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# Forced expiratory flows and diffusion capacity in infants born from mothers with pre-eclampsia

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## Abstract

**Rationale:** Animal models suggest pre-eclampsia (Pre-E) affects alveolar development, but data from humans are lacking.

**Objective:** Assess the impact of Pre-E on airway function, diffusion capacity, and respiratory morbidity in preterm and term infants born from mothers with Pre-E.

**Methods:** Infants born from mothers with and without Pre-E were recruited for this study; term and preterm infants were included in both cohorts. Respiratory morbidity in the first 12 months of life was assessed through monthly phone surveys. Raised volume rapid thoracoabdominal compression and measurement of diffusion capacity of the lung to carbon monoxide (DLCO) were performed at 6 months corrected age.

**Measurements and Main Results:** There were 146 infants in the Pre-E cohort and 143 in the control cohort. The Pre-E cohort was further divided into nonsevere ($N = 41$) and severe ($N = 105$) groups. There was no significant difference in DLCO and DLCO/alveolar volume among the three groups. Forced vital capacity was similar among the three groups, but the nonsevere Pre-E group had significantly higher forced expiratory flows than the other two groups. After adjusting for multiple covariates including prematurity, the severe Pre-E group had a lower risk for wheezing in the first year of life compared to the other two groups.

**Conclusions:** Pre-E is not associated with reduced DLCO, lower forced expiratory flows, or increased wheezing in the first year of life. These results differ from animal models and highlight the complex relationships between Pre-E and lung function and respiratory morbidity in human infants.

KEYWORDS

prematurity, wheezing

## 1 | INTRODUCTION

Pre-eclampsia (Pre-E) is a serious complication of pregnancy that occurs in approximately 5% of pregnancies in the USA.[1] Pre-E is characterized by maternal hypertension and systemic vascular endothelial dysfunction. Although the pathogenesis of Pre-E is not well-defined, several studies have demonstrated that women with Pre-E have increased circulating levels of antiangiogenic factors such as soluble FMS-like Tyrosine Kinase-1 (sFlt-1).[2,3] Infants born from mothers with Pre-E have a reduced risk for retinopathy of prematurity, a condition caused by excess retinal angiogenesis and neovascularization.[4] In addition, infants born from hypertensive women have reduced skin capillary density.[5] These observations suggest that the antiangiogenic milieu of pregnant women with Pre-E affects vascular development in the fetus. Recent evidence from a murine model of the early onset immune-mediated subtype of Pre-E suggests that the placenta plays a key role in mediating the effects of Pre-E on fetal lung development.[6,7]

Disruption of pulmonary vascular development is linked to impaired alveolar growth, a hallmark feature of bronchopulmonary dysplasia (BPD). Increased cord blood sFlt-1 is also associated with an enhanced risk of BPD in preterm infants.[8–11] A rat model of Pre-E utilizing intra-amniotic injection of sFlt-1 demonstrated decreased alveolar number and reduced pulmonary vessel density at 14 days of age, which corresponds to 1 year of human life.[10] Furthermore, a history of maternal Pre-E is associated with increased rates of asthma, allergy, and eczema.[12,13] Taken together, these clinical and animal data suggest that the effect of Pre-E on angiogenesis may affect respiratory function in infants with Pre-E. However, there are limited data on airway function and, to our knowledge, no data on the gas transfer in infants with a history of maternal Pre-E.

The objective of our study was to assess the impact of Pre-E on respiratory outcomes in early infancy, which included lung function and respiratory morbidity. We hypothesized that the in utero antiangiogenic environment of pre-E would result in impaired lung growth and development with decreased parenchymal and airway function, as well as increased respiratory morbidity in infants born of pregnant women with Pre-E. To test this hypothesis, we recruited a cohort of pregnant women with Pre-E and a cohort of normotensive pregnant women with similar gestational ages (GA) that included preterm and term infants. We evaluated parenchymal function with measurements of diffusion capacity of the lung and lung volume and airway function with measurements of forced expiratory flows (FEFs). Infant pulmonary function tests (IPFTs) were performed at approximately 6 months corrected age, and their respiratory status was followed through 12 months corrected age.

## 2 | METHODS

### 2.1 | Study population and design

This was a single-center, prospective, observational cohort study (NCT02639676). Potential study participants were recruited from three local hospitals in Indianapolis, IN, USA. Inclusion criteria for the study cohort included a clinical diagnosis of Pre-E (using definitions contained in the American College of Obstetrics and Gynecology Task Force on Hypertension in Pregnancy 2013 report) with anticipated delivery between 26 and 40 weeks GA determined by best obstetrical dating (last menstrual period confirmed by ultrasound).[14] We also recruited a comparison cohort of infants born from normotensive pregnant women with anticipated delivery between 26 and 40 weeks GA determined by best obstetrical dating. Exclusion criteria included multiple gestation pregnancy, prenatally identified fetal cardiopulmonary defects, known fetal chromosomal disorders, and women with diabetes mellitus. Women with chronic hypertension who developed gestational hypertension were included, but we excluded women who had only chronic hypertension or only gestational hypertension. Prematurity was not an exclusion criterion for either cohort, and the final cohorts were comprised of term and preterm infants. Before the initiation of this study, we received approval from the Indiana University Institutional Review Board. The mothers of infant study participants all provided written informed consent.

We used the electronic medical record to obtain maternal clinical information, such as maternal medications (e.g., antenatal steroids [ANS], magnesium sulfate, other antihypertensive therapies), tobacco use, and family history of asthma. We also obtained neonatal clinical information such as birth weight and length, GA at birth, sex, race, diagnosis of BPD, and need for interventions such as exogenous surfactant therapy, positive pressure ventilation, and supplement oxygen use.

Following discharge from the hospital, we performed monthly telephone surveys to track episodes of wheezing, respiratory medication use (e.g., inhaled bronchodilators [BDs] and inhaled corticosteroids), and hospitalizations for respiratory-related illnesses.

### 2.2 | IPFTs

Parenchymal and airway function were assessed using previously described methods.[15,16] In brief, infants were first sedated with oral chloral hydrate (85 mg/kg) and measurements of the alveolar volume (VA) and diffusion capacity of the lung to carbon monoxide (DLCO) were performed. In addition, FEFs using the raised volume rapid thoracoabdominal compression technique were measured and quantified by forced vital capacity (FVC), FEFs between 25% and 75% expired FVC ($FEF_{25-75}$), FEF at 50% and 75% expired FVC ($FEF_{50}$, $FEF_{75}$), as well as forced expired volume in 0.5 s ($FEV_{0.5}$). Data quality was determined using published guidelines,[17] and only research quality data were used for analysis.

### 2.3 | Statistical analysis

The Pre-E cohort was evaluated as a single group, as well as divided into two groups, nonsevere Pre-E and severe Pre-E, using the American College of Obstetrics and Gynecology criteria for Pre-E with severe features.[18] Basic clinical and demographic comparisons were performed using $\chi^2$ tests for categorical variables and Student's *t*-tests and Wilcoxon rank-sum tests for continuous variables, depending on the data

distributions. Pairwise comparisons were made using a Bonferroni correction. To analyze wheezing outcomes, a participant level variable of ever/never wheezed was created for participants who had at least one survey response in the first 6 months of surveys, at or after 6 months. We then analyzed all the survey data from infants meeting this criterion. For each of the main outcomes, simple bivariate analyses were first performed and those variables that had a *p*-value of ≤0.10 were included in a multivariable model. In addition to these variables, we included clinically relevant ones, for example, sex and race. For the outcome of wheezing, using the dichotomous wheezing outcome as described above, logistic regression analysis was performed using a multivariable model including Pre-E group, sex, GA, mother's smoking history, and family history of asthma, and ANS use. GA was defined as the number of weeks from the first day of the mother's last menstrual period to the date of birth, and it was obtained from the medical record. We treated GA as a continuous variable in our analyses. IPFT outcomes were analyzed with raw data adjusting for race, sex, and body length at testing in multivariable models. Simple *t*-tests were used for the bivariate analyses and analysis of covariance models were performed for the adjusted models, with the covariates sex, race, length, and GA. Fetal growth restriction (FGR), ANS use, and family history of asthma were also included as covariates based on the results of the bivariate analysis. All analytic assumptions were verified, collinearity was assessed for multivariable models, and analyses were performed using SAS v9.4 (SAS Institute).

## 3 | RESULTS

A total of 430 infants were screened, and 289 were enrolled, 146 in the Pre-E group and 143 in the normotensive comparison cohort. Figure 1 illustrates the derivation of the study cohort. From the 85 infants who had PFTs, we were able to obtain research quality DLCO data from all of them and research quality raised volume rapid thoracoabdominal compression (RVRTC) data in 67 (79%). The research quality rate of RVRTC data is similar to that of other studies.[19–22] The demographic and clinical features of the control and Pre-E (nonsevere and severe) cohorts are summarized in Table 1. There were no differences among groups for sex and maternal race; however, as expected, GA, birth weight, and birth length of the severe Pre-E infants were significantly lower compared to infants in the control and nonsevere Pre-E groups. Severe Pre-E infants were also more likely to have FGR, to be small of GA, and to be born to women treated with ANS. No significant differences were observed among the groups in terms of the need for mechanical ventilation, surfactant therapy, development of BPD, history of maternal smoking, and second-hand smoke exposure. A similar pattern of clinical features was seen when comparisons were restricted to the infants who had IPFT obtained (data not shown).

IPFTs were performed at a mean corrected age of 7.99 months (SD 2.69, range = 4.14–19.53), and the results are summarized in Table 2. DLCO, DLCO/VA, and VA were not different for the control and Pre-E group, even when the latter was divided into the nonsevere and severe Pre-E groups. In addition, hemoglobin concentration did not differ among the three groups (11.5 ± 1.2, 11.3 ± 1.4, and 11.7 ± 1.2; $p > 0.3728$). Although there were no statistically significant differences in IPFT results in the total Pre-E cohort compared to the controls, when Pre-E was divided by severity, the nonsevere Pre-E cohort had significantly higher FEFs compared to the controls and severe Pre-E infants (Table 2). In addition, $FEV_{0.5}$ was higher in the nonsevere Pre-E group, although the difference did not reach statistical significance ($p = 0.058$).

There were 234 infants (control, $N = 108$; Pre-E, $N = 126$) whose caregivers responded to at least one survey in the first 6 months of life, and again after 6 months of life. The demographics and clinical features of this group were similar to those of the entire cohort and the proportion of respondents was similar in both the control group and pre-E groups. Among all infants with respiratory questionnaires, 98 (42%) had at least one episode of wheezing reported in the first year of life. There was no significant difference in the proportion of subjects with No Wheeze among the three groups (control, nonsevere Pre-E, and severe Pre-E). Preterm birth, lower birth weight, lower birth length, and lower GA, maternal smoking, and history of asthma were also associated with a higher prevalence of wheezing. An analysis restricted to only those infants who also had IPFT revealed a similar pattern. Using covariates related to the risk of wheeze selected from the bivariate analysis (Table 3) and additional variables based on clinical relevance (listed in Section 2), we then performed multivariable logistic regression modeling for the outcome of Wheeze versus No Wheeze. The odds ratio (OR) of Wheeze was significantly lower in the combined Pre-E group compared to controls (0.47; $p < 0.009$). When the Pre-E group was divided into nonsevere and severe Pre-E, each of the Pre-E groups had OR for Wheeze of less than 1.0; however, compared to the control group, only the severe Pre-E group, which composed the majority of Pre-E subjects, had significantly lower risk for wheeze (Table 4). Family history of asthma, maternal smoking, and ANS were all included in the logistic model based upon their associated increased risk of Wheeze in the bivariate analysis (Table 3), only ANS, which were more frequent in the severe Pre-E group, was statistically significant, while family history of asthma and maternal smoking were still associated with an increased risk of wheeze with *p*-values <0.10 (Table 1). Very few infants were hospitalized for respiratory illness following discharge, precluding a detailed analysis of this respiratory outcome.

## 4 | DISCUSSION

In this single-center prospective cohort study of infants born from mothers with Pre-E, no differences were detected in the lung parenchymal function of gas exchange and lung volume, as assessed by DLCO, DLCO/VA, or VA, when compared to control infants born from normotensive mothers. This finding does not support our hypothesis nor agree with animal models of Pre-E, which suggest impaired alveolar development in the offspring of mothers with Pre-E. However, we did find that airway function, assessed by FEFs, was actually higher in the nonsevere Pre-E group compared to control and severe Pre-E groups. Although the nonsevere Pre-E group had higher FEFs, the severe Pre-E group, which did not have higher FEFs, had a lower risk for wheeze in the first year of life when adjusted for

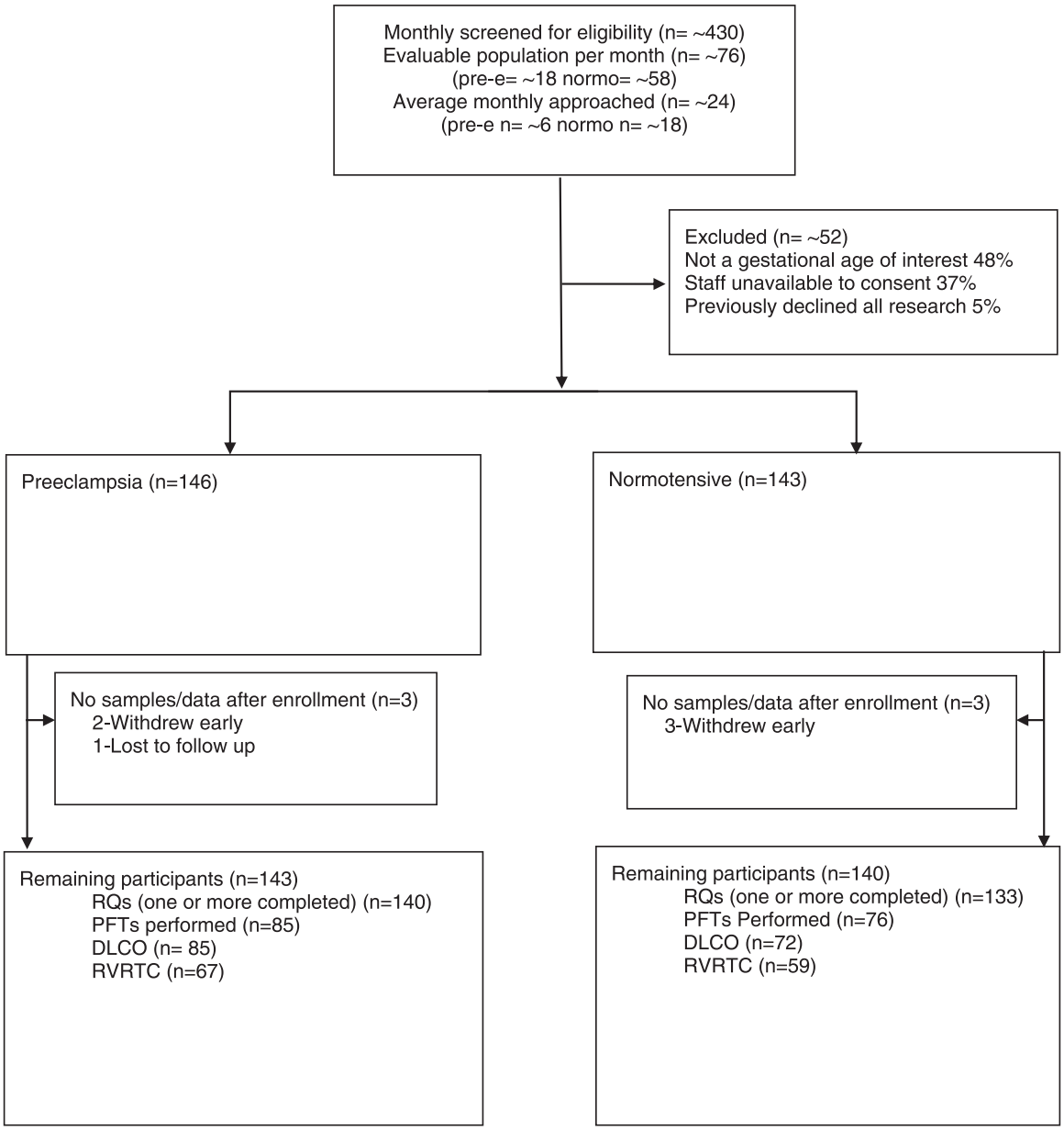


**FIGURE 1** Derivation of the study cohorts. The numbers in the screening box represent approximate monthly values. DLCO, diffusion capacity of the lung to carbon monoxide; PFT, pulmonary function test; RQ, respiratory questionnaire; RVRTC, raised volume rapid thoracoabdominal compression.

covariates including GA. These findings highlight the complex relationships among prematurity, lung function, and respiratory morbidity in human infants born from mothers with Pre-E.

We are not aware of other studies that have assessed DLCO as a respiratory outcome in offspring of mothers with Pre-E. The majority of infants born following maternal Pre-E are preterm because labor is either induced or a caesarean section is performed at a premature GA to protect the mother from severe Pre-E. Therefore, preterm birth, which is associated with impaired alveolar development and increased respiratory morbidity, becomes an important confounder in the assessment of respiratory outcomes of lung function and respiratory morbidity. We, therefore, used a control group from normotensive pregnancies that included preterm and term births. Our findings that DLCO and VA did not differ between Pre-E (nonsevere and severe) and normotensive control group suggests that Pre-E did not significantly impair alveolar development when evaluated at a mean corrected-age of 7–8 months.

Our findings related to parenchymal function do not support our initial hypothesis and are not consistent with current animal models of Pre-E. Tang et al.[10] reported that the amniotic administration of the anti-angiogenic factor FLT-1 to pregnant rats 2 days before delivering pups via caesarian section resulted in decreased alveolar number, reduced pulmonary vessel density, and right ventricular hypertrophy. More recently, Taglauer et al. used a heme oxygenase-1

**TABLE 1** Clinical features of the cohort

| | Control | Nonsevere Pre-E | Severe Pre-E | *p* Value |
|---|---|---|---|---|
| *N* | 143 | 41 | 105 | |
| Sex | | | | |
| Female | 61 (43.0) | 19 (46.3) | 56 (53.3) | 0.2695 |
| Male | 81 (57.0) | 22 (53.7) | 49 (46.7) | |
| Maternal race | | | | 0.6416 |
| Black | 67 (47.2) | 17 (41.5) | 57 (54.3) | |
| White | 67 (47.2) | 20 (48.8) | 43 (41.0) | |
| Multi | 7 (4.9) | 4 (9.8) | 4 (3.8) | |
| Unknown | 1 (0.7) | 0 (0) | 1 (1.0) | |
| Preterm delivery | 55 (38.7) | 8 (19.5) | 66 (62.9) | <0.0001[bc] |
| Gestational age | | | | <0.0001[bc] |
| Mean (SD) | 37.11 (3.55) | 37.66 (2.46) | 35.32 (3.49) | |
| Median (95% CI) | 38.4 (35.1, 39.9) | 37.6 (37.0, 39.3) | 36.3 (33.6, 37.3) | |
| Birth weight (kg) | | | | <0.0001[bc] |
| Mean (SD) | 2.98 (2.52, 3.36) | 2.9978 (0.8205) | 2.3184 (0.7744) | |
| Median (95% CI) | 2.98 (2.52, 3.36) | 3.19 (2.66, 3.51) | 2.41 (1.78, 2.89) | |
| Birth length (cm) | | | | <0.0001[ab] |
| Mean (SD) | 47.87 (5.20) | 48.48 (4.95) | 45.19 (5.07) | |
| Median (95% CI) | 49.0 (46.0, 51.0) | 49.0 (48.3, 52.0) | 47.0 (43.0, 48.5) | |
| Fetal growth restriction | 16 (11.4) | 5 (12.2) | 27 (25.7) | 0.0081[a] |
| Family history of asthma | 31 (21.8) | 11 (26.8) | 28 (26.7) | 0.6273 |
| Size for GA | | | | |
| Small for GA | 14 (9.9) | 5 (12.2) | 26 (24.8) | 0.0014[ab] |
| Appropriate for GA | 119 (84.4) | 32 (78.1) | 79 (75.2) | |
| Large for GA | 8 (5.7) | 4 (9.8) | 0 (0) | |
| Antenatal steroids | 55 (39.0) | 12 (29.3) | 63 (60.0) | 0.0004[ab] |

*Note*: Values in parentheses represent percentages except as noted. Superscripted letter indicate which pairwise comparison was made (a, control vs. severe Pre-E; b, nonsevere Pre-E vs. severe Pre-E).

Abbreviations: CI, confidence interval; GA, gestational age; Pre-E, pre-eclampsia.

null mouse model of Pre-E to demonstrate disrupted alveolar formation and altered airway development. This model was also associated with a downregulation of angiogenic and epithelial pathways, as well as an upregulation of inflammatory and extracellular matrix pathways, suggesting multiple molecular pathways contributing to the observed pulmonary phenotype. It is possible that the Pre-E infants we evaluated may have demonstrated impaired alveolar development if evaluated during the neonatal period and subsequently exhibited catch-up in alveolar development before our evaluation. However, the animal models of Pre-E that demonstrated impaired alveolar development often evaluated animal offspring at human developmental age equivalent to our study in human infants.[23] In addition, there are currently no longitudinal data in humans to indicate that there is catch-up lung growth following preterm birth or maternal pre-E. Therefore, it remains unclear how well the current animal models of Pre-E reflect clinical Pre-E, and the various subtypes, which may result from multiple different factors and be associated with multiple comorbidities, such as FGR and prematurity, which can affect lung development.

In contrast to no differences in DLCO and VA, we did find higher FEFs in infants of mothers with nonsevere Pre-E. This finding is consistent with the higher FEFs reported in older children born of mothers with Pre-E, although that study of older children was restricted to subjects born preterm with GA < 28 weeks or weighing <1000 g.[24] In both that study and ours, FVC did not differ between Pre-E and control groups, suggesting that the higher FEFs were

**TABLE 2** Infant lung function results

| PFT measure | Control ($n = 108$) | Nonsevere pre-eclampsia ($n = 34$) | Severe pre-eclampsia ($n = 92$) | Mean difference (95% CI) (control vs. nonsevere) | Mean difference (95% CI) (control vs. severe) | Mean difference (95% CI) (nonsevere vs. severe) | Omnibus $p$ value |
|---|---|---|---|---|---|---|---|
| DLCO (ml/min/mmHg) | 2.6 (0.1) | 2.6 (0.1) | 2.5 (0.1) | −0.0 (−0.3, 0.3) | 0.1 (−0.2, 0.3) | 0.1 (−0.2, 0.4) | 0.7786 |
| DLCO/VA (ml/min/mmHg/ml) | 6.9 (0.2) | 7.1 (0.3) | 7.1 (0.2) | −0.2 (−0.8, 0.4) | −0.2 (−0.6, 0.2) | −0.0 (−0.6, 0.6) | 0.6103 |
| VA (ml) | 410.6 (12.6) | 397.8 (19.3) | 389.2 (13.0) | 12.8 (−27.3, 52.8) | 21.5 (−7.6, 50.5) | 8.7 (−33.4, 50.8) | 0.3391 |
| FVC (ml) | 271.4 (6.5) | 275.2 (9.8) | 265.4 (7.1) | −3.8 (−24.3, 16.7) | 6.0 (−8.9, 20.9) | 9.8 (−12.1, 31.8) | 0.6102 |
| $V_{50}$ (ml/s) | 444.6 (17.8) | 537.0 (26.8)* | 457.9 (19.3) | −92.4 (−148.6, −36.2) | −13.3 (−54.2, 27.6) | 79.1 (18.9, 139.3) | 0.0061 |
| $FEF_{25-75}$ (ml/s) | 412.0 (16.2) | 495.0 (24.4)* | 418.5 (17.6) | −83.0 (−134.1, −31.9) | −6.5 (−43.6, 30.7) | 76.5 (21.8, 131.3) | 0.0062 |
| $V_{75}$ (ml/s) | 252.0 (12.5) | 289.1 (18.8) | 251.0 (13.5) | −37.1 (−76.4, 2.3) | 1.0 (−27.6, 29.6) | 38.1 (−4.0, 80.2) | 0.1525 |
| $FEV_{0.5}$ (ml) | 211.7 (5.4) | 231.2 (8.1)* | 210.5 (5.8) | −19.5 (−36.4, −2.5) | 1.2 (−11.2, 13.5) | 20.6 (2.5, 38.8) | 0.0578 |

*Note*: The total numbers for each group are shown in the table. Values are means (standard errors) for each group with 95% CI for the difference between means and $p$-value from ANCOVA models. * Pairwise comparison between control vs. severe Pre-E.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; DLCO, diffusion capacity of the lung to carbon monoxide; $FEF_{25-75}$, forced expiratory flow between 25% and 75% of FVC; $FEV_{0.5}$, forced expiratory volume in 0.5 s; FVC, forced vital capacity; PFT, pulmonary function test; Pre-E, pre-eclampsia; $V_{50}$, flow at 50% of FVC; $V_{75}$, flow at 75% of FVC; VA, alveolar volume.

related to differences in airway function rather than to differences in lung volume. In our study, we also found that VA did not differ between Pre-E and control groups, again suggesting that differences in FEFs were secondary to differences in airway function rather than differences in lung volumes. The only previous study evaluating infants born to women with Pre-E was by Stokholm et al.[13] These investigators reported that at 1 month of age, $FEV_{0.5}$ and $FEF_{50}$ were not significantly different comparing infants from Pre-E and non-PreE mothers; however, in that study, all infants were from mothers with asthma, which may also have an effect upon the airway function of offspring. The mechanism for our observed higher FEFs in offspring of PreE mothers is unclear and future studies might include a more direct assessment of airway size, such as high-resolution computed tomography.

The increased risk of wheeze we found related to preterm birth, maternal smoking, family history of asthma, and ANS is consistent with previous reports in the literature.[25,26] The lower risk for wheeze in the Pre-E group, after adjusting for other covariates related to wheeze (Table 3), was primarily driven by the severe Pre-E group (OR = 0.42) (Table 4). Although the nonsevere Pre-E group tended to have a lower risk of wheeze compared to controls (OR = 0.61), this was not statistically significant, which may be related to the fewer nonsevere compared to severe Pre-E infants evaluated (41 vs. 105). The mechanism by which severe Pre-E results in lower wheezing risk is unclear. It may be that maternal stress results in higher in utero exposure to stress hormones which in turn can affect the development of the lung and the immune system.[27,28]

In prior studies of airway function among full-term infants without Pre-E, higher airway function during infancy was associated with a lower risk for subsequent wheezing in the first year of life.[29] We found a similar relationship between higher FEFs and lower risk of wheeze only when all subjects were evaluated as a single group, but not for the individual groups (control, nonsevere, and severe Pre-E). Our nonsevere Pre-E group had significantly higher FEFs; however, their lower risk of wheezing did not reach statistical significance. The severe Pre-E group had a significantly lower risk of wheeze compared to controls, even after adjusting for several covariates that increase the risk of wheeze and more frequent in the severe Pre-E group; however, this group did not have significantly higher FEFs. These inconsistencies may relate to differences in these two very different respiratory outcomes, the limited number of infants in the nonsevere Pre-E group, as well as as the multiple factors that can contribute to wheezing. Spirometry is assessed while infants are sleeping and without any intercurrent respiratory illness, making FEFs a reproducible objective measurement of airway function when not symptomatic. In contrast, wheeze is determined from the parental questionnaire as a sign of airway obstruction when the infant is ill. The mechanisms that contribute to wheezing are complex and can include the baseline airway function, as well as the inflammatory responses to stimuli, such as viruses and allergen. In addition, molecular pathways that contribute to nonsevere and severe Pre-E may not be a continuous spectrum, but rather may represent differing pulmonary phenotypes. It is also possible that

**TABLE 3** Wheezing outcomes in the study cohort

| | No Wheezing | Wheezing | *p* Value |
|---|---|---|---|
| *N* | 136 | 98 | |
| Group | | | |
| Control | 55 (40.4) | 53 (54.1) | 0.1184 |
| Pre-eclamptic (low severity) | 22 (16.2) | 12 (12.2) | |
| Pre-eclamptic (high severity) | 59 (43.4) | 33 (33.7) | |
| Sex | | | |
| Female | 68 (50.0) | 43 (43.9) | 0.3548 |
| Male | 68 (50.0) | 55 (56.1) | |
| Race | | | |
| White | 62 (45.6) | 46 (46.9) | 0.8380 |
| Other | 74 (54.4) | 52 (53.1) | |
| Term | | | |
| Full Term | 81 (59.6) | 45 (45.9) | 0.0389 |
| Preterm | 55 (40.4) | 53 (54.1) | |
| Gestational age | 36.89 (3.30); 37.29 (35.79, 39.29) | 35.73 (3.84); 36.43 (34.00, 38.86) | 0.0215 |
| Birth weight (kg) | 2.7443 (0.7662); 2.79 (2.04, 3.13) | 2.5366 (0.8622); 2.63 (2.04, 3.13) | 0.0732 |
| Birth length | 47.49 (5.39); 48.50 (47.00, 50.50) | 45.89 (5.32); 46.75 (43.50, 49.53) | 0.0064 |
| Surfactant treatment | | | |
| No | 127 (93.4) | 89 (90.8) | 0.4674 |
| Yes | 9 (6.6) | 9 (9.2) | |
| Mechanical Ventilation | | | |
| No | 127 (93.4) | 88 (89.8) | 0.3217 |
| Yes | 9 (6.6) | 10 (10.2) | |
| Bronchopulmonary dysplasia | | | |
| No | 133 (97.8) | 93 (94.9) | 0.2290 |
| Yes | 3 (2.2) | 5 (5.1) | |
| Fetal growth restriction | | | |
| No | 116 (85.3) | 82 (83.7) | 0.7346 |
| Yes | 20 (14.7) | 16 (16.3) | |
| Secondhand smoke exposure | | | |
| No | 131 | 94 (41.8) | 0.8737 |
| Yes | 5 (55.7) | 4 (44.4) | |
| Mother smoked during pregnancy | | | |
| No | 111 (81.6) | 69 (70.4) | 0.0447 |
| Yes | 25 (18.4) | 29 (29.6) | |
| Family history of asthma | | | |
| No | 107 (78.7) | 67 (68.4) | 0.0748 |
| Yes | 29 (21.3) | 31 (31.6) | |

(Continues)

**TABLE 3** (Continued)

| | No Wheezing | Wheezing | *p* Value |
|---|---|---|---|
| Size for gestational age (GA) | | | |
| Small for GA | 22 (16.2) | 15 (15.3) | 0.8469 |
| Appropriate for GA | 108 (79.4) | 80 (81.6) | |
| Large for GA | 6 (4.4) | 3 (3.1) | |
| Antenatal steroids | | | |
| No | 85 (62.5) | 41 (41.8) | 0.0018 |
| Yes | 51 (37.5) | 57 (58.2) | |

*Note*: Values are means (standard deviations); medians (IQRs) for continuous variables and frequencies (row percentages) for categorical variables, with *p*-values from Wilcoxon and $\chi^2$ tests, respectively.

Abbreviations: GA, gestational age; IQR, interquartile range.

**TABLE 4** Logistic regression model for reported wheeze

| | Odds ratio (95% CI) |
|---|---|
| Group | |
| Nonsevere pre-eclampsia vs. control<br>Severe pre-eclamptic vs. control | 0.61 (0.26, 1.41)<br>*p* = 0.2439<br>0.42 (0.22, 0.70) |
| Sex | |
| Female | 0.81 (0.46, 1.42) |
| Male | Reference<br>*p* = 0.4683 |
| Gestational age | 0.96 (0.86, 1.07)<br>*p* = 0.4396 |
| Mother smoked during pregnancy | 1.88 (0.99, 3.60)<br>*p* = 0.0556 |
| Family history of asthma | 1.71 (0.91, 3.21)<br>*p* = 0.0952 |
| Antenatal steroids | 2.23 (1.04, 4.79)<br>*p* = 0.0387 |

*Note*: Values are reported as odds ratios (95% CI). The model includes independent variables selected from Table 3 with $p < 0.10$. Comparisons of dichotomous variables are for "yes" compared to "no."

Abbreviation: CI, confidence interval.

nonsevere and severe Pre-E, as well as prematurity, differ in their effects on baseline airway development and function, as well as immune development and responses to stimuli. Therefore, the relationship between airway function and wheezing previously observed in full-term infants may be more indirect and may not apply in our populations of infants.

BD responsiveness in term infants is associated with an increased risk of wheezing in infancy,[30,31] and in contrast, there is a low BD response rate in preterm infants.[22] We did not measure BD response in our study, so we could not assess its contribution to wheezing risk in Pre-E infants. However, it is possible that the higher rate of prematurity in the severe Pre-E cohort was another factor in their lower risk of wheezing.

Our study has several strengths and limitations. One of the strengths of our study was the ability to obtain a detailed assessment of lung function in infants. We were able to address the effect of Pre-E on lung parenchyma development, as well as airway function. Importantly, we evaluated control subjects from normotensive pregnancies with a balanced mix of GA and sex, as these factors can contribute to alterations in lung growth and development. Preterm infants with chronic lung disease of infancy (CLDI) have lower DLCO, but normal VA compared to full-term infants.[32] However, the effect of Pre-E upon alveolar development may be less than that observed with CLDI. Our study also had limitations. All of the infants were recruited from a single health system, which could have led to bias in the study population or treatment of Pre-E. Although our cohort size was large for an IPFT study, the number of infants evaluated was still relatively small, potentially rendering us underpowered to detect some associations. Although we accounted for multiple covariates in our analysis, we were unable to adjust for all potential confounders, such as respiratory viral infections. The number of very low GA infants was small, and it is possible that the impact of Pre-E on pulmonary outcomes in extremely low GA neonates would be different from our observations. Lastly, our DLCO measurement was obtained in infants sleeping, which may have limited our ability to detect smaller differences of impaired alveolar development, which may only be present under conditions of increased cardiac output, such as exercise.[33]

In summary, the results of our study do not support the hypothesis that in utero Pre-E exposure leads to impaired lung parenchymal development in humans. The differences between our findings in humans and those reported from animal models may be due to differences in the impact of antiangiogenic factors on lung development or the ability of the human lung to rapidly compensate for in utero antiangiogenic factors. However, we separately found better airway function and decreased wheeze, but not in the same severity group of Pre-E offspring. Therefore, differing Pre-E severity may represent different molecular pathways, which could result in differing pulmonary phenotypes. Further research is needed to obtain a more comprehensive understanding of the effect of Pre-E on lung development and respiratory morbidity.

## AUTHOR CONTRIBUTIONS

Robert S. Tepper, David M. Haas, and Laura S. Haneline were responsible for study design. Clement L. Ren, Robert S. Tepper, David M. Haas, Laura S. Haneline, and James E. Slaven contributed to data analysis and interpretation. James E. Slaven performed the statistical analysis. Christina Tiller, Graham Hogg, and Jeffrey Bjerregaard contributed to study participant enrollment and tracking and performing study procedures. Clement L. Ren wrote the first draft of the manuscript. Robert S. Tepper, David M. Haas, Laura S. Haneline, Christina Tiller, James E. Slaven, and Clement L. Ren contributed to the final version of the manuscript.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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