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Decreased lung function after preschool wheezing rhinovirus illnesses in children at risk to develop asthma

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Background: Preschool rhinovirus (RV) wheezing illnesses predict an increased risk of childhood asthma; however, it is not clear how specific viral illnesses in early life relate to lung function later on in childhood.

Objective: To determine the relationship of virus-specific wheezing illnesses and lung function in a longitudinal cohort of children at risk for asthma.

Methods: Two hundred thirty-eight children were followed prospectively from birth to 8 years of age. Early life viral wheezing respiratory illnesses were assessed by using standard techniques, and lung function was assessed annually by using spirometry and impulse oscillometry. The relationships of these virus-specific wheezing illnesses and lung function were assessed by using mixed-effect linear regression.

Results: Children with RV wheezing illness demonstrated significantly decreased spirometry values, FEV_1 ($P = .001$), $FEV_{0.5}$ ($P < .001$), FEF_{25-75} ($P < .001$), and also had abnormal impulse oscillometry measures—more negative reactance at 5 Hz ($P < .001$)—compared with those who did not wheeze with RV. Children who wheezed with respiratory syncytial virus or other viral illnesses did not have any significant differences in spirometric or impulse oscillometry indices when compared with children who did not. Children diagnosed with asthma at ages 6 or 8 years had significantly decreased FEF_{25-75} ($P = .05$) compared with children without asthma.

Conclusion: Among outpatient viral wheezing illnesses in early childhood, those caused by RV infections are the most significant predictors of decreased lung function up to age 8 years in a high-risk birth cohort. Whether low lung function is a cause and/or effect of RV wheezing illnesses is yet to be determined. (J Allergy Clin Immunol 2011;128:532-8.)

Key words: *Rhinovirus, respiratory syncytial virus, wheezing, asthma, spirometry, impulse oscillometry*

Pediatric asthma remains an important health concern as its prevalence remains at historically high levels[1] despite current treatment. Studies evaluating the natural history of asthma have shown that initial asthmalike symptoms and loss in lung function occur early in life.[2] However, wheezing in infancy is a heterogeneous condition, and the long-term prognosis varies from complete recovery to persistent asthma with demonstrable abnormalities in lung function.[2] In addition, ongoing longitudinal studies have shown that deficits in lung function are established in school-aged children with persistent asthma and, for the most part, are maintained both in magnitude and in rate of further loss into adulthood.[2-4] Genetic and/or environmental factors underlie the development of asthma, and viral respiratory tract illnesses caused by respiratory syncytial virus (RSV)[5] and rhinovirus (RV)[6] in early life have been implicated as contributing to this outcome. However, it is not clear how these illnesses impact lung function in early life.

Reproducible and reliable measurement of lung function in early life is challenging. These challenges relate to developmental maturation and coordination as only children at least 5 to 6 years of age can be expected to reliably perform reproducible forced respiratory maneuvers by spirometry.[7] In addition to spirometric evaluations, recent interest has focused on the use of impulse oscillometry (IOS). Given IOS's requirement for minimum cooperation, it is very suitable for use in young children. IOS has been used to measure the mechanical properties of the respiratory system in children with asthma[8,9] and has been successfully used in children as young as 2 years.[10] During IOS, an external pressure impulse signal is applied during tidal breathing. From the resultant flow, the total respiratory impedance (Z_{rs}) and its components respiratory resistance (R_{rs}) and reactance (X_{rs}) are calculated at various frequencies. IOS may provide additional information than that obtained from spirometry, such as functional assessment of small peripheral airways, and thus has been proposed as a more sensitive measure of abnormal pulmonary processes and airway obstruction.[11-13]

In a birth cohort of young children at high risk for developing asthma and/or allergic diseases, we first examined whether these children could successfully perform IOS at an earlier age than spirometry, and whether IOS indices correlated with specific spirometric parameters. We then prospectively explored the relationships among early life virus-specific wheezing, childhood lung function, and asthma.

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Abbreviations used
ATS: American Thoracic Society
COAST: Childhood Origins of ASThma study
FEIA: Fluorescent enzyme immunoassay
IOS: Impulse oscillometry
RSV: Respiratory syncytial virus
RV: Rhinovirus

METHODS

Subjects

Participants in this study are children enrolled in the Childhood Origin of ASThma (COAST) project at birth and have been followed up to the age of 8 years. Details about the study design and characteristics of its subjects have been previously published.[14,15] Briefly, a total of 289 newborns were enrolled from November 1998 through May 2000 in the COAST study. Of these children, 285, 275, 259, and 238 were followed prospectively for 1, 3, 6, and 8 years, respectively. To qualify, at least 1 parent was required to have respiratory allergies (defined as 1 or more positive aeroallergen skin test results) and/or a history of physician-diagnosed asthma. The Human Subjects Committee of the University of Wisconsin approved the study, and informed consent was obtained from the parents. Assent was obtained from the children at the age of 8 years.

Nasal lavage samples

Nasopharyngeal mucous samples were collected during scheduled clinic visits (2, 4, 6, 9, 12, 24, and 36 months) and during times of acute respiratory illnesses.[15] Parents notified a study coordinator when their child developed a runny nose, cough, or wheeze, and a symptom scorecard was completed.[16] If the symptom score was 5 or greater, classified as a moderate to severe respiratory illness, a nasal lavage was performed and processed as previously described[16] for the viral panel outlined under the viral methods described in the next section.

Viral diagnostics

Nasal specimens were analyzed for respiratory viruses including RSV, RV, influenza types A and B, parainfluenza virus types 1 to 4, adenovirus, and enteroviruses by using culture.[16] In addition, samples were evaluated for RV RNA by using seminested RT-PCR[16,17] and for the viruses just mentioned plus coronaviruses (OC143, NL63, and 0229), bocavirus, and metapneumoviruses by using multiplex PCR (Respiratory MultiCode PLx Assay; EraGen Biosciences, Madison, Wis).[18]

Allergen-specific IgE

Allergen-specific IgE was measured at 1, 3, and 6 years of age for dust mite, *Alternaria alternata*, dog, cat, peanut, milk, egg, and soy, as previously described using a fluorescent enzyme immunoassay (FEIA).[19] The allergen-specific IgE values of 0.35 kU/L (class I) or greater were considered positive. The presence of allergic sensitization at age 3 and 6 years was defined by having 1 or more positive values for allergen-specific IgE.

Pulmonary function testing

Spirometry and IOS were performed by using the Jaeger MasterScreen system during scheduled annual visits at ages 4, 5, 6, 7, and 8 years. The postbronchodilator spirometry test was performed at the annual visits starting at age 5 years if the child had reproducible prebronchodilator spirometry. The order of the lung function at every annual visit was as follows: IOS, prebronchodilator, and postbronchodilator spirometry. The family was instructed to give the child the prescribed asthma medications but to hold albuterol and caffeinated food products for 6 hours prior to the annual visit. If the child was ill or taking albuterol for symptoms, the visit was rescheduled. Two puffs of albuterol via metered-dose inhaler and valved spacer were adminsitered 15 minutes prior to the spirometry. Criteria for preschool lung function published by Eigen et al,[20] similar to those used in Childhood Asthma Research and Education Network studies,[21,22] were applied in this study (see Table E1 in this article's Online Repository at www.jacionline.org). These are similar to those recently recommended by the American Thoracic Society (ATS)[7] (Table E1). Ten percent of the studies performed in each year were overread by a blinded reviewer for quality assurance purposes. Only those tests that met the modified Eigen/ATS criteria were included.

Spirometric measurements include forced vital capacity (FVC), FEV_1, $FEV_{0.5}$, forced expiratory flow at 25% to 75% of FVC (FEF_{25-75}), and peak expiratory flow rate (PEFR). FVC, FEV_1, $FEV_{0.5}$, and PEFR were measured in liters; FEF_{25-75} was measured in liters per second; and FEV_1 and FVC were also expressed as percent-predicted values (FEV_1 PP and FVC PP) based on the Eigen criteria by using family-reported ethnicity for the child (see Table E2 in this article's Online Repository at www.jacionline.org).[20] $FEV_{0.5}$ was measured since young children often empty their lung volumes in less than 1 second.[7,13]

IOS was attempted before spirometry in the cases where both procedures were performed at the same visit. Further details regarding the spirometry and IOS methods are available in this article's Online Repository at www.jacionline.org. The IOS indices collected were as follows: resistance at 5 Hz (R5), resistance at 10 Hz (R10), the difference in resistance at 5 Hz and at 10 Hz (R5-R10), resistance at 20 Hz (R20), reactance at 5 Hz (X5), and area of reactance (AX). These were collected by using criteria similar to those used in Childhood Asthma Research and Education Network studies[21,22] (see Table E3 in this article's Online Repository at www.jacionline.org). At least 10% of the IOS studies were overread by a blinded reviewer to ensure that tests recorded as acceptable did meet acceptability and reproducibility criteria for quality assurance purposes.

Clinical definitions

Atopic dermatitis during the first 3 years of life was defined as described.[6,15,19] A wheezing respiratory illness during the first 3 years of life was defined as meeting 1 or more of the following criteria: (1) physician-diagnosed wheezing at an office visit; (2) an illness for which the child was prescribed short- or long-acting β-agonists and/or controller medications; or (3) an illness given the following specific diagnoses: bronchiolitis, wheezing illness, reactive airway disease, asthma, or asthma exacerbation.[6] The severity of RV illnesses was further defined as follows: a severe wheezing RV illness was defined as a wheezing respiratory illness requiring treatment with oral steroids, less severe wheezing RV illness was defined as a wheezing respiratory illness with no treatment with oral steroids, nonwheezing RV illness was defined as a moderate to severe illness that was not a wheezing respiratory illness, and no RV illness was defined as no moderate to severe illness with RV. Race was self-reported by the family at birth. Children were diagnosed as having asthma at 6 and/or 8 years of age if they fulfilled 1 or more of the following criteria: physician-diagnosed asthma (eg, frequent albuterol use for coughing or wheezing episodes prescribed by physician more than 2 times/week or more than 2 nights/month, use of a prescribed daily controller medication, an implemented step-up plan with albuterol or inhaled corticosteroids during illness as prescribed by a physician, or used prescribed oral prednisone for an asthma exacerbation). Four separate investigators, blinded to any prior histories of viral illnesses or of aeroallergen sensitization, independently evaluated each subject for the presence or absence of asthma on the basis of the above criteria to ensure that the diagnosis was reproducible across multiple providers.[6]

Statistical analysis

Spirometric and IOS measurements were obtained from children at yearly visits from age 4 to 8 years, with those at age 4 years having a relatively low rate of completing maneuvers that met the quality control criteria specified above (24% for spirometry and 21% for IOS). As a result, data only from ages 5, 6, 7, and 8 years were used for analyses. The IOS measurement AX was log-transformed for analysis. A cross-sectional analysis was performed at age 8 years. Mixed-effect linear regression models of lung function from children obtained at ages 5 through 8 years (prebronchodilator spirometry) and ages 6

through 8 years (postbronchodilator spirometry) were used to assess associations between lung function measures and lung function and the history (occurrence, severity, and frequency) of viral wheezing illnesses, both overall and for individual ages, while accounting for the repeated outcome measurements over time. Longitudinal analyses were performed separately for each lung function parameter and adjusted for age, race, gender, height, weight, asthma, passive smoke exposure, age at the earliest positive FEIA (1-2 years, 3-6 years, no positive FEIA 1-6 years); analyses of percent-predicted values (based on age, race, gender, height, and weight) were adjusted for asthma, passive smoke exposure, and FEIA only. Associations between spirometric and demographic variables and successful completion of IOS at each age were assessed by using Pearson's χ^2 test. Success rates of IOS and spirometry were compared by using McNemar's test for paired binary outcomes. A 2-sided P value of .05 was regarded as statistically significant. Analyses were performed by using SAS version 9.1 (SAS Institute, Inc, Cary, NC) and R version 2.8.1.

RESULTS

Pulmonary function testing performance

A total of 289 children were enrolled in the COAST study; 238 (82%) children completed the follow-up visit at age 8 years. The children started performing spirometry and/or IOS at 4 years of age, and these tests were subsequently done on a yearly basis. Overall, the demographic and atopic characteristics of children able to successfully perform IOS or spirometry at 8 years of age were similar to the demographic and atopic characteristics of those who could not perform successfully (Table I). Exceptions were that boys and children without a history of paternal allergy were less likely to successfully perform the maneuvers. At 4 years of age, 21% of children who attempted IOS had acceptable tests compared with 24% with successful spirometry ($P = .7$). For ages 5, 6, 7, and 8 years, percentages of acceptable tests of IOS vs spirometry were 58% vs 57% ($P = .9$), 74% vs 70% ($P = .4$), 79% vs 88% ($P = .02$), and 86% vs 90% ($P = .3$) (Fig 1). In addition, there was no association between the ability to successfully perform IOS and the ability to successfully perform spirometry at ages 5 to 8 years (data not shown).

TABLE I. Demographics of patients who ever met spirometry and IOS acceptability criteria (acceptable) at age 8 y compared with those who did not meet the acceptability criteria (not acceptable)

	Spirometry age 8 y			IOS age 8 y		
	Did not meet	Met	*P* value	Did not meet	Met	*P* value
	(20)*	(178)*		(27)*	(171)*	
Male	80%	53%	.02	81%	51%	.004
Maternal allergy	95%	82%	.14	85%	83%	.76
Maternal asthma	40%	41%	.94	48%	40%	.40
Paternal allergy	35%	84%	<.0001	74%	80%	.52
Paternal asthma	12%	34%	.06	25%	33%	.44
Asthma at age 6 or 8 y	40%	39%	.95	30%	41%	.26
Atopic dermatitis at age 6 or 8 y	40%	39%	.95	44%	39%	.56
+FEIA at age 3 or 6 y	63%	51%	.32	46%	53%	.50
Caucasian	80%	88%	.30	78%	89%	.11

*Values in parentheses denote n.

Viral isolates

In the 259 children with complete follow-up through age 6 years, 454 wheezing respiratory illnesses were documented during the first 3 years of life.[6] As previously reported, nasopharyngeal wash specimens were obtained during 442 (97%) of these wheezing illnesses. A viral etiology was identified in 398 (90%) of these specimens, and the viruses most commonly detected were RV (48%), RSV (21%), and multiple viruses (48/442 = 11%).[6]

The relationship of asthma and pulmonary function

Children with a diagnosis of asthma at 6 or 8 years of age had significantly lower FEF_{25-75} (1.41 vs 1.31, $P = .05$) and $FEV_{0.5}$/FVC (0.67 vs 0.64, $P = .01$) compared with children without the diagnosis of asthma (Table II). Postbronchodilator FEF_{25-75} was significantly lower in children who had a diagnosis of asthma than in those who did not ($P = .05$) (see Table E4 in this article's Online Repository at www.jacionline.org). No differences in IOS indices were seen between groups (data not shown). Neither age, race, gender, and passive smoke exposure nor allergic sensitization modified the associations between asthma and lung function.

We next evaluated whether a history of wheezing in the first 3 years of life was associated with changes in lung function at ages 6 to 8, and there were no significant relationships (data not shown). We then examined whether viral etiology of wheezing illnesses in the first 3 years impacted lung function at school age. At age 8 years, children with RV wheezing illnesses had significantly lower FEV_1 (1.29 vs 1.42, $P = .001$), FEV_1% (96 vs 102, $P = .03$), $FEV_{0.5}$ (0.98 vs 1.10, $P = .001$), FEF_{25-75} (1.21 vs 1.51, $P < .001$), FEV_1/FVC (0.82 vs 0.85, $P = .009$), and $FEV_{0.5}$/FVC (0.62 vs 0.66, $P = .02$) compared with children without RV wheezing illnesses (see Table E5 in this article's Online Repository at www.jacionline.org). Similar findings were observed using a longitudinal model of lung function obtained from children at ages 5 through 8 years. Children with RV wheezing illnesses had significantly lower FEV_1 (1.28 vs 1.38, $P = .001$), FEV_1% (97 vs 103, $P = .01$), $FEV_{0.5}$ (0.96 vs 1.06, $P < .001$), FEF_{25-75} (1.21 vs 1.46, $P < .001$), FEV_1/FVC (0.84 vs 0.87, $P = .01$), and $FEV_{0.5}$/FVC (0.63 vs 0.67, $P = .008$) compared with children who did not wheeze with RV (Table III; Fig 2). Similarly, children with RV wheezing illnesses also had a larger R5-R10 difference (0.20 vs 0.15, $P < .001$), a more negative X5 (0.41 vs 0.35, $P < .001$), and larger AX (3.2 vs 2.62, $P = .004$; see Table E6 in this article's Online Repository at www.jacionline.org). Significantly lower postbronchodilator FEV_1 ($P = .01$), $FEV_{0.5}$ ($P = .003$), FEF_{25-75} ($P = .01$) (Table IV) but no differences in IOS indices (see Table E7 in this article's Online Repository at www.jacionline.org) were observed in children with a history of RV wheezing illnesses compared with children who did not wheeze with RV. Children with more frequent RV wheezing illnesses did not show significantly lower lung function than children with less frequent RV wheezing illnesses (see Table E8 in this article's Online Repository at www.jacionline.org). Children who experienced severe and less severe RV wheezing episodes during RV infection had significantly lower lung function compared with children with nonwheezing RV illnesses and no RV illnesses (see Table E9 in this article's Online Repository at www.jacionline.org). These findings persisted after controlling for age, race, gender, height, weight, passive smoke exposure, and age at the first occurrence of positive aeroallergen FEIA (ages 1-2 or 3-6 years).

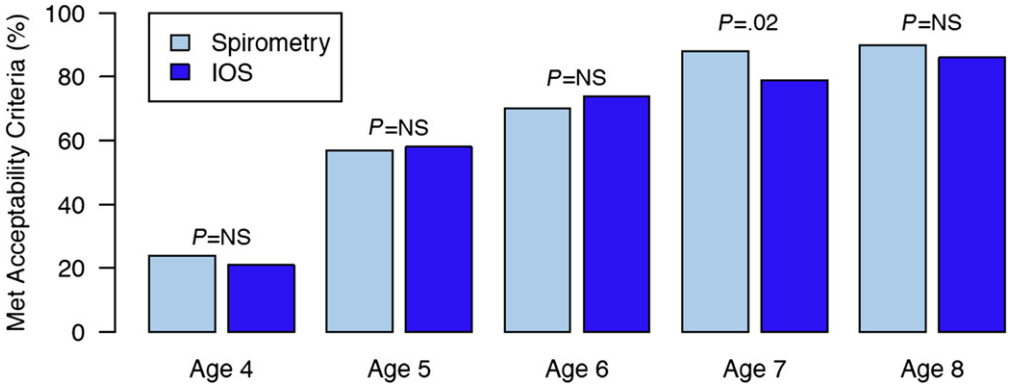

FIG 1. Percentage of children who met acceptability criteria for spirometry *(light blue)* or IOS *(dark blue)* by age group. At 4 years of age, 21% of children who attempted IOS had acceptable tests compared with 24% with successful spirometry ($P = .7$). For ages 5, 6, 7, and 8 years, percentages of acceptable tests of IOS vs spirometry were 58% vs 57% ($P = .9$), 74% vs 70% ($P = .4$), 79% vs 88% ($P = .02$), and 86% vs 90% ($P = .3$).

TABLE II. Longitudinal comparisons of prebronchodilator pulmonary function (spirometry) between groups of children from ages 5 through 8 y* with and without asthma

	Asthma†				
	No	**Yes**	**Diff**	**95% CI**	***P* value**
n	140	84			
FVC	1.58 (0.02)	1.58 (0.02)	0.00	(−0.05, 0.05)	.99
FVC PP	104 (1)	104 (1)	0	(−3, 4)	.68
FEV_1	1.35 (0.02)	1.33 (0.02)	−0.02	(−0.07, 0.03)	.37
FEV_1 PP	102 (1)	100 (1)	−1	(−5, 2)	.53
$FEV_{0.5}$	1.04 (0.02)	1.00 (0.02)	−0.04	(−0.08, 0.00)	.08
FEF_{25-75}	1.41 (0.04)	1.31 (0.04)	−0.10	(−0.20, 0.00)	.05
PEFR	2.76 (0.06)	2.68 (0.06)	−0.08	(−0.21, 0.05)	.22
FEV_1/FVC	0.87 (0.01)	0.85 (0.01)	−0.01	(−0.03, 0.00)	.06
$FEV_{0.5}$/FVC	0.67 (0.01)	0.64 (0.01)	−0.02	(−0.04, −0.01)	.01

FEF_{25-75}, Forced expiratory flow at 25% to 75% of FVC; *FEV_1 PP,* FEV_1 percent predicted; *FVC,* forced vital capacity; *FVC PP,* FVC percent predicted; *PEFR,* peak expiratory flow rate.
*Longitudinal analyses for lung function obtained from children ages 5 through 8 y adjusted for age, race, gender, height, weight, asthma, passive smoke exposure, and age at the first occurrence of positive aeroallergen FEIA. Percent-predicted values adjusted for asthma, smoke, and FEIA only. Groups summarized by least-squares means (standard error).
†Asthma defined at ages 6 and 8 y.

In contrast to RV, children with RSV wheezing illnesses did not have significant differences in any of the measured spirometric or IOS indices when compared with children who did not wheeze with RSV (Table E3), and the same was true for wheezing illnesses caused by other viruses (data not shown).

DISCUSSION

This study investigated the relationships between specific viral wheezing illnesses during the preschool years and lung function between ages 4 and 8 years in a cohort of children at high risk for developing asthma. The majority of subjects completed technically acceptable maneuvers by age 5 years. An RV wheezing illness during the first 3 years of life was associated with lower pulmonary function, and notably, this relationship did not hold true for wheezing illnesses caused by RSV or other respiratory viruses. These relationships were less pronounced but were still significantly different after administration of bronchodilator and thus are not likely explained by increased airway tone alone. We previously reported that RV wheezing illnesses were strong predictors for asthma[6]; this study underscores and extends these findings by demonstrating that wheezing illnesses with RV and not with other viruses in the first few years are also associated with lower lung function. Children who experience early life viral wheezing episodes are a heterogeneous group with over half outgrowing their wheezing episodes by school age.[2] It is possible that children who have RV-specific wheezing illnesses in early life may be at higher risk to develop asthma and lower lung function as they mature.

Lung function measurement in young children is endorsed by the National Asthma Education and Prevention Program guidelines,[23] but it is technically challenging. IOS requires minimum cooperation and therefore may have advantages for use in young children. However, success rates for IOS and spirometry were similar in our study in contrast to other studies where children as young as 2 years were able to perform IOS.[10,24] This may be because in our study, spirometry and IOS were performed only once a year and with no further attempts at training the children between visits. Our findings suggest that both IOS and spirometry can be used in a complementary fashion in a clinical setting since 80% of children were able to successfully perform either IOS or spirometry by age 5 years, and the ability to

TABLE III. Longitudinal comparisons of prebronchodilator pulmonary function (spirometry) between groups of children from ages 5 through 8 y* with early childhood RV wheezing illnesses and children without

	RV wheeze 1st 3 y					RSV wheeze 1st 3 y				
	No	Yes	Diff	95% CI	*P* value	No	Yes	Diff	95% CI	*P* value
n	152	73				160	65			
FVC	1.61 (0.02)	1.54 (0.03)	−0.07	(−0.13, 0.00)	.04	1.57 (0.02)	1.58 (0.03)	0.01	(−0.04, 0.07)	.66
FVC PP	105 (1)	102 (2)	−3	(−8, 1)	.13	104 (1)	103 (2)	0	(−4, 4)	.90
FEV_1	1.38 (0.02)	1.28 (0.02)	−0.10	(−0.16, −0.04)	.001	1.33 (0.02)	1.33 (0.02)	0.00	(−0.05, 0.05)	.97
FEV_1 PP	103 (2)	97 (2)	−6	(−11, −1)	.01	101 (1)	100 (2)	−1	(−5, 3)	.72
$FEV_{0.5}$	1.06 (0.02)	0.96 (0.02)	−0.10	(−0.16, −0.04)	.0005	0.01 (0.02)	1.01 (0.02)	−0.01	(−0.05, 0.04)	.83
FEF_{25-75}	1.46 (0.05)	1.21 (0.05)	−0.25	(−0.37, −0.12)	.0002	1.34 (0.04)	1.32 (0.05)	−0.02	(−0.13, 0.09)	.70
PEFR	2.79 (0.06)	2.59 (0.07)	−0.21	(−0.38, −0.04)	.02	2.72 (0.06)	2.66 (0.07)	−0.06	(−0.21, 0.08)	.40
FEV_1/FVC	0.87 (0.01)	0.84 (0.01)	−0.02	(−0.04, 0.00)	.01	0.85 (0.01)	0.85 (0.01)	−0.01	(−0.02, 0.01)	.55
$FEV_{0.5}$/FVC	0.67 (0.01)	0.63 (0.01)	−0.03	(−0.06, −0.01)	.008	0.65 (0.01)	0.65 (0.01)	−0.01	(−0.03, 0.01)	.48

FEF_{25-75}, Forced expiratory flow at 25% to 75% of FVC; *FEV_1 PP,* FEV_1 percent predicted; *FVC,* forced vital capacity; *FVC PP,* FVC percent predicted; *PEFR,* peak expiratory flow rate.

*Longitudinal analyses for lung function obtained from children aged 5 through 8 y adjusted for age, race, gender, height, weight, asthma, RV wheeze, RSV wheeze, non-RV/non-RSV wheeze, passive smoke exposure, and age at the first occurrence of positive aeroallergen FEIA. Percent-predicted values adjusted for asthma, RV wheeze, RSV wheeze, non-RV/non-RSV wheeze, smoke, and FEIA only. Groups summarized by least-squares means (standard error).

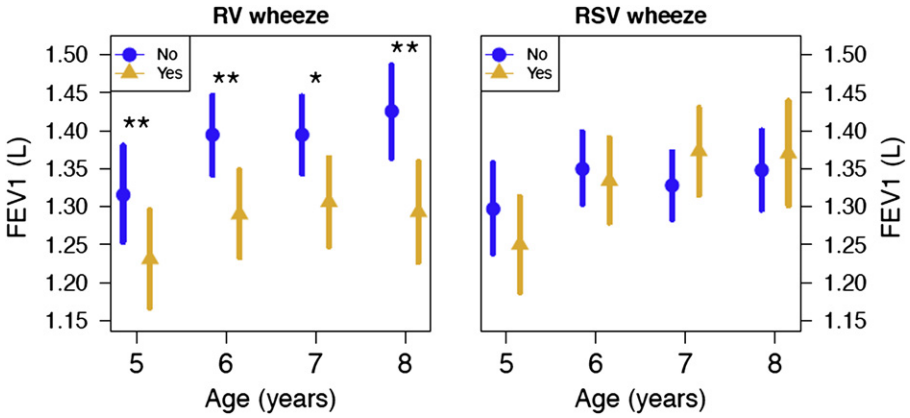

FIG 2. Children with RV wheezing illnesses had significantly lower FEV_1 at ages 5 through 8 years. In contrast with RV, children with RSV wheezing illnesses did not have significant differences in FEV_1 at any age compared with children who did not wheeze with RSV. Circles and triangles represent means, and bars represent 95% CI. Results were obtained by using linear mixed-effects regression model using FEV_1 obtained from children aged 5 through 8 years adjusted for age, race, gender, height, weight, asthma, RV wheeze, RSV wheeze, non-RV/non-RSV wheeze, passive smoke exposure, and age at the first occurrence of positive aeroallergen FEIA. Significant differences between treatment groups denoted by $*P < .05$ and $**P < .01$.

complete one test was not associated with the ability to complete the other.

IOS may measure respiratory system properties, respiratory system resistance (R_{rs}), and reactance (X_{rs}), which are not directly assessed by spirometry. We observed that children who wheezed with RV had a larger R5-R10 difference and AX, which may reflect increased resistance and/or heterogeneity of distal airways.[13,25,26] Children who wheezed with RV also had a more negative X5 and larger AX compared with those who did not wheeze with RV— results that suggest abnormal small airways. R5, R5-10, and AX all may reflect the mechanical properties of peripheral airways and their significant change after RV wheezing illnesses in early life suggest RV-specific processes in small airways. It should be noted that no differences were found between children with asthma and those without using IOS; in contrast, spirometry was able to detect small differences between groups. This suggests that in our study participants, spirometry was a more sensitive measure of lung function than IOS.

We and others[6,27] have previously demonstrated that RV wheezing illnesses in early life are associated with a subsequent diagnosis of asthma. This study provides additional novel evidence that early RV wheezing illnesses are also related to lower lung function in childhood. The causality of this association is unknown. RSV is a recognized lower airway pathogen and it has also been associated with an increased risk of asthma, the prevalence of which appears to dissipate during the first decade.[5,28,29] Previous studies also have found a relationship between lower lung function and RSV wheezing illnesses,[30,31] but these respiratory infections were severe enough to require the child to be hospitalized. Given RSV's role as a lower airway pathogen, we anticipated that RSV illnesses would be more likely to be associated with reduced lung function. Therefore, we were intrigued to find that children who wheezed during early life with RV, as opposed to RSV, were those children who were significantly more likely to have lower lung function at school age. Along these lines, pathways by which RV infection could lead to airway remodeling

TABLE IV. Longitudinal comparisons of postbronchodilator pulmonary function (spirometry) between groups of children from ages 6 through 8 y* with and without early childhood RV wheezing illnesses

	RV wheeze 1st 3 y					RSV wheeze 1st 3 years				
	No	Yes	Diff	95% CI	*P* value	No	Yes	Diff	95% CI	*P* value
n	137	67				145	59			
FVC	1.78 (0.03)	1.73 (0.03)	−0.05	(−0.12, 0.02)	.15	1.74 (0.02)	1.77 (0.03)	0.02	(−0.04, 0.08)	.49
FVC PP	110 (1)	110 (2)	0	(−5, 4)	.84	110 (1)	111 (2)	1	(−3, 5)	.59
FEV_1	1.55 (0.02)	1.47 (0.03)	−0.08	(−0.14, −0.02)	.01	1.50 (0.02)	1.52 (0.03)	0.02	(−0.04, 0.07)	.52
FEV_1 PP	110 (2)	107 (2)	−3	(−8, 1)	.18	107 (1)	109 (2)	1	(−3, 5)	.51
$FEV_{0.5}$	1.22 (0.02)	1.13 (0.02)	−0.08	(−0.14, −0.03)	.003	1.17 (0.02)	1.17 (0.02)	0.00	(−0.05, 0.05)	.95
FEF_{25-75}	1.82 (0.06)	1.62 (0.07)	−0.20	(−0.36, −0.04)	.01	1.70 (0.05)	1.73 (0.07)	0.02	(−0.11, 0.16)	.73
PEFR	3.11 (0.07)	3.01 (0.08)	−0.10	(−0.29, 0.09)	.30	3.06 (0.06)	3.07 (0.08)	0.01	(−0.16, 0.18)	.89
FEV_1/FVC	0.88 (0.01)	0.85 (0.01)	−0.02	(−0.04, 0.00)	.06	0.86 (0.01)	0.87 (0.01)	0.00	(−0.02, 0.02)	.92
$FEV_{0.5}$/FVC	0.69 (0.01)	0.66 (0.01)	−0.03	(−0.06, 0.00)	.06	0.68 (0.01)	0.67 (0.01)	0.00	(−0.03, 0.02)	.70

FEF_{25-75}, Forced expiratory flow at 25% to 75% of FVC; *FEV_1 PP,* FEV_1 percent predicted; *FVC,* forced vital capacity; *FVC PP,* FVC percent predicted; *PEFR,* peak expiratory flow rate.

*Longitudinal analyses for lung function obtained from children aged 6 through 8 y adjusted for age, race, gender, height, weight, asthma, RV wheeze, RSV wheeze, non-RV/non-RSV wheeze, passive smoke exposure, and age at the first occurrence of positive aeroallergen FEIA. Percent-predicted values adjusted for asthma, RV wheeze, RSV wheeze, non-RV/non-RSV wheeze, smoke, and FEIA only. Groups summarized by least-squares means (standard error).

have recently been identified.[32,33] Also, infants born with poor antiviral responses are more prone to repetitive illness. Indeed, recent work has demonstrated that epithelial and/or mononuclear cell innate antiviral responses to infection with RV may be deficient in atopic asthmatic patients[34,35] This deficient immune response may lead to lower lung function after one RV infection. Our data did not show that children with repeated or more severe RV wheezing illnesses had lower lung function than those with less frequent or less severe RV wheezing illnesses. However, it is possible that our study lacked sufficient power to show these associations. Although we did not find evidence that RSV wheezing illnesses were associated with reduced lung function, few of our study participants had severe illnesses requiring hospitalization. It is possible that severe RSV illnesses could lead to significant reductions in lung function.

Unlike the study by Illi and colleagues,[36] which demonstrated reduced lung function in children with early allergic sensitization and allergen exposure, we did not find that allergic sensitization lead to greater lung function deficits than RV wheezing illnesses alone. However, allergen exposure was not measured in our study. An alternate explanation is that children who wheeze with RV may have congenitally lower lung function, and so RV wheezing illnesses serve only as a marker of antecedent abnormal lung physiology. Children who have lower lung function shortly after birth are more likely to have lower lung function as they age compared with normal children, but not persistent asthma.[2,37] However, a study by Haland and colleagues demonstrated that children with lower lung function measured by tidal breathing flow-volume loops shortly after birth are more likely to have lower lung function at age 10 years[38] and the diagnosis of asthma at 10 years of age.[39] Another recent study by van der Zalm et al[40] demonstrates that increased total lung resistance measured at 2 months of age is associated with subsequent RV wheeze; however, the low viral detection rate of other non-RV viruses made it impossible to study an association between neonatal lung function and infection with other types of viruses. We cannot confirm these findings in the COAST study because infant pulmonary function tests were not performed. However, our study does provide unique assessment of numerous respiratory viruses including RV and RSV and their association with childhood lung function. Furthermore, Haland and colleagues[39] found that lung function at 10 years of age was not affected by a history of at least 1 or 3 or more lower respiratory tract illnesses in the first 2 years of life after adjusting for lung function measured at birth. However, this result may have been different if the etiology of the infection was analyzed as was done in this study.

Here we demonstrate in a large cohort of children at risk to develop asthma that lung function is reduced in children who wheeze with RV in early life but not with other viruses, and these significant reductions in lung function, while smaller, remain after bronchodilator administration. This association of early life RV wheezing illnesses and lower lung function was found by using 2 different methods of lung function measurements, spirometry and IOS, and the findings were consistent across multiple lung function parameters produced by each method. The association was best for the measures of $FEV_{0.5}$ and FEF_{25-75} rather than FEV_1. This is not an unexpected finding as young children often empty their lung volumes in less than 1 second[7,13] and FEV_1 is often normal in children with asthma.[41] Other studies have also shown that FEF_{25-75} rather than FEV_1 is often the first lung function measurement that is decreased in children with asthma compared with controls.[2,13,42] However, the children enrolled in COAST also are at high risk to develop asthma and allergies and mainly Caucasian, and so these findings may not be generalizable to all children.

In conclusion, RV wheezing illnesses, but not wheezing illnesses caused by other respiratory viruses, were associated with lower lung function in early childhood. This finding, in combination with published data that wheezing with RV predicts future and persistent wheezing[15,43] and asthma,[6] suggests that recognizing early life RV illnesses could be of prognostic significance. Additional studies confirming that infants experiencing recurrent RV wheezing illnesses have normal lung function at birth and examining mechanisms by which RV infection in early life may lead to lower lung function in later childhood and beyond are essential. Furthermore, once these disease mechanisms are understood, additional studies could explore novel interventions such as antiviral or immunosuppressant therapies to interrupt the progression from early childhood wheezing to asthma.

Clinical implications: These findings suggest that recognizing early life rhinovirus illnesses could be of prognostic significance. Whether low lung function is a cause and/or effect of rhinovirus wheezing illnesses is yet to be determined.

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METHODS

The Jaeger MasterScreen system equipment used fulfills the requirements by ATS/European Respiratory Society recommendations.[E1] Children were without an acute respiratory illness or asthma exacerbation for at least 3 weeks prior to the lung function measurements. At the time of the study, the ATS Standardization of Spirometry did not address recommendations for young children specifically.[E1] However, Eigen et al[E2] published a study evaluating spirometric lung function in preschool children between 3 and 6 years of age (Table E1) and these criteria were used.

Predicted values were calculated based on the primary racial category chosen by the parent and predicated equations from Eigen et al[E2] (Table E2). FVC, FEV_1, $FEV_{0.5}$, FEF_{25-75}, and PEFR were adjusted for the child's race and gender and the child's age, height, and weight obtained at the visit in which spirometry was performed.

For IOS, rectangular pulse signals every 250 milliseconds during at least 30 seconds of tidal breathing were applied. Throughout data acquisition, pressure and flow traces were graphically displayed at real time. The measurements were accepted when the tracing showed stable, uninterrupted tidal breathing during data acquisition and negative values for X5. The impedance parameters from 3 good quality maneuvers lasting for a minimum 15 seconds and at least 4 breaths were averaged if they fulfilled the following reproducibility criteria: coherence function at 10 Hz of 0.80 or greater, and values for R10 within 20% using the highest value (Table E3).

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TABLE E1. Spirometry acceptability criteria for preschool children

	Maneuver acceptability criteria (ATS[E1] vs Eigen et al[E2])	
Start-of-test	Extrapolated volume <5% of FVC or 0.15 L—whichever is greater	Visually satisfactory start; rapid onset of expiration; no obvious large back extrapolation
Peak flow	Clearly determined peak flow	Clearly determined peak flow; a single distinct peak in the MEFV curve
Maneuver artifact	No cough/glottic closure during the first second of exhalation, leak, or early termination	No cough/glottic closure during the first second of exhalation, leak, or early termination
End-of-test	No early termination or cut-off with volume-time tracing showing obvious plateau	No abrupt ending or truncation with sharp drop/cessation in flow from a point where flow was >25% of the PEFR
Reproducibility	Minimum of 3 maneuvers with 2 of the maneuvers having FVC and FEV_1 within 0.15 L	Minimum of 3 maneuvers; shapes of flow-volume curves visually reproducible with FVC and FEV_1 within 10%
No. of maneuvers	Minimum of 3 Maximum of 8	Minimum of 3 Maximum of 8
FET	Minimum of 6 s unless there is an obvious plateau in the volume-time display; shorter times acceptable in children	Minimum of 1 s

FET, Forced expiratory time; *FVC,* forced vital capacity; *MEFV,* maximum expiratory flow volume; *PEFR,* peak expiratory flow rate.

TABLE E2. Predicted equations for family-reported ethnicity[E2]

Family-reported ethnicity	Predicted equation used
African-American	Eigen reduced 10%
Anglo-Caucasian	Eigen
Hispanic-American	Eigen
Other	Eigen

TABLE E3. IOS maneuver acceptability criteria

Testing requirements	● 3 acceptable maneuvers containing minimum of 15 s (ideally 30 s) and at least 4 breaths
Maneuver artifact	● Consistent period of tidal breathing free of coughing, crying, or lack of signal due to discontinuation of breathing ● No abrupt ending, leak or early termination
Reproducibility	● Value for R10 within 20% using the highest value ● Coherence values of 0.80 or greater ● Negative value for X5
Maneuvers	● Minimum of 3 ● Maximum of 8

TABLE E4. Longitudinal comparisons of postbronchodilator pulmonary function between groups of children from ages 6 through 8 y* with and without asthma

	Asthma†				
	No	**Yes**	**Difference**	**95% CI**	***P* value**
Spirometry					
n	123	81			
FVC	1.77 (0.02)	1.75 (0.02)	−0.02	(−0.07, 0.03)	.43
FVC PP	110 (1)	110 (1)	0	(−3, 4)	.87
FEV_1	1.54 (0.02)	1.50 (0.02)	−0.03	(−0.08, 0.01)	.17
FEV_1 PP	109 (2)	108 (2)	−1	(−5, 2)	.49
$FEV_{0.5}$	1.20 (0.02)	1.16 (0.02)	−0.04	(−0.08, −0.00)	.06
FEF_{25-75}	1.79 (0.06)	1.67 (0.06)	−0.12	(−0.24, 0.00)	.05
PEFR	3.09 (0.07)	3.05 (0.07)	−0.05	(−0.19, 0.10)	.51
FEV_1/FVC	0.87 (0.01)	0.86 (0.01)	−0.01	(−0.03, 0.01)	.28
$FEV_{0.5}$/FVC	0.68 (0.01)	0.67 (0.01)	−0.02	(−0.04, 0.00)	.12

FEF_{25-75}, Forced expiratory flow at 25% to 75% of FVC; *FEV_1 PP,* FEV_1 percent predicted; *FVC,* forced vital capacity; *FVC PP,* FVC percent predicted; *PEFR,* peak expiratory flow rate.

*Longitudinal analyses for lung function obtained from children aged 6 through 8 y adjusted for age, race, gender, height, weight, asthma, passive smoke exposure, and age at the first occurrence of positive aeroallergen FEIA. Percent-predicted values adjusted for asthma, smoke, and FEIA only. Groups summarized by least-squares means (standard error).

†Asthma defined at ages 6 and 8 y.

TABLE E5. Cross-sectional comparisons of prebronchodilator pulmonary function between groups of children at age 8 y* who wheezed with RV and children who did not in early childhood

	RV wheeze 1st 3 y					RSV wheeze 1st 3 y				
	No	**Yes**	**Diff**	**95% CI**	***P* value**	**No**	**Yes**	**Diff**	**95% CI**	***P* value**
Spirometry										
n	123	55				130	48			
FVC	1.70 (0.03)	1.62 (0.04)	−0.08	(−0.16, 0.01)	.08	1.64 (0.03)	1.67 (0.04)	0.03	(−0.05, 0.11)	.47
FVC PP	108 (2)	106 (2)	−2	(−7, 3)	.50	106 (1)	107 (2)	1	(−4, 5)	.78
FEV_1	1.42 (0.03)	1.29 (0.03)	−0.13	(−0.21, −0.05)	.001	1.35 (0.03)	1.37 (0.03)	0.02	(−0.05, 0.09)	.53
FEV_1 PP	102 (2)	96 (2)	−6	(−11, −1)	.03	98(1)	100 (2)	1	(−3, 6)	.54
$FEV_{0.5}$	1.10 (0.03)	0.98 (0.03)	−0.12	(−0.19, −0.05)	.001	1.03 (0.02)	1.04 (0.03)	0.01	(−0.05, 0.08)	.69
FEF_{25-75}	1.51 (0.07)	1.21 (0.07)	−0.29	(−0.45, −0.13)	.0004	1.34 (0.06)	1.37 (0.07)	0.03	(−0.11, 0.18)	.67
PEFR	2.98 (0.09)	2.72 (0.10)	−0.25	(−0.49, −0.02)	.04	2.91 (0.08)	2.79 (0.10)	−0.11	(−0.33, 0.10)	.29
FEV_1/FVC	0.85 (0.01)	0.82 (0.01)	−0.03	(−0.06, −0.01)	.009	0.83 (0.01)	0.83 (0.01)	0.00	(−0.02, 0.02)	0.97
$FEV_{0.5}$/FVC	0.66 (0.01)	0.62 (0.01)	−0.04	(−0.07, 0.00)	.02	0.64 (0.01)	0.64 (0.01)	0.00	(−0.03, 0.03)	0.90

FEF_{25-75}, Forced expiratory flow at 25% to 75% of FVC; *FEV_1 PP,* FEV_1 percent predicted; *FVC,* forced vital capacity; *FVC PP,* FVC percent predicted; *PEFR,* peak expiratory flow rate.

*Cross-sectional analyses at age 8 y were adjusted for age, race, gender, height, weight, asthma, RV wheeze, RSV wheeze, non-RV/non-RSV wheeze, passive smoke exposure, and age at the earliest occurrence of positive aeroallergen FEIA. Percent-predicted values were adjusted for asthma, RV wheeze, RSV wheeze, non-RV/non-RSV wheeze, smoke, and FEIA only. Groups summarized by least-squares means (standard error).

TABLE E6. Longitudinal comparisons of prebronchodilator pulmonary function between groups of children from ages 5 through 8 y* with and without early childhood RV wheezing illnesses

	RV wheeze 1st 3 y					RSV wheeze 1st 3 y				
	No	**Yes**	**Diff**	**95% CI**	***P* value**	**No**	**Yes**	**Diff**	**95% CI**	***P* value**
Impulse oscillometry										
n	146	72				153	65			
R5	0.88 (0.02)	0.92 (0.02)	0.04	(−0.01, 0.10)	.12	0.91 (0.02)	0.90 (0.02)	−0.01	(−0.06, 0.04)	.64
R10	0.72 (0.02)	0.73 (0.02)	0.00	(−0.04, 0.05)	.85	0.71 (0.01)	0.74 (0.02)	0.03	(−0.01, 0.07)	.16
R5-10	0.15 (0.01)	0.20 (0.01)	0.05	(0.02, 0.07)	.0004	0.19 (0.01)	0.16 (0.01)	−0.02	(−0.05, 0.00)	.04
R20	0.57 (0.01)	0.54 (0.01)	−0.03	(−0.06, 0.01)	.12	0.55 (0.01)	0.56 (0.01)	0.01	(−0.02, 0.04)	.62
-X5	0.35 (0.01)	0.41 (0.01)	0.06	(0.02, 0.09)	.0008	0.39 (0.01)	0.37 (0.01)	-0.02	(−0.05, 0.01)	.12
AX	2.62	3.20	1.22	(1.07, 1.40)	.004	3.04	2.77	0.91	(0.81, 1.03)	.13

AX, Area of reactance; *R5,* resistance at 5 Hz; *R10,* resistance at 10 Hz; *R5-R10,* the difference in resistance at 5 Hz and at 10 Hz; *R20,* resistance at 20 Hz; *X5,* reactance at 5 Hz.
*Longitudinal analyses for lung function obtained from children aged 5 through 8 y adjusted for age, race, gender, height, weight, asthma, RV wheeze, RSV wheeze, non-RV/non-RSV wheeze, passive smoke exposure, and age at the first occurrence of positive aeroallergen FEIA. Groups summarized by least-squares means (standard error). AX analyzed as log(AX); AX groups summarized by least squares geometric means, and AX group differences expressed as ratios.

TABLE E7. Longitudinal comparisons of postbronchodilator pulmonary function between groups of children from ages 6 through 8 y* with and without early childhood RV wheezing illnesses

	RV wheeze 1st 3 y					RSV wheeze 1st 3 y				
	No	**Yes**	**Diff**	**95% CI**	***P* value**	**No**	**Yes**	**Diff**	**95% CI**	***P* value**
Impulse oscillometry										
n	133	63				136	60			
R5	0.72 (0.02)	0.71 (0.02)	−0.01	(−0.06, 0.04)	.70	0.72 (0.02)	0.71 (0.02)	−0.01	(−0.06, 0.03)	.62
R10	0.62 (0.02)	0.60 (0.02)	−0.02	(−0.06, 0.02)	.33	0.60 (0.01)	0.60 (0.02)	0.01	(−0.03, 0.04)	.66
R5-10	0.10 (0.01)	0.11 (0.01)	0.01	(−0.01, 0.03)	.36	0.12 (0.01)	0.10 (0.01)	−0.02	(−0.04, 0.00)	.04
R20	0.51 (0.01)	0.49 (0.01)	−0.02	(−0.06, 0.01)	.19	0.49 (0.01)	0.51 (0.01)	0.01	(−0.02, 0.05)	.40
-X5	0.30 (0.01)	0.29 (0.01)	−0.01	(−0.04, 0.02)	.35	0.31 (0.01)	0.29 (0.01)	−0.02	(−0.04, 0.01)	.17
AX	1.94	2.02	1.04	(0.86, 1.26)	.67	2.01	1.94	0.96	(0.82, 1.13)	.65

AX, Area of reactance; *R5*, resistance at 5 Hz; *R10*, resistance at 10 Hz; *R5-R10*, the difference in resistance at 5 Hz and at 10 Hz; *R20*, resistance at 20 Hz; *X5*, reactance at 5 Hz.
*Longitudinal analyses for lung function obtained from children aged 5 through 8 y adjusted for age, race, gender, height, weight, asthma, RV wheeze, RSV wheeze, non-RV/non-RSV wheeze, passive smoke exposure, and age at the first occurrence of positive aeroallergen FEIA. Groups summarized by least-squares means (standard error). AX analyzed as log(AX); AX groups summarized by least-squares geometric means, and AX group differences expressed as ratios.

TABLE E8. Longitudinal comparisons of pulmonary function from ages 5 through 8 y* between groups of children who had varying frequency of wheezing RV illness in early childhood

	Number of wheezing RV illnesses in 1st 3 y			*P* value		
	0	1	2+	0 vs 1	0 vs 2+	1 vs 2+
Spirometry						
n	152	32	41			
FVC	1.61 (0.02)	1.56 (0.03)	1.53 (0.03)	.16	.04	.49
FVC PP	105 (1)	102 (2)	102 (2)	.22	.20	.89
FEV_1	1.38 (0.02)	1.30 (0.03)	1.27 (0.03)	.02	.002	.46
FEV_1 PP	103 (2)	97 (2)	97 (2)	.03	.05	.97
$FEV_{0.5}$	1.06 (0.02)	0.97 (0.03)	0.95 (0.03)	.004	.003	.71
FEF_{25-75}	1.45 (0.05)	1.21 (0.07)	1.22 (0.07)	.001	.004	.96
PEFR	2.80 (0.06)	2.63 (0.09)	2.54 (0.09)	.09	.01	.40
FEV_1/FVC	0.87 (0.01)	0.84 (0.01)	0.85 (0.01)	.03	.08	.84
$FEV_{0.5}$/FVC	0.67 (0.01)	0.63 (0.01)	0.64 (0.01)	.01	.08	.55

FEF_{25-75}, Forced expiratory flow at 25% to 75% of FVC; *FEV_1 PP*, FEV_1 percent predicted; *FVC*, forced vital capacity; *FVC PP*, FVC percent predicted; *PEFR*, peak expiratory flow rate.

*Longitudinal analyses for lung function obtained from children aged 5 through 8 y adjusted for age, race, gender, height, weight, asthma, RV wheeze, RSV wheeze, non-RV/non-RSV wheeze, passive smoke exposure, and age at the first occurrence of positive aeroallergen FEIA. Percent-predicted values adjusted for asthma, smoke, and FEIA only. Groups summarized by least-squares means (standard error).

TABLE E9. Longitudinal comparisons of pulmonary function from ages 5 through 8 y* between groups of children with varying severity of RV illnesses in early childhood

	Most severe RV illness during 1st 3 y				*P* value						
	1 Severe wheezing RV illness	2 Less severe wheezing RV illness	3 Nonwheezing RV illness	4 No RV illness	Over-all	1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4
Spirometry											
n	29	44	110	42							
FVC	1.51 (0.04)	1.55 (0.03)	1.59 (0.02)	1.65 (0.03)	.02	.40	.05	.004	.18	.01	.10
FVC PP	101 (2)	102 (2)	105 (1)	108 (2)	.06	.82	.21	.02	.20	.02	.09
FEV_1	1.26 (0.03)	1.30 (0.03)	1.37 (0.02)	1.41 (0.03)	.0005	.36	.003	.0003	.02	.001	.15
FEV_1 PP	97 (2)	97 (2)	103 (1)	106 (2)	.009	.94	.06	.008	.03	.003	.17
$FEV_{0.5}$	0.94 (0.03)	0.97 (0.03)	1.05 (0.02)	1.09 (0.03)	.0002	.39	.002	.0002	.008	.0005	.12
FEF_{25-75}	1.19 (0.07)	1.25 (0.06)	1.44 (0.05)	1.48 (0.06)	.0008	.41	.002	.001	.006	.003	.45
PEFR	2.54 (0.09)	2.63 (0.08)	2.76 (0.06)	2.91 (0.08)	.005	.44	.04	.002	.11	.003	.05
FEV_1/FVC	0.85 (0.01)	0.85 (0.01)	0.87 (0.01)	0.86 (0.01)	.17	.90	.09	.22	.05	.18	.69
$FEV_{0.5}$/FVC	0.64 (0.01)	0.64 (0.01)	0.66 (0.01)	0.67 (0.01)	.08	.92	.11	.09	.04	.04	.69

FEF_{25-75}, Forced expiratory flow at 25% to 75% of FVC; *FEV_1 PP*, FEV_1 percent predicted; *FVC*, forced vital capacity; *FVC PP*, FVC percent predicted; *PEFR*, peak expiratory flow rate.

*Longitudinal analyses for lung function obtained from children aged 5 through 8 y adjusted for age, race, gender, height, weight, asthma, RV wheeze, RSV wheeze, non-RV/non-RSV wheeze, passive smoke exposure, and age at the first occurrence of positive aeroallergen FEIA. Percent-predicted values adjusted for asthma, smoke, and FEIA only. Groups summarized by least-squares means (standard error).