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Association of prenatal and early childhood stress with reduced lung function in 7-year-olds

Alison G. Lee, MD, MS^{*}; Yueh-Hsiu M. Chiu, ScD^{†,‡}; Maria J. Rosa, DrPH[‡]; Sheldon Cohen, PhD[§]; Brent A. Coull, PhD^{||}; Robert O. Wright, MD, MPH^{†,‡}; Wayne J. Morgan, MD[¶]; Rosalind J. Wright, MD, MPH^{†,‡}

^{*} Division of Pulmonary, Critical Care and Sleep Medicine, Icahn School of Medicine at Mount Sinai, New York, New York

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

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

[§] Department of Psychology, Carnegie Mellon University, Pittsburgh, Pennsylvania

^{||} Department of Biostatistics, Harvard Chan School of Public Health, Boston, Massachusetts

[¶] Department of Pediatrics, University of Arizona, Tucson, Arizona

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ABSTRACT

Background: No prior study has examined associations between prenatal and early-life stress on childhood lung function or identified critical windows of exposure.

Objective: To prospectively examine associations between prenatal and early-life stress and childhood lung function.

Methods: Stress was indexed by a maternal negative life events (NLEs) score ascertained during pregnancy and between 1 and 2 years post partum. Spirometry was performed when children were a mean (SD) of 6.99 (0.89) years old. Associations of prenatal and early postnatal stress with spirometry z scores were examined in 199 children using linear regression. Effect modification by child sex was explored.

Results: Most mothers were minorities (65% Hispanic, 21% African American), had 12 years or less of education (67%), and did not smoke prenatally (78%). The highest level of prenatal stress (≥ 5 NLEs) was associated with lower levels of forced expiratory volume in 1 second (FEV₁) (z score = -0.53 , $P = .03$), forced vital capacity (FVC) (z score = -0.49 , $P = .04$), and forced expiratory flow between 25% and 75% (FEF_{25%–75%}) (z score = -0.68 , $P = .01$) after covariate adjustment; effects were similar for postnatal stress considered separately. In sex-stratified analyses, high postnatal stress (≥ 5 NLEs) was associated with lower FEV₁ (z score = -0.76 , $P = .01$), FVC (z score = -0.77 , $P = .01$), and FEF_{25%–75%} (z score = -0.67 , $P = .02$) in boys but not girls, although the interaction term was not significant (P for interaction $> .10$).

Conclusion: These are the first prospective data that link perinatal stress with reduced child lung function. High levels of stress in the prenatal and postnatal periods were associated with symmetric reductions in FEV₁ and FVC consistent with impaired lung growth. Given that lung function growth patterns are established by 7 years of age, these findings have lifelong implications.

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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

birth¹ and lung function growth patterns established by 7 years of age 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 fourth 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 during 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 contribute to lung function development that may be amenable to intervention is thus important.

Reprints: Rosalind J. Wright, MD, MPH, Icahn School of Medicine at Mount Sinai, 1236 Park Ave, First Floor, New York, NY 10128; E-mail: rosalind.wright@mssm.edu.

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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 because these systems are highly reactive and labile in response to environmental stressors, particularly in the first 2 years when rapid lung development continues.¹¹

Although 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 1 second (FEV₁) by 6 to 7 years of age.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 or assessed the relative effect of prenatal 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 prenatal and/or postnatal stress in association with children's lung function by 7 years of age. Specifically, we first examined effects of prenatal and postnatal stress in independent models, then mutually adjusted for prenatal and 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 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, 500 English- or Spanish-speaking pregnant women (mean [SD] of 28.4 [7.9] weeks' gestation) receiving care at Brigham & Women's Hospital, Boston Medical Center, 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 in race/ethnicity, educational level, and income between women enrolled and those who declined; 455 gave birth to a live born infant and continued follow-up. Lung function testing was conducted on children naive to spirometry at a mean (SD) of 6.99 (0.89) years of age between March 2012 and September 2014; 230 of the 375 children actively followed up 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 7 years or older.

Negative Life Events

Prenatal and postnatal maternal stress was measured using the Crisis in Family Systems—Revised survey, validated in English and Spanish, administered within 2 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 (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. The number of domains

with one or more negative event was summed to create a negative life events (NLEs) domain score (range of 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 guidelines^{20,21} with techniques modified for children 8 years or younger.^{22,23} Subjects without acute respiratory symptoms for 3 weeks or more were eligible for testing. Short-acting β -agonists, anticholinergics, and theophylline preparations were withheld for 4 hours and long-acting β -agonists for 12 hours before testing. Parameters were recorded from a minimum of 3 (no more than 8) maneuvers and included the following: forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and forced expiratory flow between 25% and 75% of the FVC (FEF_{25%–75%}). Lung function measures, height, and weight were all approximately normally distributed. Raw FEV₁, FVC, FEF_{25%–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 (SD) of 0 (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, educational level, 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 obstetric estimates based on a second-trimester ultrasonogram if dates differed by more than 10 days on medical record review.²⁷ Sex-specific birth weight for gestational age z scores were calculated based on US 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?"

Statistical Analysis

We considered stress exposure categorized in 2 different ways. In the primary initial analysis, the NLEs score was categorized a priori as 0, 1 to 2, 3 to 4, or 5 or higher to assess exposure-response associations. Univariate and multivariable linear regressions were run to examine associations between prenatal and postnatal maternal stress and children's pulmonary function measures, including FEV₁, FVC, FEF_{25%–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 educational level and child's asthma diagnosis. We next adjusted for variables potentially on the pathway between stress and lung function, including sex-specific birth weight for gestational age z score and maternal tobacco

smoke exposure, as a sensitivity analysis. We also considered stress dichotomized as low (<5 NLEs) compared with high stress (≥ 5 NLEs) 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 prenatal 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 indexes 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, whereas numbers approaching 30 to 100 suggest moderate to strong collinearity.³⁰ The condition index in our analysis, including both prenatal and postnatal NLEs, was 3.99, indicating minimal collinearity. Analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

Of the 230 participating children, 211 (91.7%) provided acceptable spirometry; among these, 199 had data available on prenatal

and postnatal stress. Demographic characteristics of those included in analyses vs excluded participants were not significantly different.

Table 1 summarizes the 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 most did not smoke prenatally (78%). No significant differences were found between boys and girls except that boys were more likely to be diagnosed with asthma compared with girls ($P < .01$).

Independent Effects of Prenatal and Postnatal Maternal NLEs on Child Spirometry

Results of models considering prenatal and postnatal stress separately (Table 2 and Table 3) 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 with 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 with the lowest stress category was associated with lower levels of FEV₁ (z score = -0.53 , $P = .03$), FVC (z score = -0.49 , $P = .045$), and FEF_{25%–75%} (z score = -0.68 , $P = .01$), adjusting for maternal educational level, child's asthma status, birth weight z score, and prenatal smoking (Table 2). For postnatal stress, the highest vs lowest stress category was significantly associated with reduced FEV₁ (z score = -0.51 , $P = .04$) and FVC (z score = -0.51 , $P = .04$) in the fully adjusted model; there was a reduction in FEF_{25%–75%} in the highest stress group, although this finding did not reach statistical significance (z score = -0.45 , $P = .09$) (Table 3).

Table 1
Characteristics of Asthma Coalition on Community, Environment, and Social Stress Study Participants

Characteristic	All (N = 199)	Boys (n = 106)	Girls (n = 93)
Categorical variables, No. (%)			
Maternal race			
Hispanic	129 (64.8)	67 (63.2)	62 (66.7)
African American	42 (21.1)	22 (20.8)	20 (21.5)
White or other	28 (14.1)	17 (16.0)	11 (11.8)
Maternal educational level, y			
>12	65 (32.7)	36 (34.0)	29 (31.2)
≤ 12	134 (67.3)	70 (66.0)	64 (68.8)
Child ever asthma ^a			
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 ^b			
No	155 (77.9)	79 (74.5)	76 (81.7)
Yes	44 (22.1)	27 (25.5)	17 (18.3)
Continuous variables			
FEV ₁ , mean (SD), L	1.44 (0.25)	1.46 (0.23)	1.42 (0.26)
FVC, mean (SD), L	1.58 (0.29)	1.60 (0.26)	1.55 (0.32)
FEF _{25%–75%} , mean (SD), L/s	1.87 (0.46)	1.83 (0.47)	1.91 (0.44)
FEV ₁ /FVC ratio, mean (SD)	0.92 (0.05)	0.91 (0.06)	0.92 (0.05)
z score of FEV ₁ , median (IQR) ^c	-0.09 (-0.79 to 0.66)	-0.13 (-0.58 to 0.61)	-0.08 (-0.96 to 0.68)
z score of FVC, median (IQR) ^c	-0.12 (-0.74 to 0.64)	-0.02 (-0.51 to 0.68)	-0.15 (-1.03 to 0.57)
z score of FEF _{25%–75%} , median (IQR) ^c	-0.12 (-0.73 to 0.63)	-0.31 (-0.87 to 0.33)	0.29 (-0.62 to 0.96)
z score of FEV ₁ /FVC ratio, median (IQR) ^c	0.02 (-0.66 to 0.64)	-0.43 (-0.99 to 0.14)	0.59 (0.02 to 1.27)
Prenatal negative life events, median (IQR) (range, 0–8) ^d	2 (1 to 3)	2 (1 to 3)	2 (1 to 3)
Postnatal negative life events, median (IQR) (range, 0–8) ^d	2 (1 to 3)	2 (1 to 3)	2 (1 to 3)
Age at spirometry test, mean (SD), y	6.99 (0.89)	6.90 (0.78)	7.10 (0.99)
Height at spirometry test, mean (SD), cm	121.8 (7.4)	121.9 (7.3)	121.7 (7.6)
Birth weight for gestational age z score, median (IQR)	-0.11 (-0.79 to 0.57)	-0.10 (-0.76 to 0.72)	-0.11 (-0.72 to 0.54)

Abbreviations: FEF_{25%–75%}, forced expiratory flow between 25% and 75%; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range.

^aEver diagnosed with asthma before spirometry test.

^bMaternal report of smoking and/or whether others smoked in the home at each postpartum interview.

^cAdjusted for age, sex, height, and race.

^dAssessed using Crisis in Family Systems-Revised survey; multi-item survey summarized into a continuous score.

Table 2
Associations Between Prenatal Maternal NLEs and Childhood PFT z Scores: Linear Regression^a

	Univariate model		Multivariable-adjusted models ^b					
	β (SE)	P value	Model 1		Model 2		Model 3	
			β (SE)	P value	β (SE)	P value	β (SE)	P value
Outcome: FEV ₁								
0 NLEs	Reference	NA	Reference	NA	Reference	NA	Reference	NA
1–2 NLEs	–0.13 (0.20)	.49	–0.14 (0.20)	.48	–0.12 (0.19)	.54	–0.25 (0.19)	.18
3–4 NLEs	–0.03 (0.22)	.89	–0.04 (0.22)	.86	–0.05 (0.21)	.81	–0.11 (0.20)	.59
≥5 NLEs	–0.46 (0.26)	.08	–0.48 (0.25)	.06	–0.50 (0.25)	.05	–0.53 (0.24)	.03
Outcome: FVC								
0 NLEs	Reference	NA	Reference	NA	Reference	NA	Reference	NA
1–2 NLEs	–0.11 (0.20)	.58	–0.11 (0.20)	.56	–0.09 (0.19)	.63	–0.231 (0.19)	.22
3–4 NLEs	–0.01 (0.22)	.96	–0.02 (0.22)	.93	–0.03 (0.21)	.89	–0.09 (0.20)	.66
≥5 NLEs	–0.42 (0.26)	.11	–0.43 (0.25)	.09	–0.46 (0.25)	.07	–0.49 (0.24)	.045
Outcome: FEF _{25%–75%}								
0 NLEs	Reference	NA	Reference	NA	Reference	NA	Reference	NA
NLEs: 1–2	–0.28 (0.19)	.16	–0.28 (0.19)	.15	–0.27 (0.19)	.17	–0.37 (0.19)	.05
NLEs: 3–4	–0.16 (0.22)	.46	–0.17 (0.21)	.43	–0.18 (0.21)	.41	–0.22 (0.21)	.28
NLEs ≥5	–0.62 (0.25)	.02	–0.65 (0.25)	.01	–0.66 (0.25)	.01	–0.68 (0.25)	.01
Outcome: FEV ₁ /FVC ratio								
0 NLEs	Reference	NA	Reference	NA	Reference	NA	Reference	NA
1–2 NLEs	–0.15 (0.20)	.44	–0.15 (0.20)	.44	–0.18 (0.19)	.36	–0.06 (0.19)	.74
3–4 NLEs	–0.22 (0.22)	.31	–0.22 (0.22)	.32	–0.20 (0.21)	.34	–0.15 (0.21)	.47
≥5 NLEs	–0.09 (0.26)	.74	–0.08 (0.26)	.75	–0.06 (0.25)	.82	–0.03 (0.25)	.92

Abbreviations: FEF_{25%–75%}, forced expiratory flow between 25% and 75%; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; NA, not applicable; NLEs, negative life events; PFT, pulmonary function test.

^aPrenatal NLEs sample sizes: 0 NLEs, n = 37 (18.6%); 1 to 2 NLEs, n = 86 (43.2%); 3 to 4 NLEs, n = 50 (25.1%); and 5 or more NLEs, n = 26 (13.1%). The PFT z scores were adjusted for age, sex, height, and race.

^bMultivariable-adjusted linear regressions (models 1–3) predicting PFT z scores (dependent variables). Model 1 was adjusted for maternal educational level. Model 2 was adjusted for maternal educational level and child's asthma diagnosis (yes/no). Model 3 was adjusted for maternal educational level, child's asthma diagnosis (yes/no), birth weight z score, and prenatal smoking.

Because linear regression models in Table 2 and Table 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 FEF_{25%–75%} for both the prenatal and postnatal periods (Table 4). In sex-stratified

Table 3
Associations Between Postnatal Maternal NLEs and Childhood PFT z Scores: Linear Regression^a

	Univariate model		Multivariable-adjusted models ^b					
	β (SE)	P value	Model 1		Model 2		Model 3	
			β (SE)	P value	β (SE)	P value	β (SE)	P value
Outcome: FEV ₁								
0 NLEs	Reference	NA	Reference	NA	Reference	NA	Reference	NA
1–2 NLEs	0.11 (0.18)	.57	0.12 (0.18)	.50	0.14 (0.18)	.46	0.12 (0.17)	.48
3–4 NLEs	0.16 (0.22)	.47	0.16 (0.22)	.46	0.12 (0.22)	.58	0.14 (0.21)	.52
≥5 NLEs	–0.52 (0.27)	.05	–0.48 (0.26)	.07	–0.54 (0.27)	.04	–0.51 (0.25)	.04
Outcome: FVC								
0 NLEs	Reference	NA	Reference	NA	Reference	NA	Reference	NA
1–2 NLEs	0.12 (0.18)	.51	0.14 (0.18)	.45	0.15 (0.18)	.40	0.14 (0.17)	.42
3–4 NLEs	0.17 (0.22)	.43	0.18 (0.22)	.42	0.13 (0.22)	.54	0.15 (0.21)	.48
≥5 NLEs	–0.51 (0.26)	.06	–0.47 (0.26)	.07	–0.54 (0.26)	.04	–0.51 (0.25)	.04
Outcome: FEF _{25%–75%}								
0 NLEs	Reference	NA	Reference	NA	Reference	NA	Reference	NA
1–2 NLEs	0.09 (0.19)	.64	0.11 (0.19)	.55	0.12 (0.19)	.53	0.11 (0.18)	.55
3–4 NLEs	0.14 (0.22)	.53	0.14 (0.22)	.52	0.12 (0.22)	.59	0.13 (0.22)	.56
≥5 NLEs	–0.49 (0.27)	.07	–0.44 (0.27)	.11	–0.47 (0.27)	.08	–0.45 (0.27)	.09
Outcome: FEV ₁ /FVC ratio								
0 NLEs	Reference	NA	Reference	NA	Reference	NA	Reference	NA
1–2 NLEs	–0.22 (0.19)	.23	–0.22 (0.19)	.23	–0.24 (0.18)	.19	–0.23 (0.18)	.20
3–4 NLEs	–0.19 (0.22)	.40	–0.19 (0.22)	.40	–0.13 (0.22)	.57	–0.15 (0.22)	.49
≥5 NLEs	0.31 (0.27)	.25	0.30 (0.27)	.26	0.40 (0.27)	.14	0.37 (0.26)	.15

Abbreviations: FEF_{25%–75%}, forced expiratory flow between 25% and 75%; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; NA, not applicable; NLEs, negative life events; PFT, pulmonary function test.

^aPostnatal NLEs sample sizes: 0 NLEs, n = 40 (23.1%); 1 to 2 NLEs, n = 79 (45.7%); 3 to 4 NLEs, n = 35 (20.2%); and 5 or more NLEs, n = 19 (11%).

^bMultivariable-adjusted linear regressions (models 1–3) predicting PFT z scores (dependent variables). Model 1 was adjusted for maternal educational level. Model 2 was adjusted for maternal educational level and child's asthma diagnosis (yes/no). Model 3 was adjusted for maternal educational level, child's asthma diagnosis (yes/no), birth weight z score, and prenatal smoking.

Table 4Associations Between Prenatal and Postnatal NLEs and Childhood PFT z Scores in Separate Models: Linear Regression^a

NLEs score (≥ 5 vs Others)	PFT outcomes	All		Boys		Girls	
		β (SE)	P value	β (SE)	P value	β (SE)	P value
Prenatal	FEV ₁	−0.42 (0.21)	.04	−0.41 (0.27)	.12	−0.43 (0.33)	.19
	FVC	−0.40 (0.21)	.05	−0.40 (0.27)	.13	−0.39 (0.33)	.23
	FEF _{25%–75%}	−0.48 (0.21)	.02	−0.45 (0.26)	.08	−0.52 (0.32)	.11
	FEV ₁ /FVC	0.09 (0.21)	.66	0.15 (0.23)	.51	−0.01 (0.28)	.98
Postnatal	FEV ₁	−0.64 (0.23)	.01	−0.76 (0.29)	.01	−0.47 (0.38)	.22
	FVC	−0.65 (0.23)	.01	−0.77 (0.28)	.01	−0.46 (0.38)	.22
	FEF _{25%–75%}	−0.56 (0.24)	.02	−0.67 (0.29)	.02	−0.50 (0.38)	.19
	FEV ₁ /FVC	0.55 (0.23)	.02	0.67 (0.25)	.01	0.25 (0.31)	.43

Abbreviations: FEF_{25%–75%}, forced expiratory flow between 25% and 75%; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; NLEs, negative life events; PFT, pulmonary function test.

^aModel adjusted for maternal educational level and child's asthma diagnosis (yes/no). PFT z scores adjusted for age, sex, height, and race.

analyses, reductions in FEV₁, FVC, and FEF_{25%–75%} were similar in magnitude in relation to high prenatal stress exposure, although these associations did not reach statistical significance in boys or girls. However, associations between high postnatal stress exposure and lower FEV₁ (z score = −0.76, $P = .01$), FVC (z score = −0.77, $P = .01$), and FEF_{25%–75%} (z score = −0.67, $P = .02$) remained significant in boys but not girls (Table 4). Interaction terms did not reach significance (prenatal NLE dichotomous indicator $\times$ sex P for interaction $>.10$, postnatal NLE dichotomous indicator $\times$ sex P for interaction $>.10$).

Mutual Adjustment for Prenatal and Postnatal Maternal Stress

Table 5 presents results from linear regression models concurrently considering prenatal and postnatal maternal NLEs and pulmonary function testing (PFT) z scores. When prenatal stress 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, $P = .02$), FVC (z score = −0.59, $P = .01$), and FEF_{25%–75%} levels (z score = −0.48, $P = .05$). In sex-stratified analyses, this association was significant only among boys (P for interaction $>.10$).

Discussion

This is the first prospective study demonstrating that increased psychological stress in pregnancy and the first 2 years of life is associated with reductions in children's lung function by 7 years of age. 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 FEF_{25%–75%} z scores with a preserved FEV₁/FVC ratio when these exposure periods were considered separately. Although

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

The mind-body paradigm linking psychological stress and affective states to key physiologic 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 (eg, HPA axis, autonomic nervous system) 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 (eg, HPA axis disruption, enhanced nonspecific and allergen-specific lymphocyte proliferation, differential cytokine expression).^{38–40} Persistent wheeze,⁴¹ atopy,⁴² and asthma² 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 infections⁴³ and smoking behaviors.⁴⁴ Other research indicates that early-life stress can enhance the effects of other environmental factors that affect lung growth and development.^{45,46}

Our results reveal a symmetric reduction in FEV₁ and FVC with a preserved ratio in response to prenatal and postnatal stress, suggesting impaired lung growth in these critical windows. These findings expand on prior research linking prenatal maternal stress or stress correlates (eg, depression, anxiety) to impaired fetal growth⁴⁷; 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

Table 5Linear Regression Models Mutually Adjusted for Prenatal and Postnatal NLEs Predicting PFT z Scores at 6 Years of Age^a

PFT outcomes	NLEs score	All		Boys		Girls	
		β (SE)	P value	β (SE)	P value	β (SE)	P value
FEV ₁	Pre ≥ 5	−0.20 (0.21)	.34	−0.05 (0.27)	.85	−0.33 (0.34)	.34
	Post ≥ 5	−0.58 (0.24)	.02	−0.74 (0.31)	.02	−0.4 (0.39)	.30
FVC	Pre ≥ 5	−0.18 (0.21)	.40	−0.04 (0.26)	.89	−0.29 (0.34)	.40
	Post ≥ 5	−0.59 (0.24)	.01	−0.76 (0.30)	.01	−0.40 (0.38)	.30
FEF _{25%–75%}	Pre ≥ 5	−0.27 (0.22)	.21	−0.15 (0.27)	.58	−0.41 (0.34)	.23
	Post ≥ 5	−0.48 (0.24)	.05	−0.61 (0.31)	.05	−0.41 (0.38)	.29
FEV ₁ /FVC	Pre ≥ 5	−0.07 (0.21)	.73	−0.15 (0.23)	.51	−0.08 (0.28)	.78
	Post ≥ 5	0.57 (0.24)	.02	0.73 (0.26)	.01	0.26 (0.32)	.41

Abbreviations: FEF_{25%–75%}, forced expiratory flow between 25% and 75%; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; NLEs, negative life events; PFT, pulmonary function test.

^aMultivariable-adjusted linear regressions predicting PFT z scores (dependent variables). Models additionally adjusted for maternal educational level and child's asthma diagnosis (yes/no). PFT z scores adjusted for age, sex, height, and race.

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 Furthermore, these findings support those of our earlier Boston cohort study linking violence exposure (a community-level stressor) during childhood with reduced FEV₁ and FVC at 6 years of age.¹³

Sex-stratified analyses reveal that lung function was most significantly reduced in boys in the postnatal period, with a trend toward significance prenatally. Our results support the previously reported associations between maternal stress assessed using the same NLE measure and child asthma risk by 6 years of age, which also found that boys were more susceptible to both prenatal and postnatal maternal stress.³⁶ It may be the case that different types of stress have variable effects on lung development and may affect girls and boys differently, as demonstrated for other disorders.⁵⁰ This finding 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 prenatal and postnatal maternal stress have a mean 133-mL (9.2%) and 128-mL (8.9%) reduction in FEV₁ and a 142-mL (9.0%) and 148-mL (9.4%) reduction in FVC, respectively, at 7 years of age compared with 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 7 years of age 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 prenatal 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 prenatally and in the first 2 years of life (ie, 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 affected by increased stress and reduced lung function and our ability to adjust for several important confounders and potential pathway variables.

We also acknowledge limitations. Although 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 (eg, 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, during early development that may be dysregulated by stress and play a role in morphogenesis and maturation of the respiratory system. Although our sample size was large enough to detect associations between prenatal 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 hypothalamic-pituitary-gonadal axes, autonomic nervous system functioning, and immune function, during early development that may be sexually dimorphic.⁵² There should also be increased focus on placental functioning, given emerging evidence of a significant role of placenta in lung morphogenesis⁵³ and stress-elicited epigenetic programming.⁵⁴ For example, recent analyses in the Lifestyle and Environmental Factors and Their Influence on Newborns Allergy Risk study reported differentially methylated regions in calcium- and Wnt-signaling pathways involved in lung maturation prenatally among children exposed to increased prenatal stress who developed 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 that influences lung growth and development in early life. These data add to an increasing body of epidemiologic research demonstrating an association between increased perinatal maternal stress and adverse childhood respiratory outcomes. Given the increasing evidence linking perinatal stress to early respiratory morbidity, researchers should begin to develop and study interventions, at the individual and policy levels, 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. Regarding the threshold effect for stress, these analyses found that children born to mothers with the highest levels of stress exposure in these critical windows had significantly decreased lung function. Although 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.

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