivariate correlations

Variables	1	2	3	4	5	6	7
1. Asthma Age 5							
2. Asthma Age 15	**0.26****						
3. Objective Stress Reported in Pregnancy	0.07	-0.01					
4. Objective Stress Reported at Birth	0.07*	0.03	**0.56****				
5. Objective Stress Reported at Age 5	**0.09****	-0.05	**0.28****	**0.25****			
6. Subjective Stress Reported in Pregnancy	-0.002	0.008	**0.31****	**0.25****	**0.18****		
7. Subjective Stress Reported at Age 5	0.03	0.03	**0.20****	**0.16****	**0.28****	**0.42****	

Note. Values presented are bivariate Pearson correlations. *p < 0.05. **p < 0.001

Table 3
Correlations between potential covariates and offspring asthma

	Presence of Offspring Asthma			
	Age 5		Age 15	
	Pearson Correlation	Sig. (2-tailed)	Pearson Correlation	Sig. (2-tailed)
Gestational Age (weeks)	-0.003	0.935	-0.012	0.726
Birthweight (grams)	-0.004	0.902	-0.012	0.739
Income in Pregnancy	-0.040	0.273	0.008	0.833
Mother's level of education	0	0.999	**-0.101***	0.004
Cigarettes/day during pregnancy	0.034	0.342	0.016	0.639
Alcohol use during pregnancy	-0.019	0.588	0.011	0.744
Mother's history of depression	0.042	0.240	0.005	0.889
Breast-fed	0.046	0.194	0.061	0.081

Note. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$

Prenatal Maternal Stress

Logistic regression analyses predicting to asthma outcome at ages 5 and 15 showed there was no significant association between maternal reports of subjective stress (OR = 0.998, 95% CI = 0.932–1.068, $p = 0.952$) or objective stressful life events reported during the prenatal visit (OR = 1.169, 95% CI = 0.993–1.377, $p = 0.060$) and asthma at age 5. There was a significant positive association between maternal neonatal retrospective reports of objective stressful life events that occurred in the last 6 months of pregnancy and asthma at age 5 (OR = 1.206, 95% CI = 1.003, 1.450, $p = 0.047$). None of the examined PNMS variables were significantly associated with asthma at age 15, including objective stressful life events reported during the prenatal visit (OR = 0.986, 95% CI = 0.895–1.087, $p = 0.783$), objective stressful life events that occurred in the last 6 months of pregnancy (OR = 1.048, 95% CI = 0.940–1.169, $p = 0.399$) and the subjective measure of PNMS (OR = 1.004, 95% CI = 0.989–1.041, $p = 0.810$).

Role Of Postnatal Maternal Stress

Hierarchical logistic regression models adjusted for postnatal maternal stress are presented in Table 4. PNMS did *not* uniquely predict asthma outcomes above and beyond postnatal maternal stress. Nonetheless, maternal report of maternal objective stress at age 5 independently and significantly predicted child asthma at age 5, even when controlling for maternal objective stress reported in pregnancy: OR = 1.246, 95% CI = 1.014–1.532, $p = 0.036$; controlling for maternal objective stress reported at birth: OR = 1.242, 95% CI = 1.013–1.524, $p = 0.038$).

Table 4

Logistic regression analyses predicting to offspring asthma at ages 5 and 15 from objective and subjective PNMS variables

	Asthma (Age 5)	**Asthma (Age 15)**[1]
	OR (95% CI)	OR (95% CI)
	p	*p*
Objective Postnatal Maternal Stress Age 5	1.246 (1.014–1.532)	0.900 (0.784–1.032)
	0.036*	0.130
Objective Reported in Pregnancy	1.112 (0.937–1.321)	1.001 (0.904–1.109)
	0.225	0.986
Objective Postnatal Maternal Stress Age 5	1.242 (1.013–1.524)	0.885 (0.772–1.015)
	0.038*	0.080
Objective Reported at Birth	1.145 (0.942–1.390)	1.080 (0.963–1.212)
	0.173	0.188
Subjective Postnatal Maternal Stress Age 5	1.035 (0.957–1.119)	1.014 (0.972–1.058)
	0.394	0.514
Subjective Reported in Pregnancy	0.984 (0.913–1.061)	0.998 (0.959–1.039)
	0.682	0.923
[1] Age 15 analyses also control for maternal education.		
Note: *$p < 0.05$		

Biological Sex As A Moderator

Findings demonstrating the moderating effect of offspring biological sex are presented in Table 5. No biological sex interactions were found to predict child asthma at age 5. There was a significant interaction between biological sex, prenatal maternal *subjective* stress, and child asthma at age 15, when controlling for maternal education. Sex-stratified analysis revealed a significant, positive association between prenatal maternal subjective stress with asthma at age 15 in females (OR = 1.071, 95% CI = 1.014–1.131, $p = 0.014$), but not males (OR = 0.952, 95% CI = 0.904–1.001, $p = 0.056$). There was also a significant interaction between biological sex, prenatal maternal *objective* stress reported during pregnancy, and offspring asthma at age 15. Sex-stratified analyses revealed that the direction of the association between prenatal maternal objective stress and child age 15 asthma was positive for females and negative for males. Hierarchical logistic regressions demonstrated that the PNMS and

biological sex interactions remained significant above and beyond the effects of postnatal maternal stress (subjective: Wald (*N* = 805) = 9.637, *p* = 0.002; objective: Wald (*N* = 815) = 4.303, *p* = 0.038).

Table 5
Logistic regression models predicting to offspring asthma outcomes from PNMS, examining the moderating role of biological sex

	Asthma (Age 5)	**Asthma (Age 15)**[1]
	OR (95% CI)	OR (95% CI)
	p	*p*
Objective Stress Reported in Pregnancy	1.149 (0.968–1.364)	0.983 (0.890–1.086)
	0.113	0.736
Offspring Sex	1.084 (0.581–2.023)	0.902 (0.652–1.246)
	0.800	0.530
Stress*Sex	1.361 (0.966–1.916)	1.225 (1.003–1.495)
	0.078	**0.046****
Subjective Stress Reported in Pregnancy	0.995 (0.929–1.067)	1.007 (0.970–1.045)
	0.891	0.706
Offspring Sex	1.226 (0.669–2.246)	0.887 (0.640–1.229)
	0.509	0.471
Stress*Sex	1.065 (0.927–1.223)	1.125 (1.044–1.212)
	0.373	**0.002****
Objective Stress Reported at Birth	1.185 (0.980–1.434)	1.054 (0.943–1.178)
	0.080	0.359
Offspring Sex	1.129 (0.610–2.089)	0.888 (0.643–1.226)
	0.700	0.471
Stress*Sex	1.194 (0.817–1.743)	1.028 (0.822–1.284)
	0.359	0.810

[1] Age 15 analyses control for maternal education.

Note: p < 0.05. **p < 0.01.

Discussion

In the largest prospective longitudinal study examining the impacts of objective and subjective PNMS on offspring asthma through adolescence, we found that asthma associations with PNMS are indeed lasting, and evident in outcomes assessed at age 15 years. Our research encourages a new chapter in the fetal programming theory of asthma, extending the existing literature's primary focus on the first years of life and noting important associations in adolescence [11]. In addition, our findings emphasize biological sex differences in vulnerability to the effects of PNMS across development.

Perhaps our most notable findings were the sex-specific associations of PNMS and offspring asthma in adolescence. Sex moderated the association between prenatal maternal reports of subjective stress and offspring asthma at age 15 years, above and beyond the effects of subjective postnatal maternal stress. Specifically, and in line with our hypotheses, PNMS predicted adolescent asthma in females, but not males. At 15 years, stressful life events early in the prenatal period were negatively associated with asthma in males and positively associated with asthma in females. Albeit this potential protective effect of stressful life events in males is puzzling, these general adolescent patterns support the well-established *puberty switch*, whereby asthma risk switches from males to females at puberty. These findings parallel Sandman and colleagues' model of sex differences in fetal programming, which hypothesizes that male fetuses exposed to high levels of PNMS are more likely to succumb prior to birth, resulting in greater stress variability in females later in development[20]. As such, the sensitive developmental period of puberty may explain the latent effect we observed at age 15, supporting the heightened susceptibility of females to the long-term effects of PNMS on asthma.

Analyses revealed little support for the prenatal programming hypothesis in regards to offspring asthma at 5 years of age. Neither maternal subjective stress nor maternal objective stress measured early in pregnancy predicted asthma at age 5. While objective stressful life events occurring in the last 6 months of pregnancy predicted offspring asthma at age 5, this association did not hold when controlling for objective stressful life events at age 5. These associations suggest that relative to prenatal stress, concurrent postnatal maternal stress confers a greater risk for asthma outcomes in early childhood.

No evidence was found regarding a male vulnerability to PNMS with respect to asthma outcomes. Utilizing our age 5 timepoint as an early childhood marker could account for this discrepancy with the existing literature, as previous studies noting male vulnerabilities were focused on asthma outcomes measured earlier in development than age 5 [18,27,28]. Our novel results suggest that females may be more vulnerable than males to the long-term effects of PNMS, even when accounting for postnatal maternal stress.

With significant findings spanning both our maternal objective and subjective stress measures, our study suggests both components may be relevant to the PNMS-asthma connection. In the context of asthma development and risk prevention, the inclusion of multi-dimensional PNMS measures in this study granted a richer and more comprehensive exploration of PNMS. Inconsistencies in PNMS research may be remedied by a more comprehensive definition of stress, and we encourage future studies to take this approach.

Limitations

Although this study has several strengths, most notably the focus on adolescence, sex differences, and multiple types of stress, there were some limitations. First, the present study sample is limited in cultural and racial diversity and we suggest future research apply this study design to more diverse populations and select stress measures that can generalize over cultural and ethnic backgrounds. Furthermore, as the MUSP age 15 sub-cohort was originally designed to study maternal depression, and not child health outcomes, there are notable limitations with respect to the nature of the asthma outcomes examined. First, asthma incidence was assessed via maternal report. We also did not collect information on child asthma severity, phenotype, and date of diagnosis nor maternal history of asthma. Future studies may seek to utilize physician report or biomarkers of asthma incidence. Lastly, it is unclear whether measures of asthma from earlier in childhood would have revealed significant PNMS and sex interactions that we did not identify, perhaps in support of the male pre-puberty relationship. Likewise, age at menarche or data on pubertal onset was not collected. Despite these limitations, we believe our work lays the groundwork for a developmental life course perspective of PNMS and risk for health and disease.

Conclusion

Exposure to PNMS can induce long-lasting, sex-specific developmental changes in asthma risk. Documenting associations between PNMS exposure and asthma development as far as age 15, our work highlights the persistent nature of PNMS in females. Contrary to findings that females are more affected by postnatal maternal stress, relative to PNMS [11], our research supports a female vulnerability to PNMS that carries *delayed* effects. These findings may suggest the importance of pubertal hormones in the risk for asthma in females, a possibility to be explored in future studies assessing sex differences in PNMS and asthma associations. Additional evidenced-based research is needed to elucidate the underlying mechanisms of PNMS, including the timing, duration, and intensity of stress exposure on the fetus. As the world continues to adapt to the challenges posed by the COVID-19 pandemic, and expecting mothers are at elevated risk for depression, anxiety, and chronic stressors, the demand for improved prenatal interventions is rising.

Declarations

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Conflicts of Interest. The authors have no conflicts of interest to declare.

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Research Involving Human Participants

All procedures performed in this study with human participants were in accordance with the ethical standards of the institutional, relevant national guidelines on human experimentation, and with the Helsinki Declaration of 1975, and its later amendments or comparable ethical standards. Specifically, this research protocol was approved by the institutional committees and Internal Review Boards of Emory University, University of Queensland, and UCLA.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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Author Contribution Statement

Madeline Pike: Conceptualization, Methodology, Formal Analysis, Writing-Original draft preparation; Melissa Engel: Writing- Reviewing and Editing, Supervision; Emily Lipner: Visualization, Formal Analysis, Writing-Reviewing and Editing; Constance Hammen: Conceptualization, Resources, Supervision, Funding; Patricia Brennan: Conceptualization, Methodology, Supervision, Resources, Funding, Writing- Reviewing and Editing.

Data Availability Statement

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

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Figures

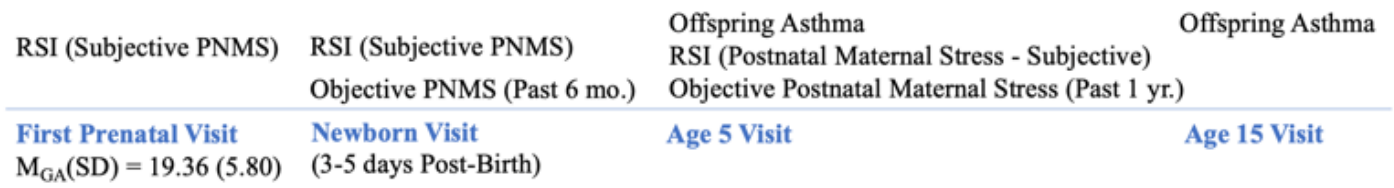

Figure 1

Timeline of maternal stress and asthma outcome measurements in MUSP cohort

Note: RSI = Reeder Stress Inventory; GA = gestational age; PNMS = prenatal maternal stress