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Prenatal and early childhood stress is associated with reduced lung function in 7 year olds

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Introduction

An important step toward identifying children at risk for chronic respiratory disease is characterizing exposures and mechanisms that lead to and maintain early predisposition. Lung function at birth [1] and lung function growth patterns established by age 7 years determine early adulthood pulmonary function [2,3]. Impaired adult maximal attained lung function is a major risk factor for the development of chronic obstructive pulmonary disease (COPD) [4], the projected 4th leading cause of death by 2020 [5]. Longitudinal studies have associated early life factors including active and passive smoking prenatally and during childhood [6], birth weight [7], gestational age [8], and asthma [9] with reduced lung function over the life course. However, these factors account for a relatively small proportion of the risk, suggesting that as yet unidentified risk factors exist. Further delineation of factors that

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Author Contributions:

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contribute to lung function development that may be amenable to intervention is thus important.

Developmental origins of lung structure and function, beginning *in utero,* involve the coordinated maturation of the immune, neural, and endocrine systems. Environmental toxins, such as psychological stress, that disrupt these interrelated systems in critical developmental periods can alter the course of lung morphogenesis and maturation, resulting in long-term changes in the respiratory system [10]. Infants remain vulnerable as these systems are highly reactive and labile in response to environmental stressors, particularly in the first two years when rapid lung development continues [11].

While studies link stress to age-related deterioration in pulmonary function [12], the few studies that have examined effects on childhood lung function present mixed results. Urban Boston children exposed to higher levels of interpersonal violence over childhood had symmetric reductions in forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) by age 6–7 years [13]. A study of adolescents in California found associations between family conflict and reductions in FEV1 among boys but not girls [14]. A study in the United Kingdom found no association between racism and adolescent lung function [15]. No prior study has examined associations between stress starting prenatally and childhood lung function nor assessed the relative impact of pre- or postnatal stress exposure to better delineate critical windows.

Leveraging an ethnically mixed prospective pregnancy cohort study, we examined the relative importance of exposure to pre- and/or postnatal stress in association with children's lung function by age seven years. Specifically, we first examined effects of pre- and postnatal stress in independent models, then mutually adjusted for pre-/postnatal stress to examine their relative importance. We also explored effect modification by child's sex.

Methods

Study Participants

Participants were from the Asthma Coalition on Community, Environment, and Social Stress (ACCESS) project, a pregnancy cohort designed to examine the effects of perinatal stress and other environmental factors on childhood respiratory disorders [16]. Between August 2002 and January 2007, n=500 English- or Spanish-speaking pregnant women (28.4 ± 7.9 weeks gestation) receiving care at Brigham & Women's Hospital (BWH), Boston Medical Center (BMC), and affiliated community health centers were enrolled. Research assistants approached women receiving prenatal care on select clinic days; 78% of those approached who were eligible agreed to enroll. There were no significant differences on race/ethnicity, education, and income between women enrolled and those who declined; n=455 gave birth to a live born infant and continued follow-up. Lung function testing was conducted on children naïve to spirometry at 6.99 ± 0.89 years of age between March 2012 to September 2014; 230 of the 375 actively followed children participated in spirometry testing. Procedures were approved by human studies committees at the Brigham and Women's Hospital and Boston Medical Center; written consent was obtained from all mothers and assent was obtained for children age ≥7 years.

Negative Life Events

Pre- and postnatal maternal stress were measured using the Crisis in Family Systems-Revised (CRISYS-R) survey, validated in English and Spanish administered within two weeks of enrollment and between 12 and 18 months postnatally [17,18]. Mothers were asked to endorse life events experienced in the past 6 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. The number of domains with one or more negative event were summed to create a negative life events (NLEs) domain score (range 0 to 8 in our sample), with higher scores indicating greater stress [19].

Pulmonary Function Testing

Trained research assistants measured child height, weight, and lung function with overreading performed for all spirometry tests to ensure quality control. Height was measured to the nearest 0.1 cm on a stadiometer and weight was measured to the nearest 0.1 kg on an electronic scale. Spirometry was performed in participant homes with a portable MedGraphics™ laptop supported spirometer, which displays real-time flow-volume plots to facilitate testing. Testing procedures met American Thoracic Society (ATS) guidelines [20,21] with techniques modified for children ≤8 years of age. [22,23] Subjects without acute respiratory symptoms for ≥3 weeks were eligible for testing. Short-acting beta-agonists, atropinics and theophylline preparations were withheld for 4 hours and long-acting beta-agonists for 12 hours before testing. Parameters were recorded from a minimum of 3 (no more than 8) maneuvers and included: forced vital capacity (FVC, milliliters), forced expiratory volume in one second (FEV1, milliliters), and forced expiratory flow between 25–75% of the FVC (FEF25-75, milliliters per second). Lung function measures, height and weight were all approximately normally distributed. Raw FEV1, FVC, FEF25-75 and FEV1/FVC values were adjusted for age, sex, height, and race/ethnicity using multivariable regression, and then converted to z-scores with a mean of 0 and a standard deviation of 1. The rationale for using z-scores in our ethnically-diverse population aged 7 years is that z-scores, unlike percent predicted,[24,25] describe each child's lung function parameter in relation to that of other children in the distribution.[26]

Covariates

Potential confounders and pathway variables were considered. Questionnaires ascertained maternal age, education, race/ethnicity, asthma history (ever having clinician-diagnosed asthma), as well as child's sex, season of birth, and birth weight. Child's gestational age was based on reported last menstrual period or obstetrical estimates based on a second trimester ultrasound if dates differed by >10 days upon medical record review [27]. Sex-specific birth weight for gestational age (BWGA) z-scores were calculated based on U.S. reference data [28]. Mothers who reported smoking at baseline and/or in the third trimester were classified as prenatal smokers; postnatal smoke exposure was based on maternal- report of smoking and/or whether others smoked in the home at each postpartum interview. Maternal-reported clinician diagnosed asthma was ascertained through interviews at approximately 3-month intervals for the first 24 months of life and then annually thereafter up to the time of

spirometry. Mothers were asked, “Has a doctor or nurse ever said that your child had asthma?”.

Analysis

We considered stress exposure categorized in two different ways. In the primary initial analysis, the NLEs score was categorized *a priori* as 0, 1–2, 3–4, or ≥5 in order to assess exposure-response relationships. Univariate and multivariable linear regressions were run to examine associations between pre- and postnatal maternal stress and children’s pulmonary function measures including FEV1, FVC, FEF25-75 and FEV1/FVC z-scores. We first examined effects of prenatal and postnatal NLEs in separate models. In addition to the covariates accounted for in deriving the spirometry measure z-scores (age, sex, height, race/ethnicity), we adjusted for potential confounders linked to stress and lung function including maternal education, and child's asthma diagnosis. We next adjusted for variables potentially on the pathway between stress and lung function, including BWGA z-score and maternal tobacco smoke exposure, as a sensitivity analysis. We also considered stress dichotomized as low (<5 NLEs) compared to high stress (≥5 NLEs) in order to facilitate our ability to consider sex differences. We examined associations with lung function by considering high and low stress exposure in separate models in the sample as a whole and then in sex stratified analyses. We next included both pre- and postnatal stress (high vs. low) in the same model to explore the relative importance of stress exposure in these developmental windows. Again, we considered the sample as a whole as well as stratifying by child sex. Effect modification was also explored by including a product term (sex by NLE) in the models using the dichotomous NLEs indicator. Because prenatal and postnatal NLEs were moderately correlated ($r=0.54$, $p<.01$), we assessed collinearity using standard collinearity diagnostics for linear regression. The condition indices are defined as the square roots of the ratio of the largest eigenvalue to each individual eigenvalue of the cross-product matrix X’X, where X is the set of the explanatory variables used in the regression model.[29] The index number of the matrix, the largest condition index, was used as an indicator of collinearity. A condition index of 10 is associated with weak collinearity while numbers approaching 30 to 100 suggest moderate to strong collinearity.[30] The condition index in our analysis including both pre- and postnatal NLEs was 3.99, indicating minimal collinearity. Analyses were performed using Statistical Analysis Software (SAS) version 9.4 (SAS Institute, Carry, NC, USA).

Results

Of the 230 participating children, 211 (91.7%) provided acceptable spirometry; among these 199 had data available on pre- and postnatal stress. Demographic characteristics of those included in analyses versus excluded participants were not significantly different.

Table 1 summarizes participant characteristics. Mothers were predominantly ethnic minorities (65% Hispanic, 21% African American), most had less than or equal to 12 years of education (67%), and the majority did not smoke prenatally (78%). There were no significant differences between boys and girls except that boys were more likely to be diagnosed with asthma compared to girls ($p<0.01$).

Independent Effects of Pre- and Postnatal Maternal NLEs on Child Spirometry

Results of models considering prenatal and postnatal stress separately (Table 2 and Table 3, respectively) did not show a clear exposure-response association. Rather the highest stress group (≥5 NLEs) was most significantly related to lower levels of lung function when compared to children of mothers reporting the lowest levels of stress in these periods (0 NLEs). In the sample as a whole, the highest level of prenatal stress compared to the lowest stress category was associated with lower levels of FEV1 (z-score −0.53, p=0.03), FVC (z-score −0.49, p=0.045) and FEF25-75 (z-score −0.68, p=0.01), adjusting for maternal education, child's asthma status, birth weight z-score and prenatal smoking (Table 2, Model 3). For postnatal stress, the highest vs. lowest stress category was significantly associated with reduced FEV1 (z-score −0.51, p=0.04) and FVC (z-score −0.51, p=0.04) in the fully adjusted model; there was a reduction in FEF25-75 in the highest stress group although this did not reach statistical significance (z-score −0.45, p=0.09) (Table 3, Model 3).

As linear regression models in Tables 2 and 3 demonstrated that the highest NLEs exposure group (≥5) was most strongly associated with reduced lung function, subsequent analyses considered stress dichotomized as high (≥5 NLEs) vs. low (<5 NLEs). Considering stress exposure as a dichotomized indicator also maintained reasonable cell sizes to facilitate examination of sex-specific effects in stratified analyses. In the sample as a whole, high stress (≥5 NLEs) vs. low stress (<5 NLEs) was significantly associated with reductions in FEV1, FVC and the FEF25-75 for both the pre- and postnatal periods (Table 4). In sex-stratified analyses, reductions in FEV1, FVC and FEF25-75 were similar in magnitude in relation to high prenatal stress exposure, although these associations did not reach statistical significance in either boys or girls. However, associations between high postnatal stress exposure and lower FEV1 (z-score −0.76, p=0.01), FVC (z-score −0.77, p=0.01) and FEF25-75 (z-score −0.67, p=0.02) remained significant in boys but not girls (Table 4). Interaction terms did not reach significance ((prenatal NLE dichotomous indicator x sex $p_{interaction}$ >0.1, postnatal NLE dichotomous indicator x sex $p_{interaction}$ >0.1).

Mutual adjustment for prenatal and postnatal maternal stress

Table 5 presents results from linear regression models concurrently considering pre- and postnatal maternal NLEs and PFT z-scores. When both pre- and postnatal stress were included in the model together (Table 5), the highest level of postnatal stress exposure remained significantly associated with lower FEV1 (z-score −0.58, p=0.02), FVC (z-score −0.59, p=0.01) and FEF25-75 levels (z-score −0.48, p=0.05). In sex-stratified analyses, this association was significant only among boys ($p_{interaction}$ >0.1).

Discussion

This is the first prospective study demonstrating that increased psychological stress in pregnancy and the first two years of life is associated with reductions in children's lung function by age 7 years. Overall the patterns reflect a threshold effect for stress in that those children exposed to the highest level of stress in either developmental window had significant reductions in FEV1, FVC and FEF25-75 z-scores with a preserved FEV1/FVC ratio when these exposure periods were considered separately. While associations were in

the same direction for both boys and girls in stratified analyses, these relationships reached significance only in boys.

The mind-body paradigm linking psychological stress and affective states to key physiological mechanisms, including neuroendocrine and immune functioning, oxidative stress, and autonomic response, provides a framework to explore plausible physiologic mechanisms through which psychological stress can influence lung development [10]. Disturbed regulation of stress systems [e.g., HPA axis, autonomic nervous system (ANS)] may modulate offspring immune function starting *in utero* [31], leading to altered systemic cytokine production [32,33]. Chronic maternal or caregiver stress in pregnancy and the early childhood period have been associated with persistent wheeze [34,35] and asthma [36,37] in early childhood as well as factors that may initiate or potentiate inflammation in the lung (e.g. HPA axis disruption, enhanced nonspecific and allergen-specific lymphocyte proliferation, differential cytokine expression) [38–40]. Persistent wheeze [41], atopy [42], and asthma [2] have, in turn, been linked to reduced lung function in childhood. Chronic psychological stress has also been linked to other risk factors that are associated with reduced lung function including respiratory infections [43] and smoking behaviors [44]. Other research demonstrates that early life stress can enhance the effects of other environmental factors that impact lung growth and development [45,46].

Our results demonstrate a symmetric reduction in FEV1 and FVC with a preserved ratio in response to both pre- and postnatal stress suggesting impaired lung growth in these critical windows. These findings expand on prior research linking prenatal maternal stress, or stress correlates (e.g., depression, anxiety), to impaired fetal growth [47]; impaired fetal growth, in turn, can limit lung growth and maturation resulting in smaller lungs. Studies have demonstrated associations between poor fetal growth and reduced lung function in adults that are independent of smoking and socioeconomic status [48]. Similar associations have been found among poor fetal growth and children's lung function that are independent of gestational age and maternal prenatal smoking [49]. Further these findings support those of our earlier Boston cohort study linking violence exposure (a community-level stressor) over childhood with reduced FEV1 and FVC at age 6 years [13].

Sex-stratified analyses demonstrate that lung function was most significantly reduced in boys in the postnatal period, with a trend towards significance prenatally. Our results support the previously reported associations between maternal stress assessed using the same NLE measure and child asthma risk by age 6 years which also found that boys were more susceptible to both pre- and postnatal maternal stress [36]. It may be the case that different types of stress have variable impact on lung development and may effect girls and boys differently, as demonstrated for other disorders [50]. This may explain disparate findings in other studies examining effects of early life stress on childhood lung function in relation to child sex.

These data indicate that children exposed to the highest levels of pre- and postnatal maternal stress have on average a 133mL (9.2%) and 128mL (8.9%) reduction in FEV1 and a 142mL (9.0%) and 148mL (9.4%) reduction in FVC, respectively, at age 7 compared to their counterparts experiencing lower stress in these critical periods. These reductions may have

lifelong implications. Prior prospective studies demonstrate that lung function growth patterns established by age 7 years track through middle adulthood with impairments in early life lung function persisting even after 20 years of follow up [1–3,51]. Furthermore, the prior paradigm that adult chronic respiratory disorders, such as COPD, result from a rapid rate of lung function decline in adulthood has been challenged by the finding that many adults with COPD have impaired maximally attained lung function reflective of impaired early life lung growth with a subsequent normal rate of lung function decline [4]. Therefore, in addition to the implications for childhood respiratory disease, reduced lung function in children exposed to elevated levels of pre- and postnatal maternal stress can predispose individuals to future chronic respiratory diseases.

Strengths of this study include the prospective study design with assessment of stress both prenatally and in the first two years of life (i.e., previously identified vulnerable developmental windows for lung growth and stress programming) using a validated measure of maternal life events. Other strengths include our focus in an ethnically diverse lower income population more likely to be impacted by both increased stress and reduced lung function, and our ability to adjust for several important confounders and potential pathway variables.

We also acknowledge limitations. While we adjust for a number of sociodemographic factors and possible pathway variables including tobacco smoke exposures and birth weight adjusted for gestational age, we were unable to consider other factors that may be associated with stress and compromised lung growth (e.g., prenatal and early life nutritional status of mothers and infants, respectively). Future studies should also incorporate biomarker measures of stress response systems including the HPA axis, autonomic nervous system functioning and immune function, over early development that may be dysregulated by stress and play a role in morphogenesis and maturation of the respiratory system. While our sample size was large enough to detect associations between pre- and postnatal maternal stress and child lung function in the sample as a whole, further exploration of sex-specific effects will be enhanced through increased sample size in future studies. Continued research examining sex differences in associations between maternal stress and child respiratory outcomes may elucidate underlying programming pathways. Thus, future studies should also incorporate biomarker measures of stress response systems including the HPA and HPG axes, ANS functioning and immune function over early development that may be sexually dimorphic [52]. There should also be increased focus on placental functioning, given emerging evidence for a significant role of placenta in lung morphogenesis [53] as well as stress-elicited epigenetic programming [54]. For example, recent analyses in the Lifestyle and environmental factors and their Influence on Newborns Allergy risk (LINA) study reported differentially methylated regions in calcium- and Wnt-signaling pathways involved in lung maturation prenatally among children exposed to increased prenatal stress who went on to develop wheeze [54]. Other evidence indicates that stress-induced epigenetic changes that influence development can be sex specific [55,56].

In summary, these data are the first to identify psychosocial stress as an important environmental factor influencing lung growth and development in early life. These data add to a growing body of epidemiologic research demonstrating an association between

increased perinatal maternal stress and adverse childhood respiratory outcomes. Given the growing evidence linking perinatal stress to early respiratory morbidity, researchers should begin to develop and study interventions, both at the individual and policy level, to reduce maternal stress to promote optimal lung development and potentially reduce the burden of childhood respiratory disease. Given known associations between child and adult respiratory disease, these interventions may have lasting implications. It is worth noting the threshold effect for stress in this context. These analyses found that children born to mothers with the highest levels of stress exposure in these critical windows had significantly decreased lung function. While it is not practical to eliminate stress, these data suggest that providing resources and supports that reduce stress experiences during pregnancy and early childhood to more normative levels can mitigate effects on the next generation. This would involve screening pregnant women and mothers in the early postpartum period for stress exposures so that we can target interventions especially to those with more extreme stress exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACCESS	Asthma Coalition on Community, Environment, and Social Stress
ANS	autonomic nervous system
ATS	American Thoracic Society
BWGA	birth weight for gestational age
COPD	chronic obstructive pulmonary disease
CRYSIS	Crisis in Family Systems-Revised Survey
FEF25-75	forced expiratory flow between 25-75% of the FVC
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
HPA	hypothalamic-pituitary-adrenal
HPG	hypothalamic-pituitary-gonadal
NLEs	negative life events

SAS Statistical Analysis Software

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Table 1

ACCESS Participant Characteristics

	All (n=199)		Boys (n=106)		Girls (n=93)	
Categorical Variables	**n**	**%**	**n**	**%**	**n**	**%**
Maternal Race						
Hispanic	129	64.8	67	63.2	62	66.7
African American	42	21.1	22	20.8	20	21.5
White/Other	28	14.1	17	16.0	11	11.8
Maternal education						
>12 yrs	65	32.7	36	34.0	29	31.2
≤12 yrs	134	67.3	70	66.0	64	68.8
Child ever asthma *						
No	164	82.4	77	72.6	87	93.6
Yes	35	17.6	29	27.4	6	6.5
Prenatal maternal smoking						
No	170	85.4	90	84.9	80	86.0
Yes	29	14.6	16	15.1	13	14.0
Postnatal household tobacco smoke †						
No	155	77.9	79	74.5	76	81.7
Yes	44	22.1	27	25.5	17	18.3
Continuous Variables						
FEV1 (L; mean, SD)	1.44	0.25	1.46	0.23	1.42	0.26
FVC (L; mean, SD)	1.58	0.29	1.60	0.26	1.55	0.32
FEF25-75 (L/s; mean, SD)	1.87	0.46	1.83	0.47	1.91	0.44
FEV1/FVC ratio (mean, SD)	0.92	0.05	0.91	0.06	0.92	0.05
z-score of FEV1 (median, IQR) ‡	−0.09	−0.79–0.66	−0.13	−0.58–0.61	−0.08	−0.96–0.68
z-score of FVC (median, IQR) ‡	−0.12	−0.74–0.64	−0.02	−0.51–0.68	−0.15	−1.03–0.57
z-score of FEF25-75 (median, IQR) ‡	−0.12	−0.73–0.63	−0.31	−0.87–0.33	0.29	−0.62–0.96
z-score of FEV1/FVC ratio (median, IQR) ‡	0.02	−0.66–0.64	−0.43	−0.99–0.14	0.59	0.02–1.27

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	All (n=199)		Boys (n=106)		Girls (n=93)	
Categorical Variables	**n**	**%**	**n**	**%**	**n**	**%**
Prenatal negative life events (range 0–8; median, IQR) [§]	2	1–3	2	1–3	2	1–3
Postnatal negative life events (range 0–8; median, IQR) [§]	2	1–3	2	1–3	2	1–3
Age at spirometry test (years; mean, SD)	6.99	0.89	6.90	0.78	7.10	0.99
Height at spirometry test (cm; mean, SD)	121.8	7.4	121.9	7.3	121.7	7.6
Birthweight for gestational age z-score (median, IQR)	−0.11	−0.79–0.57	−0.10	−0.76–0.72	−0.11	−0.72–0.54

[*] Ever diagnosed with asthma prior to spirometry test

[†] Maternal report of smoking and/or whether others smoked in the home at each postpartum interview

[‡] Adjusted for age, sex, height, race

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

Table 2

Associations between prenatal maternal NLEs* and childhood PFT z-scores†: Linear regression

	Univariate Model			Multivariable-adjusted Models‡								
				Model 1			Model 2			Model 3		
	β	s.e.	*p*	B	s.e.	*p*	β	s.e.	*p*	β	s.e.	*p*
Outcome: FEV1												
NLEs 0	Ref	--	--	Ref	--	--	Ref	--	--	Ref	--	--
NLEs:1–2	−0.13	0.20	0.49	−0.14	0.20	0.48	−0.12	0.19	0.54	−0.25	0.19	0.18
NLEs: 3–4	−0.03	0.22	0.89	−0.04	0.22	0.86	−0.05	0.21	0.81	−0.11	0.20	0.59
NLEs ≥5	−0.46	0.26	0.08	−0.48	0.25	0.06	**−0.50**	**0.25**	**0.05**	**−0.53**	**0.24**	**0.03**
Outcome: FVC												
NLEs 0	Ref	--	--	Ref	--	--	Ref	--	--	Ref	--	--
NLEs: 1–2	−0.11	0.20	0.58	−0.11	0.20	0.56	−0.09	0.19	0.63	−0.231	0.19	0.22
NLEs: 3–4	−0.01	0.22	0.96	−0.02	0.22	0.93	−0.03	0.21	0.89	−0.09	0.20	0.66
NLEs ≥5	−0.42	0.26	0.11	−0.43	0.25	0.09	−0.46	0.25	0.07	**−0.49**	**0.24**	**0.045**
Outcome: FEF25-75%												
NLEs 0	Ref	--	--	Ref	--	--	Ref	--	--	Ref	--	--
NLEs: 1–2	−0.28	0.19	0.16	−0.28	0.19	0.15	−0.27	0.19	0.17	−0.37	0.19	0.05
NLEs: 3–4	−0.16	0.22	0.46	−0.17	0.21	0.43	−0.18	0.21	0.41	−0.22	0.21	0.28
NLEs ≥5	**−0.62**	**0.25**	**0.02**	**−0.65**	**0.25**	**0.01**	**−0.66**	**0.25**	**0.01**	**−0.68**	**0.25**	**0.01**
Outcome: FEV1/FVC ratio												
NLEs 0	Ref	--	--	Ref	--	--	Ref	--	--	Ref	--	--
NLEs: 1–2	−0.15	0.20	0.44	−0.15	0.20	0.44	−0.18	0.19	0.36	−0.06	0.19	0.74
NLEs: 3–4	−0.22	0.22	0.31	−0.22	0.22	0.32	−0.20	0.21	0.34	−0.15	0.21	0.47
NLEs ≥5	−0.09	0.26	0.74	−0.08	0.26	0.75	−0.06	0.25	0.82	−0.03	0.25	0.92

*Prenatal NLEs sample sizes: NLE 0 n=37 (18.6%), NLE 1–2 n=86 (43.2%), NLE 3–4 n=50 (25.1%), NLE≥5 n=26 (13.1%)

†PFT z-scores adjusted for age, sex, height, race

‡Multivariable-adjusted linear regressions (Models 1–3) predicting PFT z-scores (dependent variables).

Model 1 adjusted for maternal education.

Model 2 adjusted for maternal education, child's asthma diagnosis (yes/no)

Model 3 adjusted for maternal education, child's asthma diagnosis (yes/no), birthweight z-score, prenatal smoking

Table 3

Associations between postnatal maternal NLEs [*] and childhood PFT z-scores [†]: Linear regression

	Univariate Model			Multivariable-adjusted Models [‡]								
				Model 1			Model 2			Model 3		
	β	s.e.	*p*	β	s.e.	*p*	β	s.e.	*p*	β	s.e.	*p*
Outcome: FEV1												
NLEs 0	Ref	--	--	Ref	--	--	Ref	--	--	Ref	--	--
NLEs: 1–2	0.11	0.18	0.57	0.12	0.18	0.50	0.14	0.18	0.46	0.12	0.17	0.48
NLEs: 3–4	0.16	0.22	0.47	0.16	0.22	0.46	0.12	0.22	0.58	0.14	0.21	0.52
NLEs ≥5	**−0.52**	**0.27**	**0.05**	−0.48	0.26	0.07	**−0.54**	**0.27**	**0.04**	**−0.51**	**0.25**	**0.04**
Outcome: FVC												
NLEs 0	Ref	--	--	Ref	--	--	Ref	--	--	Ref	--	--
NLEs: 1–2	0.12	0.18	0.51	0.14	0.18	0.45	0.15	0.18	0.40	0.141	0.17	0.42
NLEs: 3–4	0.17	0.22	0.43	0.18	0.22	0.42	0.13	0.22	0.54	0.15	0.21	0.48
NLEs ≥5	−0.51	0.26	0.06	−0.47	0.26	0.07	**−0.54**	**0.26**	**0.04**	**−0.51**	**0.25**	**0.04**
Outcome: FEF25-75%												
NLEs 0	Ref	--	--	Ref	--	--	Ref	--	--	Ref	--	--
NLEs: 1–2	0.09	0.19	0.64	0.11	0.19	0.55	0.12	0.19	0.53	0.11	0.18	0.55
NLEs: 3–4	0.14	0.22	0.53	0.14	0.22	0.52	0.12	0.22	0.59	0.13	0.22	0.56
NLEs ≥5	−0.49	0.27	0.07	−0.44	0.27	0.11	−0.47	0.27	0.08	−0.45	0.27	0.09
Outcome: FEV1/FVC ratio												
NLEs 0	Ref	--	--	Ref	--	--	Ref	--	--	Ref	--	--
NLEs: 1–2	−0.22	0.19	0.23	−0.22	0.19	0.23	−0.24	0.18	0.19	−0.23	0.18	0.20
NLEs: 3–4	−0.19	0.22	0.40	−0.19	0.22	0.40	−0.13	0.22	0.57	−0.15	0.22	0.49
NLEs ≥5	0.31	0.27	0.25	0.30	0.27	0.26	0.40	0.27	0.14	0.37	0.26	0.15

[*] Postnatal NLEs sample sizes: NLE 0 n=40 (23.1%), NLE 1–2 n=79 (45.7%), NLE 3–4 n=35 (20.2%), NLE≥5 n=19 (11%)

[†] PFT z-scores adjusted for age, sex, height, race

[‡] Multivariable-adjusted linear regression models (Models 1–3) predicting PFT z-scores (dependent variables).

Model 1 adjusted for maternal education.

Model 2 adjusted for maternal education, child's asthma diagnosis (yes/no)

Model 3 adjusted for maternal education, child's asthma diagnosis (yes/no), birthweight z-score, tobacco smoke exposure

Table 4

Associations between prenatal and postnatal NLEs and childhood PFT z-scores* in separate models: Linear regression†

NLEs score (≥5 vs. others)	PFT Outcomes	All			Boys			Girls		
		β	s.e.	*p*	β	s.e.	*p*	B	s.e.	*p*
Prenatal	FEV1	**−0.42**	**0.21**	**0.04**	−0.41	0.27	0.12	−0.43	0.33	0.19
	FVC	**−0.40**	**0.21**	**0.05**	−0.40	0.27	0.13	−0.39	0.33	0.23
	FEF25-75%	**−0.48**	**0.21**	**0.02**	−0.45	0.26	0.08	−0.52	0.32	0.11
	FEV1/FVC	0.09	0.21	0.66	0.15	0.23	0.51	−0.01	0.28	0.98
Postnatal	FEV1	**−0.64**	**0.23**	**0.01**	**−0.76**	**0.29**	**0.01**	−0.47	0.38	0.22
	FVC	**−0.65**	**0.23**	**0.01**	**−0.77**	**0.28**	**0.01**	−0.46	0.38	0.22
	FEF25-75%	**−0.56**	**0.24**	**0.02**	**−0.67**	**0.29**	**0.02**	−0.50	0.38	0.19
	FEV1/FVC	**0.55**	**0.23**	**0.02**	**0.67**	**0.25**	**0.01**	0.25	0.31	0.43

*PFT z-scores adjusted for age, sex, height, race

†Model adjusted for maternal education, child's asthma diagnosis (yes/no)

Table 5

Linear regression models* mutually adjusted for prenatal and postnatal NLEs predicting PFT z-scores† at age 6 years

PFT Outcomes	NLEs score	All			Boys			Girls		
		β	s.e.	*p*	β	s.e.	*p*	β	s.e.	*p*
FEV1	Pre ≥5	−0.20	0.21	0.34	−0.05	0.27	0.85	−0.33	0.34	0.34
	Post ≥5	**−0.58**	**0.24**	**0.02**	**−0.74**	**0.31**	**0.02**	−0.4	0.39	0.30
FVC	Pre ≥5	−0.18	0.21	0.40	−0.04	0.26	0.89	−0.29	0.34	0.40
	Post ≥5	**−0.59**	**0.24**	**0.01**	**−0.76**	**0.30**	**0.01**	−0.40	0.38	0.30
FEF25-75%	Pre ≥5	−0.27	0.22	0.21	−0.15	0.27	0.58	−0.41	0.34	0.23
	Post ≥5	**−0.48**	**0.24**	**0.05**	**−0.61**	**0.31**	**0.05**	−0.41	0.38	0.29
FEV1/FVC	Pre ≥5	−0.07	0.21	0.73	−0.15	0.23	0.51	−0.08	0.28	0.78
	Post ≥5	**0.57**	**0.24**	**0.02**	**0.73**	**0.26**	**0.01**	0.26	0.32	0.41

*Multivariable-adjusted linear regressions predicting PFT z-scores (dependent variables). Models additionally adjusted for maternal education, child's asthma diagnosis (yes/no)

†PFT z-scores adjusted for age, sex, height, race