

Pulmonary ^3He magnetic resonance imaging of childhood asthma

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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 adults with asthma, but the method has not been extended to children with asthma. Measurements of regional lung ventilation and microstructure in subjects with childhood asthma could advance our understanding of disease mechanisms.

Objective: We sought to determine whether ^3He MRI in children can identify abnormalities related to the diagnosis of asthma or prior history of respiratory illness.

Methods: Forty-four children aged 9 to 10 years were recruited from a birth cohort at increased risk of asthma and allergic diseases. For each subject, a time-resolved 3-dimensional image series and a 3-dimensional diffusion-weighted image were acquired in separate breathing maneuvers. The numbers and sizes of ventilation defects were scored, and regional maps and statistics of average ^3He diffusion lengths were calculated.

Results: Children with mild-to-moderate asthma had lower average root-mean-square diffusion length ($\overline{X_{rms}}$) values

($P = .004$), increased regional SD of diffusion length values ($P = .03$), and higher defect scores ($P = .03$) than those without asthma. Children with histories of wheezing illness with rhinovirus infection before the third birthday had lower $\overline{X_{rms}}$ values ($P = .01$) and higher defect scores ($P = .05$).

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 with those seen in children without asthma. These measures are consistent with regional obstruction and smaller and more regionally variable dimensions of the peripheral airways and alveolar spaces. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: Asthma, pediatric, hyperpolarized magnetic resonance imaging, apparent diffusion coefficient

Traditional imaging modalities are not well suited for noninvasive 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 asthmatic patients. Quantitative evaluation with x-ray computed tomography (CT) has shown promise for noninvasive 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, and therefore 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 (HRVs).⁴ Increased mucus production can also lead to complete occlusion of the small airways, further leading to abnormalities in ventilation and perfusion. In preschool-aged children with recurrent wheezing, bronchial biopsy specimens have demonstrated that a number of these pathologic events are present as early as 2 to 3 years of life.⁵ On the basis of that previous work, we hypothesized that a child's lung function and prior history of viral illness 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 nonionizing radiation that has shown promise for the study of lung diseases, including emphysema, cystic fibrosis, and asthma in adults.⁶⁻¹¹ In adult asthmatic patients, ^3He MRI of the lungs has revealed spatially heterogeneous ventilation patterns caused by 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 asthmatic patients have found that the number and size of these ventilation defects correlate with asthma severity and with

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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
HRV:	Human rhinovirus
I-HYPR:	Iterative highly constrained back-projection
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:	Intrasubject SD 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

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 patients with emphysema¹⁵⁻¹⁷ and in subjects with increasing smoking history who do not yet show clinical symptoms of lung disease.¹⁸ The diffusion MRI methodology is described in more detail in the **Methods** section in this article's Online Repository at www.jacionline.org. The goal of this pilot study was to use novel imaging techniques in children genetically at risk for asthma 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 with inhaled ^3He gas was performed on 44 children aged 9 to 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 US Food and Drug Administration Investigational New Drug application number 64,687. Subjects were recruited from among the children in the ongoing Childhood Origins of Asthma (COAST) study.¹⁹ Details on recruitment of the birth cohort for the COAST study are summarized in the **Methods** section in this article's Online Repository. MRI examinations 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 FEV₁ measured at the clinical visit at age 8 years (FEV₁ $\geq 109.9\%$ of predicted value or FEV₁ $\leq 91.4\%$ of predicted value), the last year for which data on the full cohort were available when the MRI study was initiated. Predicted FEV₁ was computed based on the Eigen²⁰ criteria using family-reported ethnicity for the child. One additional subject who did not meet the FEV₁ 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 respiratory illness (MSI) before the first birthday. MSI refers only to respiratory symptoms, as explained in the **Methods** section in this article's Online

TABLE I. Study design groups and sample sizes recruited from the COAST population for this study

Study groups (n = 43)*					
Group	MSI with HRV infection before age 1 y	FEV ₁ at age 8 y	Subjects per group	MRI at age 9 y	MRI at age 10 y
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 girl imaged at age 9 years who had MSI with HRV infection in the first year of life and FEV₁ in the bottom quartile at age 6 years but in a middle quartile at age 8 years. That subject was not included in this table or in the analysis using these groups presented in this article's Online Repository but was included in all other analyses.

Repository, and is not an indication of asthma severity. Selection and recruitment of subjects were performed independently by the study statistician and nurse coordinator so that the imaging investigators remained blind 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-induced illness with wheezing before the third birthday.⁴ The effect was less significant for other viruses studied. Therefore the adjusted imaging measures were compared for the original design groups, for diagnosis of asthma concurrent with imaging, and for different histories of HRV-induced 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 when a child had symptoms of a respiratory tract infection. On the basis of 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 means of saline irrigation, and viral cause was assessed by using multiplex PCR. Additionally, the illness was classified as a wheezing illness if it met the criteria reported earlier⁴ and also listed in the **Methods** section in this article's Online Repository. At least 1 viral pathogen was identified during 90% of wheezing illnesses.⁴

Beginning at age 4 years, pulmonary function tests (PFTs), 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 resistance at 20 Hz (R20), the difference of these 2 resistances (R5–R20), reactance at 5 Hz (X5), and reactance area (AX). For subjects participating in the MRI study, lung volumes were measured by using plethysmography (Jaeger MasterScreenBody, Hoechberg, Germany), according to 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, and therefore all children were generally healthy at the time of imaging.

The criteria for asthma diagnosis were described elsewhere.⁴ Briefly, subjects were identified as having current asthma at the time of an MRI examination if they met at least 1 of the following criteria during the prior year: physician's diagnosis of asthma; use of albuterol for coughing or wheezing episodes (prescribed by physician); use of a daily controller medication; use of a step-up plan, including use of albuterol or short-term use of inhaled corticosteroids during illness; or use of prednisone for asthma exacerbation.

MRI

^3He was polarized by using 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

TABLE II. Demographic and imaging data segregated by sex

	Both sexes	Female sex	Male sex	P value (sex)
All subjects				
No.	44	19	25	—
Height (cm)	139 (137-141)	139 (136-142)	139 (136-141)	.78
Weight (kg)	37 (34-40)	38 (34-43)	36 (32-41)	.58
TLC (L)	3.30 (3.16-3.44)	3.26 (3.04-3.48)	3.33 (3.13-3.52)	.69
$\bar{X}_{rms}$ (μm)	315 (310-321)	318 (309-327)	313 (305-321)	.42
SSDX (μm)	27 (24-30)	25 (21-30)	28 (24-32)	.46
VDS	8.7 (6.4-11.5)	12.6 (8.6-17.3)	6.2 (3.8-9.1)	.01
HRV-induced wheeze	39% (17/44)	53% (10/19)	28% (7/25)	.10
Asthma diagnosis	41% (18/44)	47% (9/19)	36% (9/25)	.45
Asthmatic subjects only				
Asthma severity	10 intermittent 5 mild persistent 3 moderate persistent	6 intermittent 1 mild persistent 2 moderate persistent	4 intermittent 4 mild persistent 1 moderate persistent	.41
Aeroallergen sensitization	73% (11/15)	71% (5/7)	75% (6/8)	.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)	.08

Results are presented as means (95% CIs). Imaging metrics are adjusted for TLC. Asthma severity was determined by using the guideline criteria of the National Asthma Education and Prevention Program.

ICS, Inhaled corticosteroid; LABA, long-acting β -agonist; LTRA, leukotriene receptor antagonist.

1.5-T clinical magnetic resonance scanner (SignaHDx; GE Healthcare, Waukesha, Wis) with broadband imaging capability. Fast MRI acquisitions were used to limit breath-hold time to 15 seconds or less and to improve robustness to respiratory motion.²⁴⁻²⁶ The anoxic doses of ^3He and N_2 did not cause any adverse effects. Further details on imaging methods are presented in [Table E1](#) and in the [Methods](#) section 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. The ^3He dose was administered by a researcher who was blind 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 the 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 blind to subject identity, asthma status, medical history, and the 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 interreader repeatability (interreader intraclass correlation coefficient >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 ($\bar{X}_{rms}$) value was computed as described in the [Methods](#) section in this article's Online Repository. The lung microstructure limits the paths over which the ^3He can diffuse enabling measurement of the average dimension of small airways and alveolar spaces within each image pixel. For each subject, 2 descriptive

statistics were therefore calculated and compared with outcomes. One was the diffusion length averaged over the full lung ($\bar{X}_{rms}$), a measure of the average small-airway dimension throughout the lung.²⁸ The second measure, the within-subject SD of $\bar{X}_{rms}$ (SSDX), reflects regional variation in the average small-airway dimension across the lung.

Statistical analysis

The 3 imaging metrics (VDS, $\bar{X}_{rms}$, and SSDX values) were compared with asthma diagnosis, history of respiratory illness, sex, and measurements from PFTs. Imaging metrics were compared between groups by using linear models, which included TLC and sex covariates. Before 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 sex and calculating the standardized residuals. The resulting z scores are standardized to have a mean of 0 and an SD of 1. The associations between imaging and PFT z scores were examined by using the Pearson correlation coefficient. A 2-sided P value of less than .05 was regarded as significant.

RESULTS

Study population

Subjects' demographics are summarized in [Table II](#). Time-resolved MRI examinations were performed successfully in 43 (98%) of 44 children, and sample images are shown in [Fig 1](#). Diffusion-weighted MRI was successful in 40 (91%) of 44 children, and sample maps of the $\bar{X}_{rms}$ values are presented in [Fig 2](#). One MRI examination was unsuccessful because of a technical error, with no useful data acquired during either of the 2 imaging sequences. For 3 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 sex lead to differences in PFTs.³⁰ Indeed, imaging measures also showed sex differences, as summarized in [Table II](#). Girls had higher VDSs

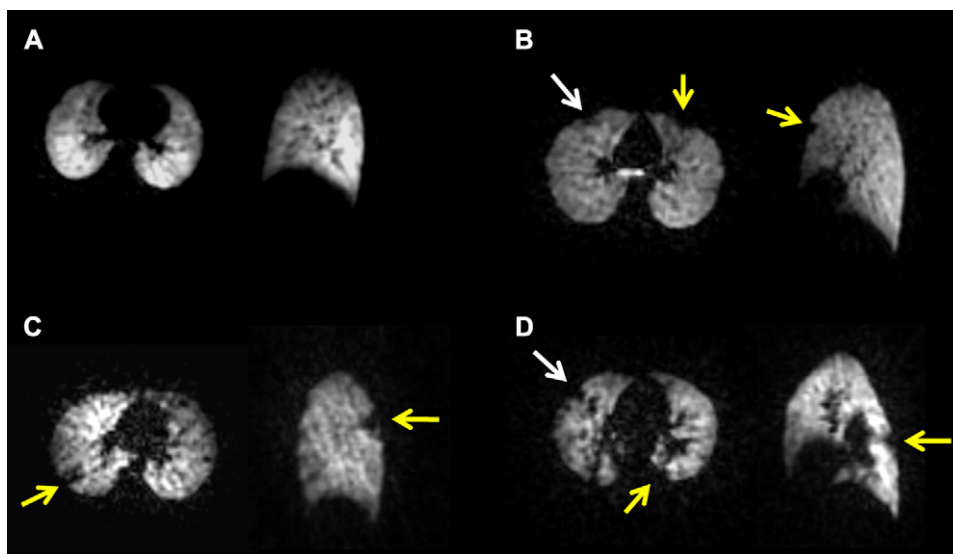


FIG 1. Dynamic MRI. Selected axial and sagittal slices of the pediatric lung taken from the breath-hold phase of the time-resolved hyperpolarized ^3He MRI series are shown to best demonstrate ventilation defects (arrows). **A**, A healthy lung with a defect score of 0. **B**, A lung with mild defects and a defect score of 11. **C**, A lung with several defects, some large; the defect score is 21. **D**, The most severely defected lung in the imaging cohort with a defect score of 37.

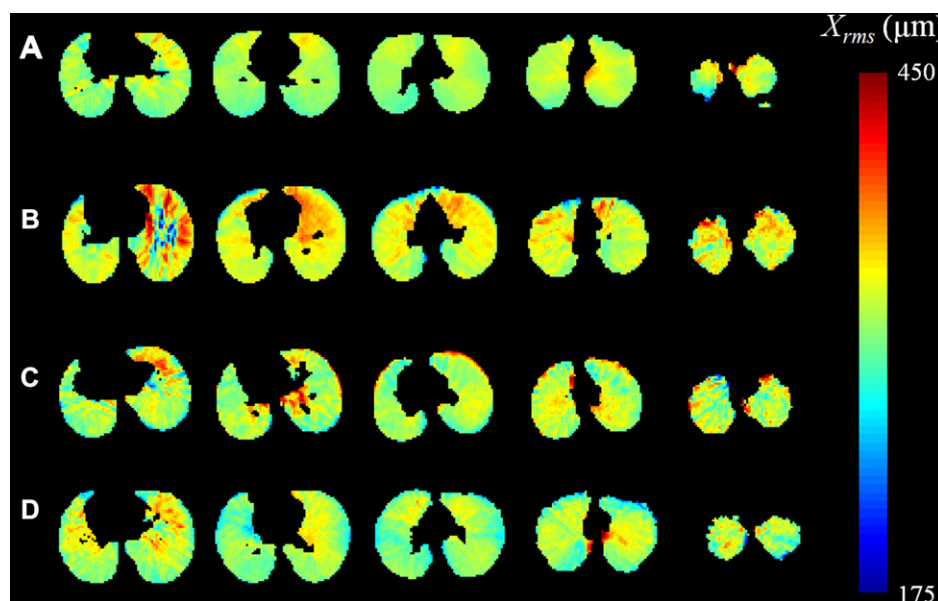


FIG 2. Diffusion-weighted MRI. Parametric maps of X_{rms} values in pediatric lungs are presented in 5 axial slices for 4 sample subjects. **A**, A 10-year-old girl with no wheezing illness before her third birthday who was not given a diagnosis of asthma. **B**, A 10-year-old girl with no wheezing illness before her third birthday who received a diagnosis of asthma at the time of imaging. **C**, A 9-year-old girl who had wheezing illnesses with HRV infection in early childhood but did not receive a diagnosis of asthma. **D**, A 10-year-old girl who had wheezing illnesses with HRV infection in early childhood and was given a diagnosis of asthma at the time of imaging.

than boys ($P = .01$), whereas $\overline{X_{rms}}$ and SSDX values were similar between the sexes. TLC was also found to be correlated with $\overline{X_{rms}}$ values ($r = +0.44$, $P = .005$) and tended to correlate with both SSDX values ($r = -0.27$, $P = .09$) and VDSs ($r = +0.26$, $P = .09$). On the basis of these findings, all subsequent comparisons were adjusted for the effects of sex and TLC by using z scores.

In comparing the z scores of the image metrics themselves, there was no significant correlation between VDSs and $\overline{X_{rms}}$ values ($r = -0.07$, $P = .65$) or SSDX values ($r = -0.05$, $P = .75$). The SSDX value was negatively correlated with the $\overline{X_{rms}}$ value ($r = -0.44$, $P = .004$), indicating increased spatial heterogeneity with smaller $\overline{X_{rms}}$ values. When comparing the original design groups, SSDX values were less in the highest quartile of

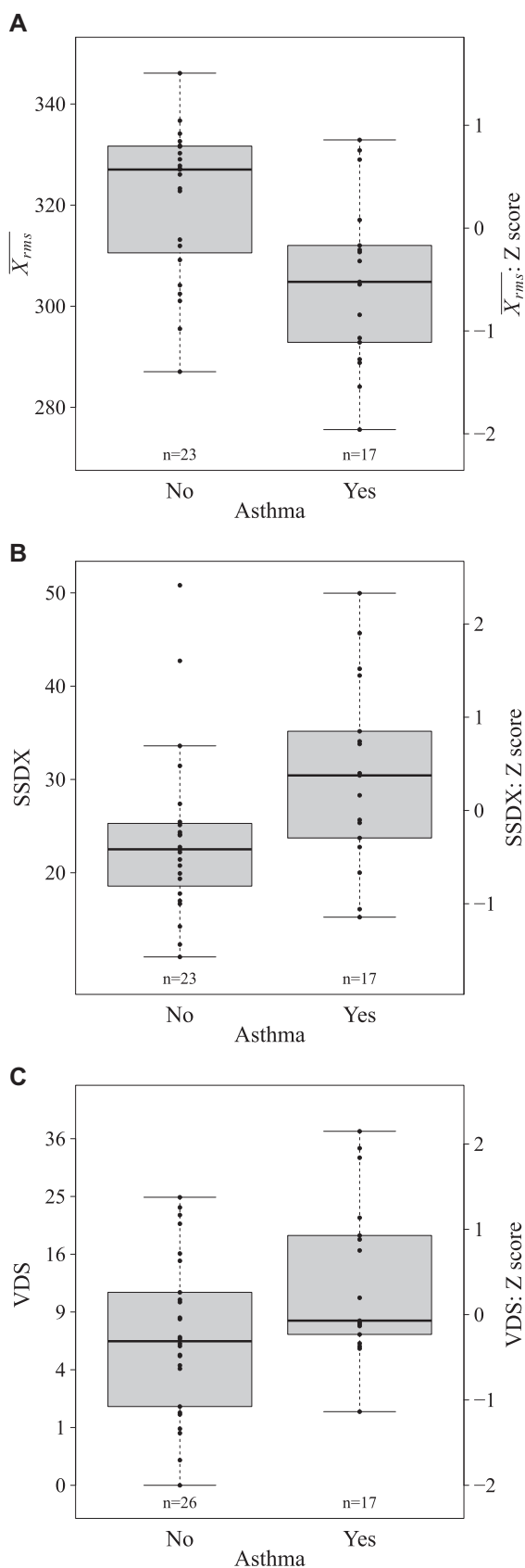


FIG 3. Current asthma. Subjects are grouped based on whether they have a diagnosis of asthma at the time of imaging. $\overline{X}_{rms}$ values (A), SSDX values (B), and VDSs (C) are plotted, with points representing measurements of

FEV₁ at age 8 years ($P = .04$), but VDSs and $\overline{X}_{rms}$ values 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 at www.jacionline.org). Further correlations between imaging metrics and PFT results are presented in the Results section in this article's Online Repository at www.jacionline.org.

Relationship of imaging to asthma and HRV-induced wheezing

Subjects given a diagnosis of asthma at the time of the MRI study had a higher VDS ($P = .03$), a lower $\overline{X}_{rms}$ value ($P = .004$), and a higher SSDX value ($P = .03$) compared with those in non-asthmatic patients (Fig 3 and Table III). Subjects with HRV-induced wheezing illness before the third birthday also showed higher VDSs ($P = .05$) and lower $\overline{X}_{rms}$ values ($P = .01$), as shown in Fig 4 and Table III.

The adjusted PFT results were compared with asthma diagnosis and history of HRV-induced wheezing illness for 44 subjects in the imaging cohort to investigate whether the imaging metrics were detecting changes in the lung that were also detectable by using standard whole-lung PFTs. After adjusting for height, age, and sex, TLC in children with asthma (3.29 L; 95% CI, 3.13-3.45 L) was similar to that seen in children without asthma (3.26 L; 95% CI, 3.13-3.40 L; $P = .78$). Indeed, PFT comparisons found significant differences only in IOS measures. Subjects with asthma had lower X5 ($P = .003$), higher AX ($P = .008$), and higher R5–R20 ($P = .01$) values; these 3 IOS parameters are thought to be sensitive to small-airway abnormalities. No significant difference was found in R20 values, which are primarily determined by the resistance of the central airways. Subjects with HRV-induced wheezing illness before the third birthday also had significant differences for X5, AX, and R5–R20 values. However, spirometric and plethysmographic measures did not differ significantly between groups. Other relationships between lung function and asthma diagnosis or HRV-induced 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 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 (ie, larger VDSs) and smaller lung microstructure (ie, smaller $\overline{X}_{rms}$ values) relative to nonasthmatic 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 preadolescent asthmatic subjects. Interestingly, girls as a group also had significantly higher VDSs compared with boys, which is an unanticipated result that might foreshadow more pronounced decreases

individual subjects. The shaded boxes indicate the interquartile range, and the estimated median, corrected for sex and TLC, is shown as the solid line inside the box. Significance levels, which are also corrected for sex and TLC, are as follows: $P = .004$ for $\overline{X}_{rms}$ values, $P = .03$ for SSDX values, and $P = .03$ for VDSs.

TABLE III. Differences between subjects with asthma diagnosis or history of HRV-induced wheezing illness

No. of subjects	Current asthma		<i>P</i> value	HRV/wheeze first 3 y		<i>P</i> value
	No 26	Yes 18		No 27	Yes 17	
No. of female subjects	10	9		9	10	
$\bar{X}_{rms}$ (μm)	323 (314 to 332)	306 (297 to 316)	.004	322 (312 to 332)	307 (297 to 316)	.01
SSDX (μm)	24 (18 to 29)	30 (25 to 36)	.03	25 (19 to 31)	29 (23 to 34)	.33
VDS	7.0 (3.8 to 11.1)	12.7 (8.1 to 18.3)	.03	7.1 (3.7 to 11.5)	12.5 (8.0 to 18.0)	.05
FVC (L)	2.43 (2.32 to 2.53)	2.41 (2.30 to 2.52)	.75	2.39 (2.29 to 2.50)	2.46 (2.35 to 2.56)	.29
FEV ₁ (L)	2.00 (1.86 to 2.13)	1.95 (1.82 to 2.09)	.58	1.97 (1.83 to 2.10)	2.00 (1.86 to 2.13)	.71
FEV ₁ /FVC ratio	0.82 (0.79 to 0.86)	0.81 (0.77 to 0.85)	.57	0.82 (0.78 to 0.86)	0.81 (0.78 to 0.85)	.74
R5 (kPa · s/L)	0.62 (0.54 to 0.71)	0.72 (0.63 to 0.80)	.07	0.64 (0.54 to 0.73)	0.70 (0.62 to 0.79)	.20
R20 (kPa · s/L)	0.44 (0.38 to 0.51)	0.43 (0.37 to 0.50)	.82	0.45 (0.38 to 0.52)	0.42 (0.36 to 0.48)	.45
R5–R20 (kPa · s/L)	0.18 (0.12 to 0.25)	0.28 (0.22 to 0.35)	.01	0.18 (0.11 to 0.25)	0.28 (0.22 to 0.35)	.02
AX (kPa/L)	1.53 (1.16 to 2.02)	2.40 (1.81 to 3.17)	.008	1.51 (1.13 to 2.02)	2.47 (1.88 to 3.25)	.005
X5 (kPa · s/L)	–0.26 (–0.31 to –0.21)	–0.35 (–0.40 to –0.30)	.003	–0.26 (–0.32 to –0.21)	–0.35 (–0.40 to –0.30)	.01
RV/TLC	0.28 (0.25 to 0.31)	0.27 (0.24 to 0.31)	.82	0.29 (0.26 to 0.32)	0.26 (0.23 to 0.29)	.13

The cohort is divided based on asthma diagnosis at the time of the MRI study and on record of HRV-induced wheezing illness in the first 3 years of life. Estimates of imaging measures and PFT results, as corrected for sex and TLC, are reported with 95% CIs. FVC, Forced vital capacity; RV, residual volume.

in lung function in girls compared with boys after adolescence.³² Children who experienced an HRV-induced wheezing illness during the first 3 years of life also had increased VDSs and smaller $\bar{X}_{rms}$ values 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 because 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-airways function in adult asthma,³³ suggesting that a regional biomarker of small-airways disease early in progression might 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 (percent predicted) and the ratio of FEV₁ to forced vital capacity.^{12,14} However, in our cohort VDSs did not correlate significantly with PFT measures, and spirometric measures in the groups were similar. Previous studies have shown that spirometric results are often normal in asthmatic children,³⁴ and our findings suggest that regional measures of obstruction on MRI might be more sensitive indicators of pathologic changes in childhood asthma before these abnormalities are discernible by using conventional spirometry. In contrast, IOS measures, such as reactance, resistance, and frequency dependence (R5–R20), were significantly different for both asthmatic subjects and subjects with HRV-induced wheezing illness, which is consistent with changes on imaging and possibly indicative of small-airway differences between these groups. In addition, there was no significant correlation between $\bar{X}_{rms}$ values and VDSs, even though both metrics were significantly different between subjects with and without asthma. Therefore the 2 measures are likely capturing different regional components that are both aspects of the asthma phenotype evaluated in this cohort.

In the current study $\bar{X}_{rms}$ values were found to be approximately 15 μm (5%) smaller in children with asthma compared with those seen in 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 $\bar{X}_{rms}$ values in asthmatic subjects. These areas should then correlate strongly with areas of ventilation defect, but VDSs showed no correlation with $\bar{X}_{rms}$ values. 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 $\bar{X}_{rms}$ and SSDX values with the specific IOS measures AX and X5 (see Table E3 in this article's Online Repository at www.jacionline.org), which are known to be sensitive to peripheral airway changes. In addition, the SSDX value was negatively correlated with the $\bar{X}_{rms}$ value, indicating that children with greater heterogeneity of lung microstructure had smaller microstructural dimension on average. In contrast, studies of the 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 might already be occurring in children with 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 because, 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 might 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, subjects were recruited for imaging if lung function, as determined based on FEV₁, was in the highest or lowest quartile of the entire COAST cohort to increase the chances of observing differences in the imaging studies. The decision to seek

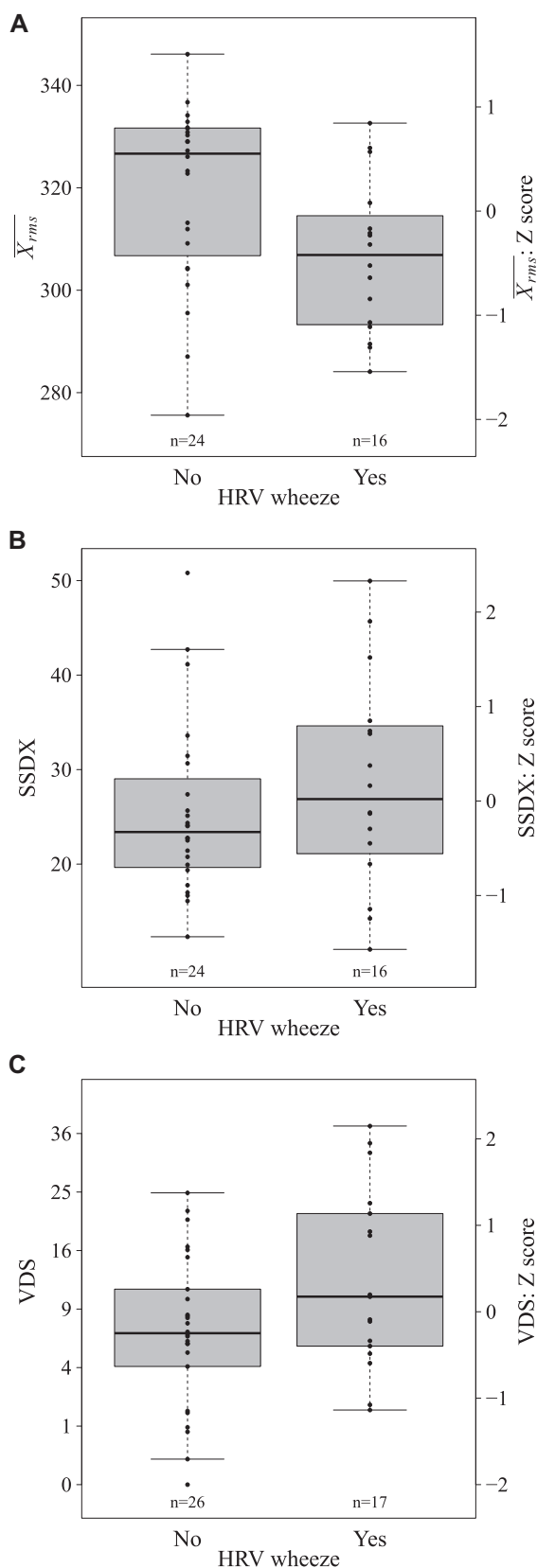


FIG 4. Wheezing with HRV in early childhood. Subjects are grouped based on whether they experienced a wheezing illness with HRV infection in early childhood. $\overline{X}_{rms}$ values (**A**), SSDX values (**B**), and VDSs (**C**) are plotted, and the symbols are as in Fig 3. Both $\overline{X}_{rms}$ values ($P = .01$) and VDSs ($P = .05$)

equal numbers of subjects who did and did not have HRV infection with MSI before the first birthday also might have biased this cohort compared with the general population of 9- and 10-year-olds.

In conclusion, significant signs of regional obstruction and structural change were observed by 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 the 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 might be a foreshadowing for the subsequent development of physiologic 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 asthmatic subjects and that this noninvasive technique might be useful to identify mechanisms of disease expression and progression in childhood asthma.

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Key messages

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

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← differ between the 2 groups. SSDX values did not differ significantly ($P = .33$) between the 2 groups. Z scores and significance levels are corrected for sex and TLC.

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METHODS

COAST recruitment and study procedures

For the COAST study, 289 children were enrolled at birth between November 1998 and May 2000.^{E1} Inclusion criteria for children enrolled in COAST included being at increased risk for allergies or asthma, which was defined by having at least 1 parent with respiratory allergies (≥ 1 positive aeroallergen skin test result) or a history of physician-diagnosed asthma.

Before a subject's third birthday, parents contacted a study coordinator when the child had respiratory symptoms. Symptom severity was evaluated by using a respiratory scorecard^{E2} with a maximum score of 31. The illness was classified as moderate if it scored between 5 and 9 inclusive and severe if the score was 10 or greater. Wheezing added 5 points to the score, and therefore all wheezing illnesses were also MSIs. Wheezing was defined as 1 or more of the following: physician-diagnosed wheezing at an office visit, an illness for which β -agonists or controller medications were prescribed, or an illness given a specific diagnosis of bronchiolitis, wheezing illness, reactive airway disease, asthma, or asthma exacerbation.^{E3}

MRI

³He gas was polarized for at least 18 hours before an imaging examination, producing approximately 30% polarization for a typical examination. A gas volume equal to 14% of the subject's TLC was prepared in a Tedlar bag (Jensen Inert Products, Coral Springs, Fla) by diluting polarized ³He with N₂. The subject inhaled the contents of the Tedlar bag through a Tygon tube (Cole-Parmer, Vernon Hills, Ill) attached to the bag. Depending on availability, the imaging coil was either a flexible quadrature coil (Medical Advances, Milwaukee, Wis) or a single-channel, elliptical, 12-leg volume coil (Rapid Biomedical, Rimpf, Germany), both of which were tuned to the ³He Larmor frequency of 48.64 MHz. Images were reconstructed by using iterative highly constrained back-projection (I-HYPR).^{E4}

Time-resolved MRI

The first image acquisition was a 3-dimensional multi-echo radial pulse sequence designed for rapid data acquisition and time-resolved imaging of respiratory dynamics.^{E5} Subjects performed a respiratory maneuver during this sequence as follows. After the imaging sequence was initiated, the subject was cued to inhale and hold the dose of ³He. After a breath hold of 7 to 10 seconds, the subject was cued to perform a rapid forced exhalation and then breathe normally. For each RF excitation pulse, 3 full echoes and 2 half echoes were acquired. Imaging and reconstruction parameters are given in Table E1. The I-HYPR algorithm^{E4} was seeded with an 8-second sliding window composite and iterated 6 times to reconstruct 1-second time frames,^{E5} with finer temporal depiction of respiratory dynamics at 0.5-second intervals obtained through view sharing to improve visualization and interpretation. VDSs were evaluated by an imaging scientist with extensive (10 years) experience with hyperpolarized gas MRI who was blinded to the subject's identity, diagnosis, and risk history.

Diffusion imaging

Diffusion MRI of inhaled noble gases is known to be sensitive to lung disease. The ADC has been shown to increase in patients with emphysema^{E6-E8} and in subjects with increasing smoking history who do not yet show clinical symptoms of lung disease.^{E9} In adult asthmatic subjects ADC is similarly increased relative to that seen in healthy control subjects, although not to the same degree as in patients with chronic obstructive pulmonary disease.^{E10} The relationship between increasing ADC and increasing small-airway dimension has been verified in a study of *ex vivo* human lungs showing remodeling of the lung structure on histology.^{E11} Improved diffusion imaging methods enable more accurate measurement of structures on the scale of airway and alveolar dimensions.^{E12,E13} In the "q-space analysis" method, the motion of all ³He atoms in the lung is measured during the diffusion-weighting time in a spectroscopic sequence, and from these data, the mean diffusion length is computed.^{E14} Recently, this technique has been used to evaluate the dimensions of pulmonary microstructure during lung development in pediatric subjects.^{E15} Studies have shown that these techniques accurately measure gas space dimensions and change predictably in healthy

normal lungs at different inflation volumes.^{E16} In the present work the q-space analysis was combined with constrained reconstruction methods to permit measurement of diffusion length within an individual image pixel.^{E16}

Diffusion-weighted MRI was performed after the time-resolved image series by using a q-space acquisition during a 15-second breath hold after inhalation of a second dose of ³He. This image sequence was a radial stack of stars with 8 phase-encoded axial slices and also used constrained reconstruction with I-HYPR. Imaging and reconstruction parameters are shown in Table E1 and have been previously described in more detail.^{E16} A trapezoidal, bipolar, diffusion-weighting gradient was applied along the subject's superior-inferior axis with the following timing parameters: diffusion time, 2.3 ms; full width of a single trapezoid, 2.3 ms; and ramp time, 0.3 ms. Eight non-zero gradients were applied, varying linearly from 0.238 G/cm to 1.9 G/cm, as described in previous work.^{E16} Although the first 7 subjects were imaged with the non-zero gradients decreasing monotonically, the remaining subjects were imaged with non-zero gradients alternating between high and low values to improve sensitivity to longer diffusion distances ($>400 \mu\text{m}$).

The procedure for reconstructing these images and computing the X_{rms} value for each pixel is also described in a previous work.^{E16} Briefly, the I-HYPR method was used to reconstruct an image for each amplitude of the diffusion gradient, with data acquired for all diffusion gradient amplitudes used as an initial constraint. These images were fit pixel by pixel to obtain X_{rms} values for each pixel. This diffusion length is a direct measurement of the motion of ³He atoms in the image pixel, specifically the SD of the atoms' displacement along the subject's superior-inferior axis during the 4.6 ms interval when the bipolar diffusion-encoding gradient is active. This distance is decreased in the lung parenchyma because the walls of airways and alveoli restrict diffusion. Because most gas volume and most ³He atoms are in the acini, X_{rms} values relate directly to a characteristic size of the structures in the distal pulmonary airways. When interpreting the data presented here, the most important point is that smaller X_{rms} values strongly indicate smaller spaces between the distal airway walls, smaller alveoli, or a combination.

The average diffusion length, $\overline{X_{rms}}$, was computed from the mean value of the child's parametric map of X_{rms} values. The measure of regional heterogeneity of the dimensions of lung microstructure was the SSDX over the child's entire parametric map. Previous studies have measured regional heterogeneity in ADC,^{E6,E7} and we use SSDX as an analogous measure of regional heterogeneity of X_{rms} values. SSDX is identified by the acronym mainly to avoid confusion with the SD of $\overline{X_{rms}}$ values over a group of children and also to emphasize that it is a measure of heterogeneity of the lung, which might have different sensitivity to lung dysfunction than that of $\overline{X_{rms}}$.

RESULTS

The original design groups were recruited from the highest and lowest quartiles of FEV₁ measured at the age 8-year clinic visit (FEV₁ $\geq 109.9\%$ of predicted value or FEV₁ $\leq 91.4\%$ of predicted value). Those 2 groups were subdivided according to whether they had HRV infection with MSI before the first birthday. SSDX values were smaller in the highest quartile of FEV₁ at age 8 years ($P = .04$), but VDSs and $\overline{X_{rms}}$ values 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 (Table E2).

Pearson correlation coefficients comparing imaging metric z scores with PFT z scores are summarized in Table E3. VDSs were not correlated with any PFT measure after adjusting for TLC and sex. The $\overline{X_{rms}}$ value, which is related to the average dimensions of the small airways and alveolar spaces, was significantly correlated with 2 measures of low-frequency airflow impedance: AX ($r = -0.36$, $P = .03$) and X5 ($r = +0.39$, $P = .02$). The SSDX value, which reflects regional heterogeneity in the dimension of the small airways and alveolar spaces, was significantly correlated with the FEV₁/forced vital capacity ratio ($r = -0.40$, $P = .01$) and also with R5 ($r = +0.51$, $P = .001$) and AX ($r = +0.36$, $P = .03$) values.

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TABLE E1. Imaging parameters for the MRI pulse sequences used in this work

	Dynamic	q-Space
Flip angle	1°	2°
Repetition time (ms)	4.4	7.2
Echo time (ms)	0.22 (first echo)	5.4
Acquisition time (s)	60	15
Matrix size	128 ³	128 × 128
Field of view	42 × 42 × 42 cm ³	42 × 42 cm ²
Slice thickness (mm)	3.3	30
Resolution (mm ³)	3.3 isotropic	3.3 × 3.3 × 30

TABLE E2. Comparison of the original design groups used for subject recruitment

FEV₁ at age 8 y	Highest		Lowest		P value (FEV₁)	P value (HRV-induced MSI)
	No	Yes	No	Yes		
HRV-induced MSI, first year						
No.	9	14	9	11		
$\bar{X}_{rms}$ (μm)	316 (302-330)	319 (304-333)	316 (298-334)	310 (297-324)	.44	.81
SSDX (μm)	25 (18-32)	22 (15-29)	30 (21-39)	30 (24-37)	.04	.72
VDS	7.8 (3.2-14.4)	11.6 (5.8-19.4)	8.3 (2.5-17.4)	8.9 (4.3-15.1)	.61	.40

Estimates of imaging metrics and 95% CIs are presented for the 4 groups used to recruit children for the MRI study. Statistical tests are adjusted for sex and TLC.

TABLE E3. Correlation of imaging measures with PFTs

	$\overline{X_{rms}}$		SSDX		VDS	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
RV/TLC	−0.08	.61	0.09	.56	0.12	.46
FEV ₁	0.17	.30	−0.27	.09	−0.06	.70
FVC	−0.01	.97	−0.06	.73	−0.14	.37
FEV ₁ /FVC ratio	0.29	.07	−0.40	.01	0.04	.81
R5	−0.29	.08	0.51	.001	−0.08	.63
R20	−0.20	.24	0.37	.03	−0.13	.42
R5−R20	−0.18	.28	0.30	.07	0.02	.90
AX	−0.36	.03	0.36	.03	0.05	.76
X5	0.39	.02	−0.47	.004	−0.17	.29

Pearson correlation coefficients for imaging measures and selected PFTs are presented. Correlation coefficients were computed from *z* scores, which were adjusted for sex and TLC.

FVC, Forced vital capacity; RV, residual volume.