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Pulmonary ^3He Magnetic Resonance Imaging of Childhood Asthma

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Abstract

Background—Magnetic resonance imaging (MRI) with ^3He does not require ionizing radiation and has been shown to detect regional abnormalities in lung ventilation and structure in adult asthma, but the method has not been extended to childhood asthma. Measurements of regional lung ventilation and microstructure in childhood asthma could advance our understanding of disease mechanisms.

Objective—To determine whether ^3He MRI in children can identify abnormalities related to diagnosis of asthma or prior history of respiratory illness.

Methods—Forty-four children aged 9–10 years were recruited from a birth cohort at increased risk of developing asthma and allergic diseases. For each subject a time-resolved three-dimensional (3D) image series and a 3D diffusion-weighted image were acquired in separate breathing maneuvers. The number and size of ventilation defects were scored, and regional maps and statistics of average ^3He diffusion length were calculated.

Results—Children with mild to moderate asthma had lower average diffusion length, $\overline{X_{rms}}$ ($p=0.004$), increased regional standard deviation of diffusion length ($p=0.03$), and higher defect scores ($p=0.03$) than those without asthma. Children with histories of wheezing illness with rhinovirus infection prior to the third birthday had lower $\overline{X_{rms}}$ ($p=0.01$) and higher defect score ($p=0.05$).

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Conclusion—MRI with ^3He detected more and larger regions of ventilation defect and a greater degree of restricted gas diffusion in children with asthma compared to those without asthma. These measures are consistent with regional obstruction and smaller and more regionally variable dimensions of the peripheral airways and alveolar spaces.

Keywords

asthma; pediatric; hyperpolarized MRI; apparent diffusion coefficient

INTRODUCTION

Traditional imaging modalities are not well-suited for non-invasive monitoring of lung function and peripheral airway changes associated with asthma, and this has limited the role of imaging as a tool for studying regional disease in asthma. Quantitative evaluation of x-ray computed tomography (CT) has shown promise for non-invasive detection of structural abnormalities in the central airways.^{1, 2} However, neither CT nor other conventional imaging techniques yield details of the sites of airflow obstruction distally, so little is known about the role of distal airways in the disease or whether the obstruction is global or limited to specific locations. Moreover, use of CT to assess asthma in children is a concern due to the risks of early exposure to low-dose ionizing radiation.³

Major risk factors for childhood asthma include the early development of allergic sensitization and virus-induced wheezing episodes, particularly those caused by human rhinoviruses (HRV).⁴ Increased mucus production can also lead to complete occlusion of small airways leading to abnormalities in ventilation and perfusion. In preschool aged children with recurrent wheezing, bronchial biopsies have demonstrated that a number of these pathologic events are present as early as two to three years of life.⁵ Based on that previous work, we hypothesized that a child's lung function and prior history of viral illnesses would be associated with regional patterns of airway obstruction at age 9 and 10 years.

Pulmonary magnetic resonance imaging (MRI) of hyperpolarized noble gases is an investigational modality using non-ionizing radiation that has shown promise for the study of lung diseases including emphysema, cystic fibrosis, and asthma in adults.⁶⁻¹¹ In adult asthma subjects, ^3He MRI of the lungs has revealed spatially heterogeneous ventilation patterns due to focal ventilation defects¹² in regions of the lung parenchyma that are not filled completely by the ^3He gas when the subject inhales. Studies in adult asthmatics have found that the number and size of these ventilation defects correlate with asthma severity and with decreasing lung function.^{13, 14} In addition, diffusion MRI of noble gases can be used to measure average dimensions of lung microstructure. Traditionally this has been expressed as the mean apparent diffusion coefficient (ADC), which has been shown to increase in emphysema patients¹⁵⁻¹⁷ and in subjects with increasing smoking history who do not yet show clinical symptoms of lung disease.¹⁸ Diffusion MRI methodology is described in more detail in this article's Online Repository. The goal of this pilot study was to use novel imaging techniques in children genetically at risk for asthma development to test the hypothesis that ^3He MRI measures of regional ventilation and dimensions of pulmonary microstructure are related to lung function and history of viral illness. Three imaging metrics were evaluated to test this hypothesis.

METHODS

Study Population

Pulmonary MRI using inhaled ^3He gas was performed on 44 children age 9-10 years with Institutional Review Board approval, parental informed consent, and assent from the child. The study procedures complied with the Health Insurance Portability and Accountability Act of 1996. Hyperpolarized ^3He gas was used as an inhaled contrast agent under FDA IND #64,687. Subjects were recruited from among the children in the ongoing Childhood Origins of Asthma (COAST) study¹⁹. Details on recruitment of the birth cohort for the COAST study are summarized in this article's Online Repository. MRI exams were scheduled on the same day as the COAST study visits at age 9 or 10 years. A subset of children in the COAST study were recruited to represent a broad range of both lung function and history of respiratory illness in the first year of life according to the study grid shown in Table I. Subjects were recruited from the highest and lowest quartiles of forced expiratory volume in one second (FEV_1) measured at the clinical visit at age 8 years (FEV_1 109.9% of predicted or FEV_1 91.4% of predicted), the last year for which data on the full cohort were available when the MRI study was initiated. Predicted FEV_1 was computed based on the Eigen²⁰ criteria using family-reported ethnicity for the child. One additional subject who did not meet the FEV_1 criteria was also included in the MRI substudy but was not included in the analysis of the original design groups. Subjects were also recruited from among those who did and did not experience HRV infection coincident with a moderate-to-severe illness (MSI) before the first birthday. MSI refers only to respiratory symptoms as explained in this article's Online Repository and is not an indication of asthma severity. Selection and recruitment of subjects was performed independently by the study statistician and nurse coordinator so that the imaging investigators remained blinded to the study subject's history throughout the data acquisition and analysis phases of the study.

After selection of the design groups, analysis of the full COAST cohort showed that the odds ratio for asthma diagnosis was highest among children who had HRV illness with wheezing before the third birthday.⁴ The effect was less significant for other viruses studied. The adjusted imaging measures were, therefore, compared for the original design groups, to the diagnosis of asthma concurrent with the imaging and histories of HRV-wheezing illness in the first 3 years of life.

COAST Study Procedures

Before the child's third birthday, parents were instructed to contact a study coordinator whenever a child developed symptoms of a respiratory tract infection. Based on the parent's report of symptoms, a respiratory scorecard was completed to determine severity.²¹ If symptoms met the conditions of MSI, a nasopharyngeal mucus specimen was obtained by saline irrigation and viral etiology was assessed using multiplex polymerase chain reaction. Additionally, the illness was classified as a wheezing illness if it met the criteria reported earlier⁴ (the criteria are also listed in this article's Online Repository). At least one viral pathogen was identified during 90% of wheezing illnesses.⁴

Beginning at age 4 years, pulmonary function tests (PFT) including spirometry and impulse oscillometry (IOS) were performed during annual study visits according to methods described previously.²² The IOS measures recorded included resistance at 5 Hz (R5) and 20 Hz (R20), the difference of these two resistances (R5–R20), reactance at 5 Hz (X5), and reactance area (AX). For subjects participating in the MRI study, lung volumes were measured by plethysmography (Jaeger MasterScreenBody, Hoechberg, Germany) following guidelines of the American Thoracic Society and the European Respiratory Society.²³

Parents were asked to reschedule their child's visits to the clinic if the child had a respiratory illness on the day of a visit, so all children were generally healthy at the time of imaging.

Criteria for asthma diagnosis were described elsewhere.⁴ Briefly, subjects were identified as having current asthma at the time of MRI exam if they met at least one of the following criteria during the prior year: physician diagnosis of asthma, use of albuterol for coughing or wheezing episodes (prescribed by physician), use of a daily controller medication, step-up plan including use of albuterol or short-term use of inhaled corticosteroids during illness, or use of prednisone for asthma exacerbation.

Magnetic Resonance Imaging

³He was polarized by spin-exchange optical pumping in a prototype commercial polarizer (HeliSpin, GE Healthcare, Durham, NC). Once polarized, the ³He gas was diluted with nitrogen to produce a volume adjusted for each subject as described below. Imaging studies were performed on a 1.5-T clinical magnetic resonance scanner (SignaHDx, GE Healthcare, Waukesha, WI) with broadband imaging capability. Fast MRI acquisitions were used to limit breath-hold time to 15 s or less and to improve robustness to respiratory motion.²⁴⁻²⁶ The anoxic doses of ³He and N₂ did not cause any adverse effects. Further details on imaging methods are presented in this article's Online Repository.

Standardization of Lung Volume

Previous studies have shown that ³He diffusion measurements of distal airway dimensions are sensitive to lung inflation volume.^{27, 28} As in prior work,²⁴ a gas volume individualized to 14% of the subject's total lung capacity (TLC) was prepared (typically 350-600 mL) to standardize lung inflation for comparison between subjects. The ³He doses were inhaled from functional residual capacity (FRC). The ³He dose was administered by a researcher who was blinded to the subjects' clinical status, and identical instructions were given to all subjects.

Defect Score

A series of images was acquired during respiratory inflow, breath-hold, and outflow of the polarized gas. Ventilation defects observed in these images are indicative of restrictions to the flow of hyperpolarized gas to regions of the lung. The extent of defects observed was evaluated for all subjects by a single reviewer to compute a discrete score¹⁴ similar to that of de Lange *et al.*¹³ Briefly, each defect was assigned a score based on its extent of lobar involvement: 1, less than 25%; 2, 26% to 50%; 3, 51% to 75%; or 4, at least 76% of a lobe. The total ventilation defect score (VDS) was the sum of the scores for all defects across the whole lung. The reviewer was blinded to subject identity, asthma status, medical history, and results of other study tests. The related ventilated volume measures were compared for multiple reviewers in an independent study of the ³He MRI technique²⁹ and showed high inter-reader repeatability (inter-reader intraclass correlation coefficient greater than 0.9).

Diffusion Length

The second MRI acquisition measured ³He diffusion during a 4.6 ms interval. For each image pixel, the root-mean-square diffusion length (X_{rms}) was computed as described in this article's Online Repository. The lung microstructure limits the paths over which the ³He may diffuse enabling measurement of the average dimension of small airways and alveolar spaces within each image pixel. For each subject, two descriptive statistics were therefore calculated and compared to outcomes. One was the whole-lung average of X_{rms} , or $\overline{X_{rms}}$, a measure of the average small airway dimension throughout the lung.²⁸ The second measure,

the within-subject standard deviation of X_{rms} (SSDX), reflects regional variation in the average small airway dimension across the lung.

Statistical Analysis

The three imaging metrics (VDS, $\overline{X_{rms}}$, and SSDX) were compared to asthma diagnosis, history of respiratory illness, gender, and measurements from pulmonary function tests (PFTs). Imaging metrics were compared between groups using linear models which included TLC and gender covariates. Prior to analysis, VDS was square-root transformed and AX was log-transformed to produce approximately normal distributions. Adjusted Z-scores for the imaging and PFT metrics were obtained by regressing each metric on TLC and gender and calculating the standardized residuals. The resulting Z-scores are standardized to have mean 0 and standard deviation 1. The associations between imaging and PFT Z-scores were examined using Pearson's correlation coefficient. A two-sided p 0.05 was regarded as significant.

RESULTS

Subject Population

Subject demographics are summarized in Table II. Time-resolved MRI exams were performed successfully in 43 of 44 children (98%), and sample images are shown in Figure 1. Diffusion-weighted MRI was successful in 40 of 44 children (91%), and sample maps of the diffusion length X_{rms} are presented in Figure 2. One MRI exam was unsuccessful due to a technical error, with no useful data acquired during either of the two imaging sequences. For three additional subjects, diffusion-weighted images could not be analyzed because of technical errors or respiratory motion during the scan.

Normalization of Imaging Measures

Expected variations in lung development with gender lead to differences in PFTs.³⁰ Indeed, imaging measures also showed gender differences as summarized in Table II. Girls had higher VDS than boys ($p = 0.01$), while $\overline{X_{rms}}$ and SSDX were similar between genders. TLC was also found to be correlated with $\overline{X_{rms}}$ ($r = +0.44$, $p = 0.005$), and tended to correlate with both SSDX ($r = -0.27$, $p = 0.09$) and VDS ($r = +0.26$, $p = 0.09$). Based on these findings, all subsequent comparisons were adjusted for the effects of gender and TLC by using Z-scores.

In comparing the Z-scores of the image metrics themselves, there was no significant correlation between VDS and $\overline{X_{rms}}$ ($r = -0.07$, $p = 0.65$) or SSDX ($r = -0.05$, $p = 0.75$). The SSDX was negatively correlated with $\overline{X_{rms}}$ ($r = -0.44$, $p = 0.004$) indicating increased spatial heterogeneity with smaller $\overline{X_{rms}}$. When comparing the original design groups, SSDX was smaller in the highest quartile of FEV₁ at age 8 years ($p = 0.04$), but VDS and $\overline{X_{rms}}$ were similar in the highest and lowest quartiles. There were no differences in imaging measures related to MSI with HRV infection in the first year of life (see Table E2 in this article's Online Repository). Further correlations between imaging metrics and PFTs are presented in this article's Online Repository.

Relationship of Imaging to Asthma and HRV Wheezing

Subjects diagnosed with asthma at the time of the MRI study had a higher VDS ($p = 0.03$), lower $\overline{X_{rms}}$ ($p = 0.004$), and higher SSDX ($p = 0.03$) compared with non-asthma subjects (Figure 3 and Table III). Subjects with HRV-wheezing illness before the third birthday also showed higher VDS ($p = 0.05$) and lower $\overline{X_{rms}}$ ($p = 0.01$), as shown in Figure 4 and Table III.

To investigate whether the imaging metrics were detecting changes in the lung that were also detectable by standard whole-lung PFTs, the adjusted PFTs were compared to asthma diagnosis and history of HRV-wheezing illness for 44 subjects in the imaging cohort. After adjusting for subject height, age, and gender, TLC in children with asthma (3.29 L, 95% confidence interval [3.13, 3.45]) was similar to those without asthma (3.26 L, 95% confidence interval [3.13, 3.40], $p = 0.78$). Indeed, PFT comparisons found significant differences only in IOS measures. Subjects with asthma had lower X5 ($p = 0.003$), higher AX ($p = 0.008$), and higher R5–R20 ($p = 0.01$); these three IOS parameters are thought to be sensitive to small airway abnormalities. No significant difference was found in R20, which is primarily determined by the resistance of the central airways. Subjects with HRV-wheezing illness before the third birthday also had significant differences for X5, AX, and R5–R20. However, spirometry and plethysmography measures did not differ significantly between groups. Other relationships between lung function and asthma diagnosis or HRV-wheezing illness are shown in Table III.

DISCUSSION

The current report describes a pilot study using novel imaging techniques in children genetically at risk for asthma development to test the hypothesis that ^3He MRI measures of ventilation and pulmonary microstructure are related to lung function and history of viral illness. The results show that the lungs of children with asthma have more and larger ventilation defects (i.e. larger VDS) and smaller lung microstructure (i.e. smaller $\overline{X_{rms}}$) relative to non-asthmatic children in this cohort. The association between asthma and ventilation defects in this pediatric population is noteworthy because ventilation defects are a known characteristic of adult asthma.^{12, 13, 31} To the authors' knowledge, this study has shown, for the first time, that such defects are present in pre-adolescent asthma subjects. Interestingly, girls as a group also had significantly higher VDS compared to boys, which is an unanticipated result that may foreshadow more pronounced decreases in lung function in girls compared to boys post-adolescence.³² Children who experienced an HRV-wheezing illness during the first three years of life also had increased VDS and smaller $\overline{X_{rms}}$ than those who did not. The association of differences in lung microstructure at age 9 or 10 years with history of wheezing in early childhood is a noteworthy finding since it potentially links a measurable lung phenotype with an early childhood risk factor. Moreover, recent studies are finding a strong link between therapeutic response and measures of small airway function in adult asthma³³ suggesting a regional bio-marker of small airways disease early in progression may be useful for monitoring long term responses to therapy.

As a measure of regional ventilation, the VDS has been linked to obstructive physiology in prior studies of asthma. In asthmatic adults, studies have observed a significant correlation between ventilation defects and both FEV₁ (% of predicted) and the ratio of FEV₁ to forced vital capacity (FVC).^{12, 14} However, in our cohort, VDS did not correlate significantly with PFT measures, and spirometry measures in the groups were similar. Previous studies have shown that spirometry is often normal in children with asthma,³⁴ and our findings suggest that regional measures of obstruction on MRI may be more sensitive indicators of pathologic changes in childhood asthma before these abnormalities are discernible using conventional spirometry. In contrast, IOS measures, such as reactance, resistance, and frequency dependence (R5–R20), were significantly different for both asthma and HRV with wheeze consistent with changes on imaging and possibly indicative of small airway differences between these groups. In addition, there was no significant correlation between $\overline{X_{rms}}$ and VDS even though both metrics were significantly different between subjects with and without asthma. The two measures are therefore likely capturing different regional components that are both aspects of the asthma phenotype evaluated in this cohort.

In the current study, $\overline{X_{rms}}$ was found to be approximately 15 μm (5%) smaller in children with asthma compared to children without asthma. The mechanism underlying this difference remains unknown. One explanation might be differences in lung inflation affecting the small airway dimensions such as air trapping or atelectasis. A decrease in small airway and alveolar dimensions is opposite to the expected trend if focal air trapping alone were the explanation. Alternatively, regional atelectasis could reduce $\overline{X_{rms}}$ in subjects with asthma. These areas should then correlate strongly with areas of ventilation defect, but VDS showed no correlation with $\overline{X_{rms}}$. We therefore speculate that dimensions of the lung microstructure of children with asthma are smaller than those of healthy children. This interpretation is further supported by significant correlations of both $\overline{X_{rms}}$ and SSDX with specific IOS measures, AX and X5 (see Table E3 in this article's Online Repository), that are known to be sensitive to peripheral airway changes. In addition, the SSDX was negatively correlated with $\overline{X_{rms}}$, indicating that children with greater heterogeneity of lung microstructure had smaller microstructural dimension on average. In contrast, studies of ADC, which is also directly related to alveolar and small airway dimensions, have shown the opposite relationship in adults.^{13, 31, 35} Clearly, further study is needed to better understand the mechanisms underlying this apparent difference between measures of lung microstructure in childhood and adult asthma, but one explanation would implicate smaller airway dimensions as predisposing children to factors leading to wheeze and airway obstruction. Alternatively, some element of peripheral airway remodeling and inflammation may already be occurring in childhood asthma. Longitudinal imaging of the same cohort of children into early adulthood is planned, which should shed light on progressive changes through puberty and adulthood.

There are several limitations to the present study, chief of which is the small sample size. This is by definition a pilot study, since to the best of the authors' knowledge it is the first time childhood asthma has been investigated systematically with the hyperpolarized noble gas MRI technique. Findings in this cohort may not reflect the general population, because all subjects in the current study had a parent with a history of asthma or respiratory allergies. In addition, to increase the chances of observing differences in the imaging studies, subjects were recruited for imaging if lung function, as determined by FEV₁, fell in the highest or lowest quartile of the entire COAST cohort. The decision to seek equal numbers of subjects who did and did not have HRV infection with MSI before the first birthday also may have biased this cohort compared to the general population of 9- and 10-year-olds.

In conclusion, significant signs of regional obstruction and structural change were observed using ³He MRI in the lungs of children with mild to moderate asthma. These imaging measurements provide evidence that childhood asthma is associated with reduced dimensions of small airways and alveolar spaces, which contrasts with findings in adults and further suggests that there are age-related differences in structural features of asthma. Moreover, the observed differences in the extent of ventilation defects between prepubescent girls and boys may be a foreshadowing for the subsequent development of physiological abnormalities during adolescence when incidence and prevalence rates for asthma undergo noticeable shifts for unknown reasons. Overall, these novel observations indicate that ³He MRI can provide new insights into patterns of regional ventilation and peripheral airway changes in asthma, and that this non-invasive technique may be useful to identify mechanisms of disease expression and progression in childhood asthma.

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Abbreviations Used

ADC	apparent diffusion coefficient
AX	reactance area (an impulse oscillometry measurement)
COAST	Childhood Origins of ASThma study
CT	x-ray computed tomography
FEV₁	forced expiratory volume in one second
FRC	functional residual capacity
HRV	human rhinovirus
I-HYPR	Iterative HighlY-constrained back-PProjection
IOS	impulse oscillometry
MRI	magnetic resonance imaging
MSI	moderate-to-severe (respiratory) illness
PFT	pulmonary function test
R5	IOS resistance at 5 Hz
R20	IOS resistance at 20 Hz
SSDX	intra-subject standard deviation of X_{rms}
TLC	total lung capacity
VDS	ventilation defect score
X5	IOS reactance at 5 Hz
X_{rms}	root-mean-square diffusion length of ^3He
$\overline{X_{rms}}$	diffusion length averaged over the full lung

Key Messages

- Greater number and size of ventilation defects were found in children with asthma.
- Measurements of ^3He diffusion indicate smaller dimensions of small airways and alveolar spaces in children with asthma.
- Noble gas MRI provides a unique window into pulmonary structure and function in childhood asthma.

Figure 1. Dynamic MRI

Selected axial and sagittal slices of the pediatric lung, taken from the breath-hold phase of the time-resolved hyperpolarized ^3He MRI series, are shown to best demonstrate ventilation defects (arrows). (A) A healthy lung with defect score 0. (B) A lung with mild defects and defect score 11. (C) A lung with several defects, some large; defect score is 21. (D) The most severely defected lung in the imaging cohort with defect score of 37.

Figure 2. Diffusion-weighted MRI

Parametric maps of X_{rms} in pediatric lungs are presented in six axial slices for four sample subjects. (A) A 10-year-old female with no wheezing illness before her third birthday who was not diagnosed with asthma. (B) A 10-year-old female with no wheezing illness before her third birthday who was diagnosed with asthma at the time of imaging. (C) A 9-year-old female who had wheezing illnesses with HRV infection in early childhood but was not diagnosed with asthma. (D) A 10-year-old female who had wheezing illnesses with HRV infection in early childhood and was diagnosed with asthma at the time of imaging.

Figure 3. Current Asthma

Subjects are grouped based on whether or not they have a diagnosis of asthma at the time of imaging. $\overline{X_{rms}}$ (A), SSDX (B), and VDS (C) are plotted with points representing measurements of individual subjects. The shaded boxes indicate the interquartile range, and the estimated median, corrected for gender and TLC, is shown as the solid line inside the box. Significance levels, which are also corrected for gender and TLC, are as follows: $p = 0.004$ for $\overline{X_{rms}}$, $p = 0.03$ for SSDX, and $p = 0.03$ for VDS.

Figure 4. Wheezing with HRV in early childhood

Subjects are grouped based on whether or not they experienced a wheezing illness with HRV infection in early childhood. $\overline{X_{rms}}$ (A), SSDX (B), and VDS (C) are plotted, and the symbols are as in Figure 3. Both $\overline{X_{rms}}$ ($p = 0.01$) and VDS ($p = 0.05$) differ between the two groups. SSDX did not differ significantly ($p = 0.33$) between the two groups. Z-scores and significance levels are corrected for gender and TLC.

Study design groups and sample sizes recruited from the COAST population for this study. MSI: moderate to severe illness.

Table 1

Study Groups (n = 43) [†]					
Group	MSI with HRV infection before age 1 year	FEV ₁ at age 8 years	subjects per group	MRI at age 9	MRI at age 10
A	Yes	Bottom quartile	11 [‡]	2 [‡]	9
B	Yes	Top quartile	14	4	10
C	No	Bottom quartile	9	7	2
D	No	Top quartile	9	2	7

[†] One additional subject was a female imaged at age 9 who had MSI with HRV infection in the first year of life and FEV₁ in the bottom quartile at age 6 but in a middle quartile at age 8. That subject was not included in this table or the analysis in Table E2 in this article's Online Repository but was included in all other analyses.

Table II
Demographic and imaging data segregated by gender

Results are presented as the mean [95% confidence interval]. Imaging metrics are adjusted for TLC.

	both genders	Female	Male	<i>p</i> (gender)
<i>n</i>	44	19	25	—
Height (cm)	139 [137, 141]	139 [136, 142]	139 [136, 141]	0.78
Weight (kg)	37 [34, 40]	38 [34, 43]	36 [32, 41]	0.58
TLC (L)	3.30 [3.16, 3.44]	3.26 [3.04, 3.48]	3.33 [3.13, 3.52]	0.69
$\overline{X}_{rms}$ (μm)	315 [310, 321]	318 [309, 327]	313 [305, 321]	0.42
SSDX (μm)	27 [24, 30]	25 [21, 30]	28 [24, 32]	0.46
VDS	8.7 [6.4, 11.5]	12.6 [8.6, 17.3]	6.2 [3.8, 9.1]	0.01
HRV wheeze	39% (17/44)	53% (10/19)	28% (7/25)	0.10
asthma diagnosis	41% (18/44)	47% (9/19)	36% (9/25)	0.45
<i>asthma subjects only:</i>				
asthma severity	10 intermittent	6 intermittent	4 intermittent	0.41
	5 mild persistent	1 mild persistent	4 mild persistent	
	3 mod. persistent	2 mod. persistent	1 mod. persistent	
aeroallergen sensitization	73% (11/15)	71% (5/7)	75% (6/8)	0.88
ICS use	56% (10/18)	56% (5/9)	56% (5/9)	1.00
LABA use	11% (2/18)	11% (1/9)	11% (1/9)	1.00
LTRA use	22% (4/18)	0% (0/9)	44% (4/9)	0.08

ICS: inhaled corticosteroid; LABA: long acting beta agonist, LTRA: leukotriene receptor antagonist. Asthma severity was determined using the guideline criteria of the National Asthma Education and Prevention Program.

Table III
Differences between subjects with asthma diagnosis or history of HRV-wheezing illness

The cohort is divided based on asthma diagnosis at the time of the MRI study and on record of HRV-wheezing illness in the first three years of life. Estimates of imaging measures and PFTs, corrected for gender and TLC, are reported with 95% confidence intervals.

	Current asthma			HRV/wheeze first three years		
	No	Yes	p	No	Yes	p
number of subjects	26	18		27	17	
number of females	10	9		9	10	
$\overline{X}_{rms}$ (μm)	323 [314, 332]	306 [297, 316]	0.004	322 [312, 332]	307 [297, 316]	0.01
SSDX (μm)	24 [18, 29]	30 [25, 36]	0.03	25 [19, 31]	29 [23, 34]	0.33
VDS	7.0 [3.8, 11.1]	12.7 [8.1, 18.3]	0.03	7.1 [3.7, 11.5]	12.5 [8.0, 18.0]	0.05
FVC (L)	2.43 [2.32, 2.53]	2.41 [2.30, 2.52]	0.75	2.39 [2.29, 2.50]	2.46 [2.35, 2.56]	0.29
FEV ₁ (L)	2.00 [1.86, 2.13]	1.95 [1.82, 2.09]	0.58	1.97 [1.83, 2.10]	2.00 [1.86, 2.13]	0.71
FEV ₁ /FVC	0.82 [0.79, 0.86]	0.81 [0.77, 0.85]	0.57	0.82 [0.78, 0.86]	0.81 [0.78, 0.85]	0.74
R5 [†]	0.62 [0.54, 0.71]	0.72 [0.63, 0.80]	0.07	0.64 [0.54, 0.73]	0.70 [0.62, 0.79]	0.20
R20 [†]	0.44 [0.38, 0.51]	0.43 [0.37, 0.50]	0.82	0.45 [0.38, 0.52]	0.42 [0.36, 0.48]	0.45
R5-R20 [†]	0.18 [0.12, 0.25]	0.28 [0.22, 0.35]	0.01	0.18 [0.11, 0.25]	0.28 [0.22, 0.35]	0.02
AX (kPa _w /L)	1.53 [1.16, 2.02]	2.40 [1.81, 3.17]	0.008	1.51 [1.13, 2.02]	2.47 [1.88, 3.25]	0.005
X5 [†]	-0.26 [-0.31, -0.21]	-0.35 [-0.40, -0.30]	0.003	-0.26 [-0.32, -0.21]	-0.35 [-0.40, -0.30]	0.01
RV/TLC	0.28 [0.25, 0.31]	0.27 [0.24, 0.31]	0.82	0.29 [0.26, 0.32]	0.26 [0.23, 0.29]	0.13

[†]Units for R5, R20, R5-R20, and X5 are kPa-s/L.