

Reduced Infant Lung Function, Active Smoking, and Wheeze in 18-Year-Old Individuals

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Importance: This is the first study to link reduced lung function in early life, before the development of symptoms, to wheeze in 18-year-olds. Additionally, the study gives insight into factors other than reduced lung function that are also associated with persistent wheeze in young adults.

Objective: To test the hypothesis that reduced lung function in early life is associated with increased risk for persistent wheeze at age 18 years.

Design: Birth cohort study.

Setting: Perth, Western Australia.

Participants: Individuals followed up from age 1 month to 18 years.

Main Outcome Measures: Maximal flow at functional residual capacity ($V'_{max}FRC$) was measured in 1-month-old infants who were followed up at ages 6, 12, and 18 years. Based on reported symptoms, individuals were categorized as having remittent wheeze, later-onset wheeze, persistent wheeze, and no wheeze. Smoking status was noted at age 18 years.

Results: Of the 253 individuals originally recruited, 150 were followed up at age 18 years; 37 of the 150 had re-

cent wheeze. Compared with the no-wheeze group ($n=96$), persistent wheeze ($n=13$) was independently associated with reduced percentage of predicted $V'_{max}FRC$ (mean reduction, 43%; 95% CI, 13-74). Compared with the no-wheeze group, persistent wheeze was also associated with atopy in infancy (odds ratio=7.1; 95% CI, 1.5-34.5), maternal asthma (odds ratio=6.8; 95% CI, 1.4-32.3), and active smoking (odds ratio=4.8; 95% CI, 1.0-21.3). When only wheeze at age 18 years was considered, reduced percentage of predicted $V'_{max}FRC$ was associated with wheeze at age 18 years only among current smokers ($P=.04$).

Conclusions and Relevance: Wheeze persisting from ages 6 to 18 years is associated with multiple factors, including reduced infant lung function, infant-onset atopy, maternal asthma, and active smoking. Wheeze at age 18 years (regardless of previous wheeze status) is associated with active smoking, but only among those with reduced lung function in infancy. These findings give unique insight into the cause of obstructive airways disease in 18-year-olds, and follow-up of this cohort might be expected to further extend our understanding.

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ABNORMAL AIRWAY FUNCTION is characteristic of asthma and chronic obstructive airways disease, and cohort studies have demonstrated that reduced lung function is already apparent in childhood and thereafter tracks throughout adulthood.¹⁻³ Cohort studies of individuals recruited in the 1980s are now able to demonstrate tracking of lung function from early infancy into adolescence and early adulthood.^{4,5} Further evidence that the level of airway function is determined in early life comes from a study in which first-trimester fetal size was related to forced expiratory volume in the first second of expiration (FEV_1) in 10-year-olds.⁶

Wheeze is a symptom of obstructive airways disease, but the relationship between wheeze and age at onset of airway dysfunction has not been clarified. Several studies have described associations between reduced premorbid infant lung function and increased risk for early wheeze,⁷⁻¹⁰

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but the relationship with wheeze beyond age 3 years is inconsistent. Reduced lung function in early life has been associated with increased risk for wheeze in early life, but in some studies the relationship does not persist to ages 10 years¹¹ and 22 years.⁴ In other studies, however, abnormalities

of airflow in early infancy have been associated with wheeze at ages 10 years¹² and 12 years⁸ but not beyond childhood.

It is known is that early wheeze persists into adulthood for many individuals and that childhood-onset (allergic) asthma is a well-recognized precursor of adult asthma.¹³⁻¹⁵ It is also understood that childhood wheeze can resolve by early adulthood,¹⁶ and this suggests that separate factors may be important to wheeze in childhood compared with adulthood. The relevance of reduced infant lung function to wheeze beyond age 12 years remains uncertain. The Perth Infant Asthma Cohort has now been followed up to age 18 years. We tested the hypothesis, based on our earlier findings,⁸ that reduced maximal flow at functional residual capacity (V'maxFRC) at age 1 month is associated with increased risk for persistent wheeze at age 18 years. We subsequently explored the unexpected relationship between reduced V'maxFRC at age 1 month and later active smoking for wheeze at age 18 years. Finally, we took the opportunity to explore the relationship between lung function at age 1 month and lung function and current respiratory symptoms at age 18 years to confirm (or not) the results of a previous study.⁴

METHODS

STUDY DESIGN

Mothers attending an antenatal clinic at a local maternity hospital were invited to enroll. There was no selection for maternal asthma or atopy. Fuller details of enrollment are presented elsewhere.¹⁷ At enrollment, details of maternal smoking and asthma status were obtained using a standard questionnaire.¹⁸ Their infants attended an assessment of lung function and skin prick allergen reactivity at age 1 month. The presence of reported wheeze in the previous year and current physician-diagnosed asthma was obtained from respiratory questionnaires completed at ages 6, 12, and 18 years. The assessment at age 18 years also included lung function testing, skin prick reactivity, and smoking history; individuals were considered current smokers if they responded positively to the question "Do you now smoke cigarettes?" All assessments of this cohort have been approved by the Human Research Ethics Committee, University of Western Australia. Written informed consent was provided by parents while participants were children and by participants at age 18 years.

INFANT LUNG FUNCTION

Fuller details are presented elsewhere.¹⁷ After sleep was induced with chloral hydrate, the rapid thoracoabdominal compression test was carried out during tidal breathing. The V'maxFRC was reported as the average from 5 technically acceptable flow-volume loops. Infant lung function was standardized by age, sex, length, and weight and expressed as percentage of predicted.¹⁹

SKIN PRICK REACTIVITY

The skin prick test²⁰ was used to determine reactivity to the following allergens during infancy: cow's milk, egg white, rye grass, and *Dermatophagoides farinae*. For assessments after infancy, reactivity to the following additional 6 allergens was also assessed: mixed grass, *Dermatophagoides pteronyssinus*, cat dander, dog dander, *Alternaria alternans*, and *Aspergillus fumigatus*.

All allergens were supplied by Hollister-Stier Laboratories. Positive and negative controls were used. A positive weal was defined as one with a maximal dimension of at least 2 mm in infancy and 3 mm in later assessments. Infantile atopy was defined as a positive weal on at least 1 occasion during infancy.²¹

SPIROMETRY AT AGE 18 YEARS

A portable spirometer (KoKo spirometer; Pulmonary Data Service Instrumentation, Inc) was used to measure FEV₁, forced vital capacity, forced expiratory flow at midexpiratory phase (FEF_{25%-75%}), and peak expiratory flow in accordance with international guidelines.²² The FEV₁ was expressed as percentage of predicted using a standard reference population.²³

STATISTICAL ANALYSIS

First, differences between those who were and were not placed into wheezing categories were analyzed using χ^2 test and *t* test where appropriate. Second, logistic and linear regression models were created to study the relationship between percentage of predicted V'maxFRC (%V'maxFRC) and respiratory outcomes (ie, symptoms and spirometry) at age 18 years while adjusting for confounders known to be associated with adverse respiratory outcomes: maternal smoking, maternal asthma, infant atopy, and active smoking at age 18 years. Third, to study the relationship between %V'maxFRC and age at onset of wheeze, individuals were categorized into the following groups depending on their asthma status at ages 6, 12, and 18 years: persistent wheeze (wheeze at age 18 years and on ≥ 1 earlier occasion), no wheeze (no wheeze on any occasion), remittent wheeze (wheeze at age either 6 or 12 years but not at age 18 years or, in cases in which no data were available at age 18 years, wheeze at age 6 but not 12 years), and later-onset wheeze (wheeze at age 18 years but not at age 6 years and/or wheeze at age 12 years). A multinomial logistic model was created to study the relationship between wheeze group and %V'maxFRC at age 1 month adjusting for the same confounders in the linear regression model. A logistic regression model was created to describe the interaction term between current smoking and %V'maxFRC for current wheeze adjusting for confounders. Standard statistical software was used (SPSS version 18.0.0; SPSS Inc) and *P* < .05 was assumed to be statistically significant.

RESULTS

STUDY PARTICIPANTS

There were 253 individuals recruited, of whom 243 attended the assessment at age 1 month, 123 at age 6 years, 194 at age 12 years, and 150 at age 18 years (mean [SD] age, 18.8 [1.1] years; including 88 [59%] males). At age 18 years, 37 individuals (25%) had recent wheeze and 20 (13%) were diagnosed as having asthma. One hundred forty-three individuals were categorized as having persistent wheeze (*n* = 13), later-onset wheeze (*n* = 19), remittent wheeze (*n* = 15), and no wheeze (*n* = 96) (eTable 1 [http://www.jamapeds.com] shows a detailed breakdown of the wheezing pattern in each of these 4 groups). **Table 1** demonstrates that individuals placed into wheezing categories were representative of the original cohort with the exception of having a lower proportion of mothers who smoked during pregnancy (24% vs 32% for the original cohort; *P* = .003).

Table 1. Characteristics of Those Who Were and Were Not Placed Into a Wheeze Outcome Group

Characteristic	Individuals Placed Into Wheeze Categories	Entire Cohort
Male, No. (%)	83/143 (58)	142/253 (56)
Maternal history of asthma, No. (%)	27/143 (19)	51/253 (20)
Mothers who smoked during pregnancy, No. (%)	34/143 (24) ^a	80/252 (32)
%V _{max} FRC at age 1 mo, mean (SD) ^b	104 (50)	99 (48)
Geometric PC ₄₀ at age 1 mo, mean (SEM), mg histamine/mL ^c	0.89 (0.35)	0.89 (0.27)
Atopy during infancy, No. (%)	20/143 (14)	32/153 (13)
Wheeze at age 2 y, No. (%)	21/100 (21)	23/106 (22)
At age 6 y, No. (%)		
Physician-diagnosed asthma	17/87 (19)	30/123 (24)
Wheeze	18/87 (21)	27/123 (22)
Atopy	25/77 (32)	39/112 (34)
At age 12 y, No. (%)		
Physician-diagnosed asthma	19/141 (13)	29/194 (15)
Wheeze	22/141 (16)	32/193 (17)
Atopy	74/140 (53)	94/182 (52)
At age 18 y, No. (%)		
Physician-diagnosed asthma	18/143 (13)	20/150 (13)
Wheeze	32/141 (23)	37/149 (25)
Atopy	66/135 (49)	68/142 (48)
Current smoker	30/140 (21)	33/148 (22)
FEV ₁ at age 18 y, mean (SD) ^d	104 (12)	104 (12)

Abbreviations: FEV₁, forced expiratory volume in the first second of expiration; PC₄₀, concentration of histamine provoking at least a 40% reduction in maximal flow at functional residual capacity; %V_{max}FRC, percentage of predicted maximal flow at functional residual capacity.

^a P = .003 compared with the entire cohort. There were no differences between the 2 groups for the remaining outcomes.

^b For individuals placed into wheeze categories, n = 136; for the entire cohort, n = 241.

^c For individuals placed into wheeze categories, n = 116; for the entire cohort, n = 202.

^d For individuals placed into wheeze categories, n = 134; for the entire cohort, n = 141.

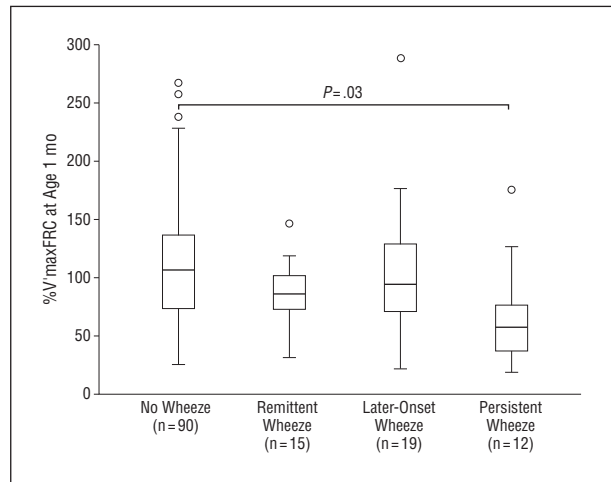


Figure 1. Box and whisker plot comparing median and interquartile values of the percentage of predicted maximal flow at functional residual capacity (%V_{max}FRC) at age 1 month across groups characterized by pattern of wheeze at ages 6, 12, and 18 years. The P value is from analysis of variance. No wheeze indicates no wheeze at ages 6, 12, and 18 years; remittent wheeze, wheeze at ages 6 and/or 12 years but not at age 18 years; later-onset wheeze, wheeze at age 18 years but not at age 6 years; and persistent wheeze, wheeze at ages 6, 12, and 18 years.

FEATURES ASSOCIATED WITH WHEEZE GROUPS

The persistent-wheeze group had the lowest %V_{max}FRC at age 1 month (P = .03, analysis of variance) (**Figure 1**), the highest prevalence of atopy during infancy (38% vs 14% in the no-wheeze group; P = .03 for

trend across groups), and reduced %FEV₁ (96% vs 105% for the no-wheeze group; P = .01, t test) (**Table 2**). In the multivariate analysis (eTable 2 shows full details of each group) and with reference to the no-wheeze group, each 1% reduction in %V_{max}FRC at age 1 month was associated with a 2% increased risk for persistent wheeze (95% CI, 1-3; P = .02). Additionally, persistent wheeze was also independently associated with atopy during infancy (odds ratio [OR] = 7.1; 95% CI, 1.5-34.5; P = .01), maternal asthma (OR = 6.8; 95% CI, 1.4-32.3; P = .02), and active smoking at age 18 years (OR = 4.8; 95% CI, 1.0-21.3; P = .04). Later-onset wheeze was more likely to develop in females compared with males (OR = 4.1; 95% CI, 1.4-12.3; P = .01). No risk factors studied were related to remittent wheeze. For groups categorized by diagnosed asthma (rather than wheeze) outcomes at age 18 years, asthma at ages 6, 12, and 18 years was associated with maternal asthma (OR = 6.6; 95% CI, 1.3-34.5) and atopy in infancy (OR = 10.4; 95% CI, 2.1-52.6) but not V_{max}FRC at age 1 month (eAppendix).

INTERACTION BETWEEN SMOKING, V_{max}FRC AT AGE 1 MONTH, AND WHEEZE AT AGE 18 YEARS

In the retrospective analysis, %V_{max}FRC was lower in smokers with wheeze compared with smokers without wheeze and nonsmokers without wheeze (P = .04, analysis of variance) (**Figure 2** and **Table 3**). There was a significant interaction between %V_{max}FRC and smoking (but not for infant atopy and smoking) for wheeze at age 18 years (P = .01) (eTable 3 shows output of logistic regression).

Table 2. Outcomes Measured in Early Life and at Age 18 Years Across Groups Characterized by Wheeze Outcome at Age 18 Years

Characteristic	Wheeze				P Value for Trend Test Across Wheezing Groups ^a
	None	Remittent	Later Onset	Persistent	
Male, No. (%)	62/96 (65)	7/15 (45)	6/19 (32)	8/13 (62)	.046
Maternal asthma, No. (%)	13/96 (14)	4/15 (27)	5/19 (26)	5/13 (38)	.10
Mothers who smoked during pregnancy, No. (%)	20/96 (21)	6/15 (40)	4/19 (21)	2/13 (15)	.41
%V _{max} FRC at age 1 mo					
Mean (SD)	111 (50)	90 (27)	104 (59)	68 (44)	.03
Participants, No.	90	15	19	12	
Geometric PC ₄₀ at 1 mo					
Mean (SEM), mg histamine/mL	1.01 (0.39)	0.66 (1.11)	1.29 (1.30)	0.69 (0.21)	.41
Participants, No.	79	14	16	7	
Atopy during infancy, No. (%)	13/96 (14)	0/15	2/19 (11)	5/13 (38)	.03
Wheeze at age 2 y, No. (%)	11/68 (16)	3/9 (33)	2/14 (14)	5/9 (56)	.04
Asthma at age 18 y, No. (%)	1/96 (1)	0/13	5/19 (26)	14/17 (82)	<.001
FEV ₁ at age 18 y, %					
Mean (SD)	105 (12)	106 (12)	107 (14)	96 (13) ^b	.10
Participants, No.	91	13	18	12	
FEV ₁ /FVC at age 18 y					
Mean (SD)	101 (8)	100 (8)	99 (8)	97 (11)	.46
Participants, No.	91	13	18	12	
Atopy at age 18 y, No. (%)	37/92 (40)	7/13 (53)	12/18 (67)	10/12 (83)	.01
Current smoker at age 18 y, No. (%)	15/95 (16)	3/13 (23)	6/19 (32)	6/13 (46)	.05

Abbreviations: FEV₁, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; PC₄₀, concentration of histamine provoking at least a 40% reduction in maximal flow at functional residual capacity; %V_{max}FRC, percentage of predicted maximal flow at functional residual capacity.

^aThe χ^2 test, analysis of variance, and Kruskal-Wallis test were used as appropriate.

^bP = .01 using *t* test for comparison with the no-wheeze group.

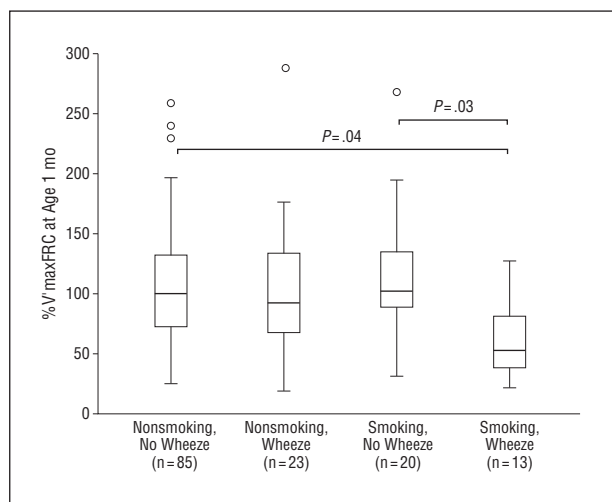


Figure 2. Box and whisker plot comparing the percentage of predicted maximal flow at functional residual capacity (%V_{max}FRC) at age 1 month in 4 groups stratified by the presence or absence of active smoking and wheeze at age 18 years. The P values are from analysis of variance.

ASSOCIATIONS BETWEEN V_{max}FRC AT AGE 1 MONTH AND RESPIRATORY OUTCOMES AT AGE 18 YEARS

Each 1% increase in %V_{max}FRC was associated with an average of 1% reduced risk of wheeze (95% CI, 0-3; P = .046 in the univariate analysis; in the multivariate analysis, the same effect size was seen [P = .07]). For asthma at age 18 years, each 1% increase in V_{max}FRC was associated with a 1% reduced risk for asthma (95% CI, 0-2; P = .047 for univariate analysis and P = .05

Table 3. Proportion of Individuals With Wheeze Within Groups Categorized by Quartile of Percentage of Predicted Maximal Flow at Functional Residual Capacity at Age 1 Month and Smoking Status at Age 18 Years

Quartile of %V _{max} FRC at Age 1 mo	Proportion With Wheeze At Age 18 y, No. (%) ^a	
	Current Smokers	Current Nonsmokers
Lowest	7/9 (78)	6/21 (29)
Second lowest	4/8 (50)	6/27 (22)
Second highest	0/9	4/26 (15)
Highest	2/7 (29)	7/34 (21)

Abbreviation: %V_{max}FRC, percentage of predicted maximal flow at functional residual capacity.

^aBy χ^2 test, P = .03 for overall trend across both groups, P = .007 for trend across current smokers, and P = .75 for trend across current nonsmokers.

for multivariate analysis). Each 1% increase in V_{max}FRC was associated with a mean increase of 0.1 in %FEF_{25%-75%} (95% CI, 0.02-0.17).

COMMENT

Reduced lung function is associated with increased respiratory symptoms, and cohort studies are able to give insight into the origins of respiratory morbidity. The challenges in measuring infant lung function and following up with those individuals over time are considerable, and the present understanding of how early physiology relates to respiratory symptoms in adulthood is limited to

1 study.⁴ To our knowledge, this study is the first to report an association between reduced lung function in infancy and wheeze beyond childhood. Reduced V_{max}FRC was associated with persistent wheeze but not with transient or later-onset wheeze (Figure 1) or persistent diagnosed asthma. Unexpectedly, we observed that a reduced V_{max}FRC at age 1 month was associated with increased risk for wheeze only in young adults who were also current smokers (Table 3 and Figure 2). These results suggest that reduced early airway function and later exposures such as smoking are important to the cause of obstructive respiratory diseases in young adults. Interventions aimed at preventing young children with asthma symptoms and reduced lung function from smoking might prevent persisting symptoms of obstructive airways disease.

To our knowledge, this is the first study to describe an association between reduced infant lung function and wheeze in 18-year-olds, but the results were consistent with earlier publications from this cohort^{5,8} and elsewhere.^{4,6,12,24} We have demonstrated that reduced V_{max}FRC is associated with persistent wheeze at age 12 years.⁸ Håland et al¹² have also reported abnormal tidal breathing parameters in neonates as a risk factor for asthma at age 11 years. Our findings are consistent with a study suggesting that the level of lung function is determined antenatally by linking reduced first-trimester fetal size with persistent wheeze and reduced lung function at age 10 years.⁶ A cohort study²⁴ in Tucson, Arizona, with a design similar to ours in which infant lung function was measured in 120 two-month-old infants, observed tracking of reduced lung function from infancy into adulthood,⁴ and we have replicated this finding. Both the Tucson cohort²⁴ and our cohort⁵ demonstrated that reduced V_{max}FRC per se is associated with transient wheeze in preschool-aged children; we have, however, demonstrated that persistent wheeze at age 12 years was present in those with both reduced V_{max}FRC and atopy.⁸ The results of the present study support the paradigm that persistent wheeze in adolescents is a complex condition in which early onset of airway dysfunction, atopy in infancy, genetic factors (as evidenced by maternal asthma), and active smoking are important.

Childhood-onset atopic asthma is a recognized precursor of the adult asthma phenotype,^{13,14} and our study confirmed an association between early atopy and prolonged asthma symptoms (Table 2 and eAppendix). What is novel about our study is that we can describe the age at onset of atopy and symptoms, something unachievable with studies in which recruitment began in adulthood. We have demonstrated that for those with persistent wheeze, the onset of atopy was (for the majority) in infancy and that approximately half already had symptoms at age 2 years (Table 2). Given that approximately one-third of adult asthma can be categorized as childhood-onset atopic asthma,^{13,15} our findings are relevant to the causation of many cases of adult asthma.

The association we describe between reduced lung function in early life, active smoking, and wheeze is novel and may have public health implications, but it is based on a relatively small number of individuals and ideally

should be confirmed in other cohorts. The prevalence of smoking among adolescents with asthma or a history of asthma is generally no less than among their nonasthmatic peers,²⁵ but our study is not the first to find increased smoking among adolescents with asthma.²⁶ In adults, smoking is associated with reduced lung function,²⁷ accelerated decline in FEV₁,²⁷ asthma,²⁸ and chronic obstructive airways disease.²⁹ The presumption has been that active smoking causes primary abnormalities in airway function, but the “healthy smoker” phenomenon suggests that some individuals may apparently be protected from the severe adverse effects of smoking on respiratory symptoms. Our results (Figure 2) suggest that the presence or absence of airway dysfunction in very early life (as evidenced by reduced lung function) may at least partly explain the inconsistent relationship between smoking and respiratory symptoms. What remains to be determined is whether targeting smoking prevention interventions at children with asthma symptoms and reduced lung function may be effective in preventing the progression to persistent obstructive airways disease throughout adulthood.

Some factors need to be considered when interpreting our results. First, as in many studies of this nature, follow-up was incomplete and the individuals on whom this article is based were less likely to have had mothers who smoked during pregnancy (Table 1). This bias is likely to weaken, not strengthen, the associations reported, and we do not believe it will substantially affect the main outcomes reported. Second, the number of individuals recruited was relatively small (this is reflected in the small symptomatic subgroups studied) and some of the analyses may have been underpowered; our findings need to be replicated elsewhere but provide preliminary proof of concept that early airway abnormalities are important to respiratory outcomes in 18-year-olds. Third, we did not confirm smoking status, eg, using salivary cotinine levels, and cannot be sure that all active smoking was genuinely reported; the prevalence of smoking in our 18-year-olds was 22%, and this is similar to the 19% reported by 18- to 24-year-old Australian individuals in 2007.³⁰ Finally, as in our earlier evaluation of this cohort,⁸ herein we report an association between reduced V_{max}FRC and wheeze but not asthma. Ours is a community-based study and some individuals with symptoms of asthma may not seek medical diagnosis and treatment. The association between reduced V_{max}FRC and FEF_{25%-75%} (Figure 1 and previously reported elsewhere⁴) suggests that early lung function is important to respiratory physiology and asthma symptoms (if not asthma diagnosis).

In summary, we report interactions between early-onset airway dysfunction and active smoking in 18-year-olds for wheeze. Genetic susceptibility and early-onset atopy are also relevant cofactors. These findings give unique insight into the cause of obstructive airways disease in 18-year-olds, and follow-up of this cohort might be expected to further extend our understanding.

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Author Contributions: Dr Turner had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Turner, Landau, and le Souëf. *Acquisition of data:* Mullane and Cox. *Analysis and interpretation of data:* Turner, Goldblatt, Landau, and le Souëf. *Drafting of the manuscript:* Turner, Landau, and le Souëf. *Critical revision of the manuscript for important intellectual content:* Mullane, Turner, Cox, Goldblatt, Landau, and le Souëf. *Statistical analysis:* Turner. *Obtained funding:* Mullane, Goldblatt, and le Souëf. *Administrative, technical, and material support:* Mullane, Cox, Landau, and le Souëf. *Study supervision:* Goldblatt, Landau, and le Souëf. **Conflict of Interest Disclosures:** None reported.

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Online-Only Material: The eAppendix and eTables are available at <http://www.jamaped.com>.

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