

Symptom-pattern phenotype and pulmonary function in preschool wheezers

Samatha Sonnappa, MD, FRCPCH, PhD,^{a,b} Cristina M. Bastardo, MD,^a Angela Wade, PhD,^c Sejal Saglani, MRCPCH, MD,^d Sheila A. McKenzie, FRCPCH, MD,^e Andrew Bush, FRCP, FRCPCH, MD,^d and Paul Aurora, MRCPCH, PhD^{a,b} London, United Kingdom

Background: Pulmonary function in preschool wheezing phenotypes based on wheeze onset and duration and atopic status has been extensively described but has not been studied in symptom-pattern phenotypes of episodic (viral) and multiple-trigger wheeze.

Objective: We investigated whether multiple-trigger wheezers were more likely to have abnormal pulmonary function and increased fraction of exhaled nitric oxide (FeNO) than episodic (viral) wheezers and whether multiple-breath wash-out was more sensitive at detecting abnormal pulmonary function than specific airways resistance (sR_{aw}) in preschool wheezers.

Methods: FeNO, multiple-breath wash-out indices (lung clearance index [LCI] and conductive airways ventilation inhomogeneity [S_{cond}]) and sR_{aw} were measured in healthy children and those with recurrent wheeze aged 4 to 6 years. Subgroup analysis was performed according to current symptom-pattern (multiple-trigger vs episodic [viral]), atopic status (atopic vs nonatopic), and wheeze status (currently symptomatic vs asymptomatic).

Results: Seventy-two control subjects and 62 wheezers were tested. Multiple-trigger wheezers were associated with an average increase of 11% (95% CI, 7% to 18%; $P < .001$) in LCI, 211% (95% CI, 70% to 470%; $P < .001$) in S_{cond}, and 15% (95% CI, 3% to 28%; $P = .01$) in sR_{aw} compared with episodic (viral) wheezers. Pulmonary function in episodic (viral) wheezers did not differ significantly from control subjects. The presence of current atopy or wheeze was associated with higher FeNO ($P = .05$) but did not influence pulmonary function significantly. On average, LCI was abnormal in 39% (95% CI, 32% to 45%), S_{cond} was abnormal in 68% (95% CI, 61% to 74%), and sR_{aw}

was abnormal in 26% (95% CI, 16% to 35%) of multiple-trigger wheezers.

Conclusions: Multiple-trigger wheeze is associated with pulmonary function abnormalities independent of atopic and current wheeze status. S_{cond} is the most sensitive indicator of abnormal pulmonary function in preschool wheezers. (J Allergy Clin Immunol 2010;■■■■:■■■■-■■■■.)

Key words: Children, episodic (viral) wheeze, multiple-trigger wheeze, phenotype, preschool wheeze, pulmonary function, symptom-pattern

Studies suggest that most asthma originates in early childhood. Nearly 30% of children have at least 1 episode of wheezing before their third birthday, and by 6 years, the figure is almost 50%.¹ Although wheeze resolves spontaneously in some children, it persists in those at risk of asthma.¹

The natural course of preschool wheezing disorders is heterogeneous, and objective distinction between wheezing phenotypes is clinically important because etiology, pathophysiology, potential for therapy, and outcome might differ.² Phenotypes based on wheeze onset and duration (transient, persistent, and late-onset wheeze)^{1,3-7} and atopy⁸⁻¹⁰ have been validated by pulmonary function tests (PFTs) and measures of airway inflammation, such as fraction of exhaled nitric oxide (FeNO). Although these phenotypes have improved our understanding of preschool wheezing disorders and are useful in epidemiologic studies, they are of limited use in clinical practice.¹¹ Hence the use of episodic (viral) and multiple-trigger wheezing phenotypes based on symptom-pattern (also referred to as temporal phenotype) has been recommended.^{11,12} However, symptom-patterns of wheeze have not been objectively validated by PFTs or markers of airway inflammation.

Despite specific challenges posed by preschool children, a number of pulmonary function techniques, including plethysmographic specific airways resistance (sR_{aw}), have gained popularity in recent years.^{13,14} Nevertheless, such measurements might not be sensitive enough to detect early airways disease in young children.¹⁵ In preschool children with cystic fibrosis, the lung clearance index (LCI), a measure of overall ventilation inhomogeneity derived from the multiple-breath wash-out (MBW) technique, has been shown to be more sensitive than spirometry and sR_{aw} measurement in detecting pulmonary function abnormalities.¹⁵ Ventilation inhomogeneity in asthmatic subjects is clinically important because it can impair both gas exchange efficiency and the distribution of inhaled medications.^{16,17} However, it is not known whether indices of ventilation inhomogeneity in preschool wheezers are abnormal compared with those in healthy children, irrespective of whether they are more

From ^aPortex Unit: Respiratory Medicine and Physiology and ^bthe Department of Epidemiology and Biostatistics, UCL Institute of Child Health; ^cthe Department of Respiratory Medicine, Great Ormond Street Hospital for Children NHS Trust; ^dthe Department of Paediatric Respiratory Medicine, Royal Brompton Hospital and Imperial College; and ^ethe Department of Paediatric Respiratory Medicine, Royal London Hospital.

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Reprint requests: Samatha Sonnappa, MD, FRCPCH, PhD, Portex Unit: Respiratory Medicine and Physiology, UCL Institute of Child Health and Great Ormond Street Hospital for Children, 30 Guilford St, London WC1N 1EH, United Kingdom.

E-mail: s.sonnappa@ich.ucl.ac.uk.

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Abbreviations used

BDR:	Bronchodilator reversibility
FeNO:	Fraction of exhaled nitric oxide
FRC:	Functional residual capacity
ICS:	Inhaled corticosteroid
LCI:	Lung clearance index
MBW:	Multiple-breath wash-out
PFT:	Pulmonary function test
S _{acin} :	Acinar airways ventilation inhomogeneity
S _{cond} :	Conductive airways ventilation inhomogeneity
SPT:	Skin prick test
sR _{aw} :	Specific airways resistance

sensitive in detecting pulmonary function abnormalities than conventional PFTs and whether symptom-pattern phenotypes of preschool wheeze are associated with abnormal pulmonary function.

We tested the hypothesis that preschool children with multiple-trigger wheeze were more likely to have abnormal pulmonary function and airway inflammation (by using FeNO as a surrogate) compared with episodic (viral) wheezers and healthy control subjects and that MBW indices were more sensitive at detecting pulmonary function abnormalities than sR_{aw} in preschool wheezers.

METHODS

This prospective cross-sectional study was conducted at the UCL Institute of Child Health, London, United Kingdom. The Joint UCL/UCLH Ethics Committees and the local hospital ethics committees approved the study. Parents provided informed written consent for their children to participate.

Subjects

Preschool children with wheeze. Children aged 4 to 6 years with physician-diagnosed recurrent wheeze (defined as >3 episodes in 12 months) before age 3 years (irrespective of current wheezing status) were included. Children with wheeze were recruited from a cohort of preschool wheezers previously studied at the Royal Brompton Hospital¹⁸ and from outpatient clinics at Royal London Hospital and Great Ormond Street Hospital for Children. Children with radiologically documented lower respiratory tract infection, ventilation or oxygen supplementation in the neonatal period, and congenital cardiac disease surgically repaired or requiring medical therapy and those who were born before 36 weeks' gestation and small for gestational age were excluded. PFTs were performed when children were well (ie, no clinical evidence of upper respiratory tract infection and no acute exacerbation in the previous 3 weeks). In addition, parents were requested to withhold short-acting bronchodilators for 8 hours and long-acting bronchodilators for 24 hours before PFTs.

Healthy control subjects. Healthy control subjects were recruited from 2 sources: (1) children previously enrolled as infants in an epidemiologic study at the Institute of Child Health who were mainly of white origin^{19,20} and (2) children from the community, including friends or siblings of children with wheeze, so that the healthy control group reflected the ethnic diversity of the wheezers. Children were ineligible if they had been hospitalized for any respiratory illness (eg, croup, pneumonia, and bronchiolitis), had physician-diagnosed asthma, were currently using inhaled bronchodilators, or had ever used inhaled steroids. Other exclusion criteria were similar to those of the wheezing group.

Assessments

All children had anthropometric measurements and a clinical respiratory examination to ensure the absence of acute wheeze or upper respiratory tract

infection. Baseline FeNO values, MBW indices (LCI, conductive airways inhomogeneity [S_{cond}], acinar airways inhomogeneity [S_{acin}], and functional residual capacity [FRC]), and sR_{aw} were measured in all subjects in that order. In the wheezers only, bronchodilator reversibility (BDR) was assessed by measuring MBW and sR_{aw} 20 minutes after administration of 200 µg of salbutamol through a spacer. Full reversibility was defined as pulmonary function reverting to normal after bronchodilator administration (ie, postbronchodilator MBW indices and sR_{aw} significantly better than baseline values and not significantly different from the baseline values in healthy control subjects). Part reversibility was defined as postbronchodilator MBW indices and sR_{aw} being significantly better than baseline values but significantly worse than baseline values in healthy control subjects. Atopic sensitization (skin prick tests [SPTs] to house dust mite, cat, dog, grass, tree, and *Aspergillus fumigatus* [Soluprick SQ; ALK-Abelló A/S, Horsholm, Denmark]) was ascertained in all participants; sensitization was defined as a wheal at least 3 mm greater than that elicited by the negative control.

FeNO values were measured at an expiratory flow of 50 mL/s by using the single-breath online method according to American Thoracic Society guidelines,²¹ with computerized equipment and a chemiluminescence EcoMedics AG analyzer CLD 88 (EcoMedics, Durten, Switzerland). MBW was performed as previously described in preschool children.^{13,15} Sulfa hexafluoride was the inert marker gas used for calculation of gas-mixing indices reported in this study, as measured with a respiratory mass spectrometer (AMIS 2000; Innovision A/S, Odense, Denmark). LCI was calculated by dividing the cumulative expired volume by the FRC, and S_{cond} and S_{acin} were estimated by calculating phase III slopes, as previously described.²² The mean LCI, S_{cond}, S_{acin}, and FRC values from 3 technically acceptable wash-outs are reported. sR_{aw} was measured with a constant-volume body plethysmograph (Master Screen Body Plethysmograph, version 5; VIASYS Healthcare, Hochberg, Germany). Children sat alone in the plethysmograph wearing a nose clip. They were guided to breathe at a rate of 30 to 45 breaths per minute through the mouthpiece; 3 trials of 10 loops were recorded. Results were excluded if fewer than 5 technically acceptable loops were obtained. The mean total sR_{aw} values from the 3 trials are reported.

All wheezers were categorized according to the following:

1. Current symptom-pattern (episodic [viral] or multiple-trigger wheeze). Episodic (viral) wheezers were defined as those children who wheezed only with discrete viral respiratory tract infections and were asymptomatic between episodes. Multiple-trigger wheezers were defined as those who wheezed with viral respiratory tract infections but were also symptomatic between episodes with other triggers, such as dust allergy, tobacco smoke, exercise, and cold air.¹¹
2. Current atopic status (atopic: positive SPT response, current eczema, or both; nonatopic: negative SPT response and no eczema).
3. Presence or absence of wheeze in the previous 12 months. Those with at least 1 wheezing episode were defined as currently symptomatic and those without wheeze as currently asymptomatic.

Healthy control subjects were compared with all wheezers, and subgroup analysis was performed according to the phenotypes described above.

Statistical analyses

The study was powered to detect group differences between episodic (viral) and multiple-trigger wheezers, with MBW as the primary outcome. It was assumed from our previous studies that body size might account for 20% to 40% of the MBW indices' variability, particularly LCI and FRC.²³ Furthermore, ethnicity is considered an independent predictor of pulmonary function as differences in pulmonary function between Asian and white children persist even after correction for body size.^{24,25} A sample size of 56 subjects for each ethnic group (28 in each group) would be sufficient to detect an additional 10% variability in MBW indices caused by disease, with at least 80% power at the 5% significance level.²⁶

Data are presented as geometric means (95% CIs) or medians (interquartile ranges). Baseline characteristics of healthy control subjects and wheezers were compared by using χ^2 , Mann-Whitney *U*, or *t* tests, as appropriate. Demographic differences and unadjusted FeNO values and pulmonary

TABLE I. Baseline characteristics, FeNO levels, and pulmonary function of healthy control subjects and episodic (viral) and multiple-trigger wheezers

Parameter	Healthy control subjects (n = 72)	Episodic (viral) wheezer (n = 28)	Multiple-trigger wheezer (n = 34)	Kruskal-Wallis P value
Age (y)	5.5 (5.1-6.2)	4.8 (4.5-5.7)	5.1 (4.7-5.8)	.003
Weight (kg)	19.4 (17.7-22.3)	19 (17.3-20.9)	17.8 (17-23)	.35
Height (cm)	110.8 (108-114.2)	109.9 (107-114.3)	109.1 (105-113.6)	.12
Sex (male/female)	37/35	16/12	23/11	.29
Gestation (wk)	40 (39-40)	40 (39-40)	40 (39-40)	.68
Birth weight (kg)	3.24 (2.9-3.57)	3.17 (2.87-3.57)	3.04 (2.8-3.51)	.49
Atopy, no. (%)	15 (21)	16 (57)	23 (68)	<.001
Current ICS treatment, no. (%)	NA	8 (29)	25 (74)	NA
Exacerbations in last 12 mo	NA	2 (range, 0-4)	4 (range, 0-5)	NA
FeNO (ppb)	4.8 (4-5.8)	6.6 (4.6-9.5)	9.5 (6.9-13)	.002
LCI	6.6 (6.5-6.7)	6.7 (6.5-6.9)	7.4 (7.1-7.8)	<.001
S _{cond}	0.010 (0.007-0.014)	0.014 (0.009-0.023)	0.042 (0.030-0.058)	<.001
S _{acin}	0.042 (0.035-0.051)	0.050 (0.039-0.064)	0.047 (0.033-0.066)	.33
FRC (L)	0.73 (0.70-0.77)	0.67 (0.62-0.73)	0.73 (0.68-0.8)	.25
sR _{aw} (kPa.s)	1.03 (0.98-1.08)	1.1 (1-1.1)	1.2 (1.1-1.3)	.02

Subjects' characteristics are presented as medians (interquartile ranges), unless otherwise stated. FeNO and pulmonary function values are presented as geometric means (95% CIs). NA, Not applicable.

function results between healthy control subjects and the subgroups of episodic (viral) and multiple-trigger, nonatopic and atopic, and currently asymptomatic and symptomatic were compared by using the Kruskal-Wallis test (or the χ^2 test, as appropriate), followed by Mann-Whitney *U* tests with the Bonferroni correction.

Multivariable linear regression was used to compare the differences in pulmonary function between wheezers and healthy control subjects and between wheezing subgroups and healthy control subjects after adjustment for the potential confounders of age, sex, ethnicity, current and birth weight, height, gestational age, exposure to cigarette smoke (antenatal and current), atopy, and current inhaled steroid therapy. Wheeze, birth and current weight, age, and height were included in all the models, whereas other variables were retained only if they made a statistically significant contribution ($P < .05$). Because of skewness, the outcome variables were logged, and model coefficients were exponentiated to provide the multiplicative effect of the presence of the factor represented by the predictor variable: multiple-trigger versus episodic (viral) wheezer, atopic versus nonatopic, and currently symptomatic versus asymptomatic.

Upper limits of normality, defined as mean + 1.96 SD, were calculated for all indices from healthy control data and are presented with 95% confidence limits to show imprecision caused by limited sample size. Wheezers were compared with these limits, and abnormality was defined as a value above the upper limit of normality. Wheezers were also categorized as abnormal or not by using the confidence limits of the upper limit of normality to see whether using these extremes altered the interpretation of results.

Receiver operating characteristic curves were calculated to measure and compare the discriminatory power of MBW indices and sR_{aw} for differentiating wheezers from healthy control subjects and episodic (viral) from multiple-trigger wheezers.

Mean differences before and after BDR are presented with 95% confidence limits and compared by using paired *t* tests. The postbronchodilator measurements in the wheezers were compared with the baseline measurements in healthy control subjects by using Mann-Whitney *U* tests to ascertain full or partial reversibility.

All analyses were performed with SPSS software for Windows (version 15; SPSS, Inc, Chicago, Ill). Graphs were created with GraphPad Prism (version 5; GraphPad Software, San Diego, Calif).

RESULTS

One hundred thirty-four children were recruited (see Table E1 in this article's Online Repository at www.jacionline.org). The

distribution of sexes and ethnic groups was similar in the wheezers and healthy control subjects. A physician had previously assessed 58 of the 62 wheezers when acutely unwell and confirmed the presence of wheeze. Wheezers as a group were significantly younger and shorter, and more were atopic, with significantly higher FeNO, LCI, S_{cond}, and sR_{aw} values than healthy control subjects (see Tables E1 and E2 in this article's Online Repository at www.jacionline.org).

Episodic (viral) versus multiple-trigger wheezers

Episodic (viral) wheezers were significantly younger than the healthy control subjects ($P < .005$), but there were no significant differences in the demographic variables between current episodic (viral) and multiple-trigger wheezers after Bonferroni correction (Table I). However, significantly more multiple-trigger wheezers were currently using inhaled corticosteroids (ICSs; $P < .001$) and had significantly more exacerbations than episodic (viral) wheezers ($P = .009$, Table I). Multiple-trigger wheezers had significantly higher unadjusted LCI ($P < .001$; $P < .005$), S_{cond} ($P < .001$; $P < .001$), and sR_{aw} ($P < .005$; $P < .05$) values than healthy control subjects and episodic (viral) wheezers, respectively, and significantly higher unadjusted FeNO values ($P < .005$) than healthy control subjects after Bonferroni correction (Table I and Fig 1). However, after taking into account that the child was a wheezer and adjusting for atopy and current symptoms status, multiple-trigger wheeze was the patient characteristic most significantly associated with higher LCI, S_{cond}, and sR_{aw} values. There was a trend for multiple-trigger wheeze to be associated with higher FRC values, but there was no significant variability in FeNO and S_{acin} values (Table II).

Nonatopic versus atopic wheezers

Atopic wheezers were significantly younger than the healthy control subjects ($P < .005$), but there were no significant differences in the demographic variables between nonatopic and atopic wheezers after Bonferroni correction (see Table E3 in this article's Online Repository at www.jacionline.org). Atopic wheezers

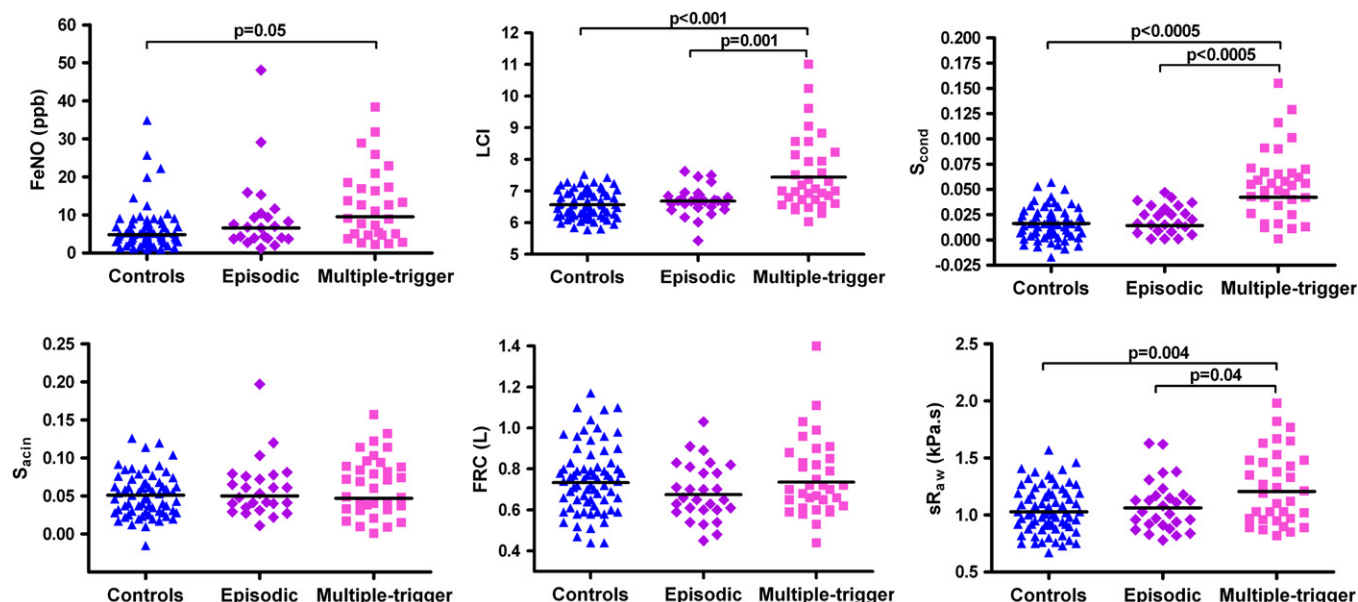


FIG 1. Comparison of FeNO values, MBW indices, and sR_{aw} among healthy control subjects and current episodic (viral) and multiple-trigger wheezers. Note that multiple-trigger wheezers have significantly higher LCI, S_{cond} , and sR_{aw} values compared with healthy children and episodic (viral) wheezers. There is no difference between episodic (viral) wheezers and healthy children for any of the outcome measures.

had significantly higher unadjusted FeNO ($P < .001$), LCI ($P < .001$), and S_{cond} ($P < .001$) values than healthy control subjects after Bonferroni correction (see Table E3). However, there was no significant difference between nonatopic and atopic wheezers or between nonatopic wheezers and healthy control subjects after Bonferroni correction. After taking into account that the child was a wheezer and adjusting for multiple-trigger and currently symptomatic wheeze, atopic wheeze was not significantly associated with abnormal pulmonary function but was associated with significantly higher FeNO values (Table II).

Currently asymptomatic versus symptomatic wheezers

Both currently asymptomatic ($P = .005$) and symptomatic ($P = .006$) wheezers were significantly younger than healthy control subjects, but there were no significant differences in the demographic variables between currently asymptomatic and symptomatic wheezers after Bonferroni correction (see Table E4 in this article's Online Repository at www.jacionline.org). Currently symptomatic wheezers had significantly higher unadjusted FeNO ($P < .001$), LCI ($P < .001$), and S_{cond} ($P < .001$) values than healthy control subjects after Bonferroni correction (see Table E4). Of interest, although there was no difference between currently asymptomatic wheezers and healthy control subjects for most of the pulmonary function parameters, the asymptomatic wheezers had significantly higher S_{acin} values than healthy control subjects ($P = .04$, Table II and see Table E4) after Bonferroni correction. However, there were no significant differences in FeNO or pulmonary function values between currently asymptomatic and symptomatic wheezers. After taking into account that the child was a wheezer and adjusting for multiple-trigger and atopic wheeze, currently symptomatic wheeze was not significantly associated with abnormal pulmonary function but was associated with significantly higher FeNO values (Table II).

Relative sensitivity and specificity of MBW indices and sR_{aw} in differentiating wheezers from healthy control subjects and episodic (viral) from multiple-trigger wheezers

The upper limits of normality (upper 95% confidence limits) for LCI were determined as 7.42 (7.25-7.59), S_{cond} 0.045 (0.039-0.052), and sR_{aw} 1.44 kPa.s (1.36-1.52 kPa.s) from healthy control subjects studied. From these limits of normality and upper 95% confidence limits, among all wheezers, LCI was found to be abnormal in 16 (12, 18) of 62 wheezers (26% [19% to 29%]), S_{cond} in 22 (19, 26) of 60 wheezers (37% [33% to 43%]), and sR_{aw} in 12 (9, 16) of 62 wheezers (19% [15% to 26%]).

In current multiple-trigger wheezers LCI was abnormal in 12 (10, 14) of 31 children (39% [32% to 45%]), S_{cond} in 21 (19, 23) of 31 children (68% [61% to 74%]), and sR_{aw} in 8 (5, 11) of 34 children (26% [16% to 35%], Fig 2). Nearly all wheezers with abnormal LCI and sR_{aw} values had abnormal or near-abnormal S_{cond} values, suggesting that S_{cond} was the most predictive variable among the PFTs measured. The sensitivity and specificity of LCI, S_{cond} , and sR_{aw} values assessed by using receiver operating characteristic curves for discriminating wheezers from healthy control subjects and multiple-trigger wheezers from episodic (viral) wheezers are presented in Tables E5 and E6 (available in this article's Online Repository at www.jacionline.org). S_{cond} was the most sensitive indicator of abnormal pulmonary function in wheezers, particularly multiple-trigger wheezers.

BDR assessment

BDR was assessed in all 62 wheezers, of whom 61 completed the protocol successfully. Analysis according to current symptom-pattern phenotype is summarized in Table III. In multiple-trigger wheezers significant BDR was seen with LCI, S_{cond} , and sR_{aw} . However, only part reversibility was seen with LCI and S_{cond} .

TABLE II. Multiple linear regression analysis showing the relationship between FeNO and pulmonary function values with wheeze and wheezing categories

Outcome	Wheeze and wheezing categories	Adjusted coefficients* (95% CI)	P value	R ² for model
FeNO	Wheeze	0.7 (0.4-1.4)	.35	0.22
	Atopic	1.4 (1-1.9)	.05	
	Multiple-trigger wheeze	1.3 (0.8-2)	.23	
	Currently symptomatic	2 (1-3.9)	.05	
LCI	Wheeze	1 (0.9-1.1)	.71	0.30
	Atopic	1 (1-1.1)	.26	
	Multiple-trigger wheeze	1.1 (1.1-1.2)	<.001	
	Currently symptomatic	1 (0.9-1)	.48	
S _{cond}	Wheeze	1.3 (0.5-3.1)	.61	0.28
	Atopic	1.3 (0.8-2.1)	.24	
	Multiple-trigger wheeze	3.1 (1.7-5.7)	<.001	
	Currently symptomatic	1 (0.4-2.4)	.95	
S _{acin}	Wheeze	2.0 (1.1-3.8)	.03	0.06
	Atopic	1.2 (0.8-1.6)	.38	
	Multiple-trigger wheeze	0.8 (0.6-1.5)	.89	
	Currently symptomatic	0.5 (0.3-1)	.04	
FRC	Wheeze	1 (0.9-1.1)	.71	0.46
	Atopic	1 (1-1.1)	.53	
	Multiple-trigger wheeze	1.1 (1-1.2)	.07	
	Currently symptomatic	1 (0.9-1.1)	.99	
sR _{aw}	Wheeze	1.2 (1.0-1.4)	.03	0.16
	Atopic	1 (0.9-1)	.27	
	Multiple-trigger wheeze	1.1 (1-1.3)	.01	
	Currently symptomatic	0.9 (0.8-1)	.12	

*All models were adjusted for age, birth and current weight, height, and sex. The coefficients are exponentiated and represent the multiplicative effect (95% CIs) of the predictor variable on the outcome.

whereas full reversibility was seen with sR_{aw} (see Fig E1 in this article's Online Repository at www.jacionline.org). In episodic (viral) wheezers, although baseline measurements were normal, significant BDR was seen with FRC and sR_{aw}.

DISCUSSION

This study for the first time externally validates the hitherto strictly clinical concept of episodic (viral) and multiple-trigger wheeze. Multiple-trigger wheeze is associated with abnormal pulmonary function, whereas episodic (viral) wheeze is not. The symptom-pattern phenotype of preschool multiple-trigger wheeze is the patient characteristic most significantly associated with abnormal pulmonary function independent of atopic and current symptom status. In preschool wheezers, particularly multiple-trigger wheezers, an abnormal S_{cond} value is the most sensitive indicator of airways disease, and abnormal MBW indices are only partly acutely reversible after bronchodilator administration in multiple-trigger wheezers.

The Tucson group showed that both transient and persistent wheezers had abnormal pulmonary function at age 6 years.⁵ In our study, although the currently symptomatic wheezers had significantly higher FeNO, LCI, and S_{cond} values than healthy control

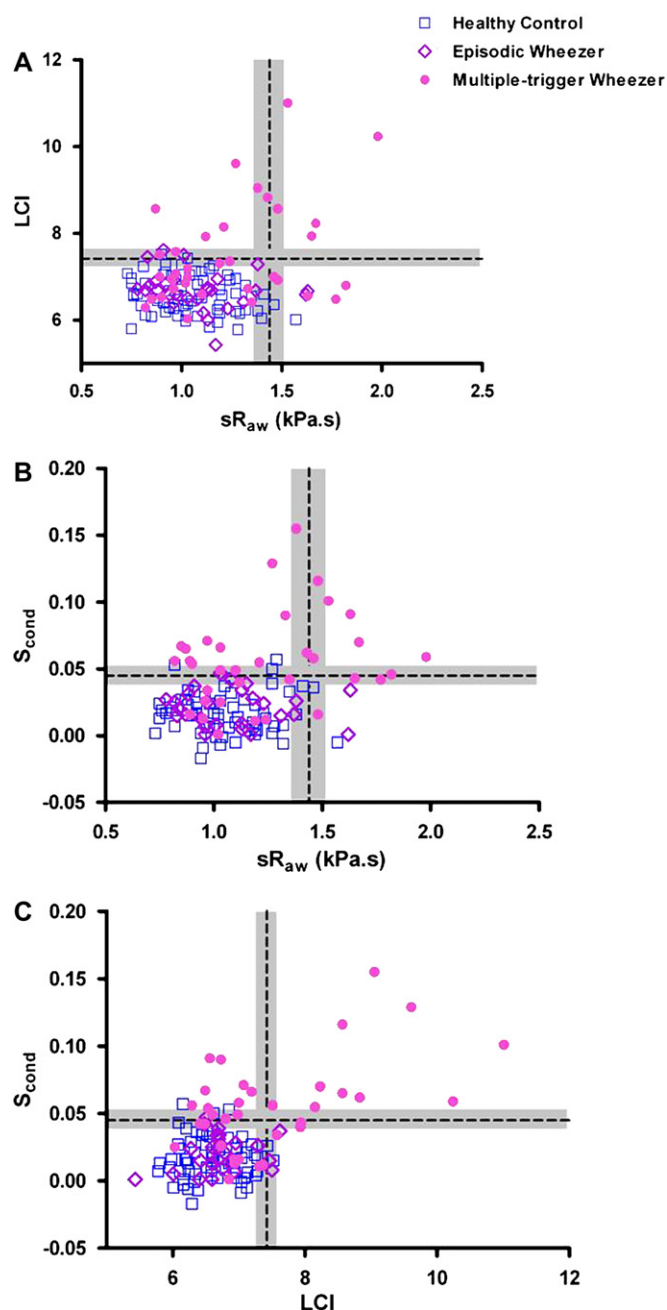


FIG 2. LCI and S_{cond} plotted against sR_{aw} and S_{cond} plotted against LCI. **A**, LCI plotted against sR_{aw}. **B**, S_{cond} plotted against sR_{aw}. **C**, S_{cond} plotted against LCI. Broken lines represent estimated upper 95% limits of normality calculated as the mean + 1.96 SD (7.42 for LCI, 0.045 for S_{cond}, and 1.44 kPa/s for sR_{aw}) based on data from healthy control subjects in this study. The gray shaded areas around the broken lines represent the 95% confidence limits for the estimated upper 95% limits of normality.

subjects, there was no difference between currently asymptomatic and symptomatic wheezers. Of interest, the currently asymptomatic wheezers demonstrated significantly higher S_{acin} values compared with those seen in healthy control subjects, although there was no difference compared with those seen in currently symptomatic wheezers. It is difficult to explain this seemingly counterintuitive finding, which could have occurred by chance. It is often assumed that the terms transient and episodic (viral) and persistent

TABLE III. Comparison of BDR according to symptom-pattern phenotype

Outcome	Episodic (viral) wheezers (n = 21)				Multiple-trigger wheezers (n = 31)			
	Baseline GM (95% CI)	Postbronchodilator GM (95% CI)	Mean difference (95% CI)	P value	Baseline GM (95% CI)	Postbronchodilator GM (95% CI)	Mean difference (95% CI)	P value
LCI	6.7 (6.5 to 6.9)	6.8 (6.6 to 7.1)	−0.16 (−0.35 to 0.03)	.09	7.4 (7.1 to 7.8)	7.2 (6.9 to 7.5)	0.28 (0.01 to 0.56)	.04
S _{cond}	0.014 (0.009 to 0.023)	0.014 (0.009 to 0.024)	−0.002 (−0.011 to 0.006)	.57	0.042 (0.030 to 0.058)	0.021 (0.014 to 0.032)	0.021 (0.012 to 0.031)	<.001
S _{acin}	0.050 (0.039 to 0.064)	0.035 (0.024 to 0.051)	0.015 (−0.001 to 0.030)	.07	0.047 (0.033 to 0.066)	0.046 (0.033 to 0.064)	−0.000 (−0.017 to 0.018)	.99
FRC (L)	0.67 (0.62 to 0.73)	0.64 (0.59 to 0.69)	0.04 (−0.00 to 0.07)	.05	0.73 (0.68 to 0.8)	0.71 (0.66 to 0.77)	0.02 (−0.00 to 0.05)	.08
sR _{aw} (kPa.s)	1.1 (1 to 1.1)	0.91 (0.83 to 0.98)	0.15 (0.09 to 0.21)	<.001	1.2 (1.1 to 1.3)	0.99 (0.91 to 1.08)	0.22 (0.15 to 0.29)	<.001

GM, Geometric mean.

and multiple-trigger wheeze can be used interchangeably, but there is no evidence for this. Episodic (viral) wheeze can persist into midchildhood, and multiple-trigger wheeze can abate before school age. The Tucson study did not categorize children into episodic (viral) and multiple-trigger wheeze groups, and it is likely that the Tucson epidemiologic categories of transient and persistent wheezers each contained a mix of episodic (viral) and multiple-trigger wheezers, which might be the reason that both groups had abnormalities of pulmonary function at age 6 years. Indeed, our findings that multiple-trigger but not episodic (viral) wheezers have abnormalities of pulmonary function underscores that these categories are not synonymous with persistent and transient wheeze, and the 2 classifications should not be confused.

Our findings of the greater discriminative power of multiple-trigger wheeze independent of atopic and current wheeze status have been confirmed by using pathologic studies in older children. Turato et al⁹ showed that inflammatory and structural changes characteristic of asthma are present to a similar degree in nonatopic and atopic children with multiple-trigger wheeze at a median age of 5 years (range, 2–15 years). It is interesting that although atopic wheeze is associated with significantly higher FeNO, LCI, and S_{cond} values, which is in agreement with other studies,⁸ atopy *per se* did not significantly influence pulmonary function after adjusting for multiple-trigger wheeze. Furthermore, in a recent meta-analysis the presence of atopy did not predict the response to ICSs in preschool wheezers.²⁷

Ventilation inhomogeneity detected by means of MBW is increasingly being recognized as a more sensitive measure of early airways disease in young children.¹⁵ Studies in older children and adults report that even in patients with mild asthma, the most consistent pattern of ventilation inhomogeneity is in the conducting airways.^{28–31} This is consistent with our findings, which show that conductive airways ventilation inhomogeneity is demonstrable at a median age of 4.9 years in preschool children with recurrent wheeze, particularly multiple-trigger wheeze. Moreover, S_{cond} best differentiated multiple-trigger wheezers from episodic (viral) wheezers and healthy control subjects. A recent study in school-aged asthmatic subjects also showed evidence of overall and conducting airways inhomogeneity, but the magnitude of abnormality in S_{cond} was not to the same extent as the other studies.³² The authors speculated this to be due to poorer control or longer duration of asthma in the subjects recruited to the other studies. S_{cond} is an independent index of ventilation inhomogeneity and represents inhomogeneity in the conducting airways (approximately airway generations 1–15), where convection dominates gas transport. It is clear from our results that S_{cond} is a more sensitive marker of abnormal airway function in preschool wheezers than either LCI or sR_{aw}. Our study did not show significant acinar airways inhomogeneity in the whole group of

wheezers or the subgroup of multiple-trigger wheezers. Similarly, the absence of acinar airways involvement has also been described in older children and adults with mild asthma.^{28,30,32}

Our BDR data imply an abnormality in the conductive zone of the airways that is not completely bronchodilator reversible, at least acutely, in multiple-trigger wheezers. This finding is strikingly similar to that reported by Verbanck et al,³⁰ who showed that conductive airways ventilation inhomogeneity in adults with mild asthma was nonreversible and was associated with a deficit in midexpiratory flows. It is speculated that persistent airflow limitation occurs as a result of structural changes caused by airway remodeling, but whether the lack of reversibility represents a progressive process of airway inflammation and remodeling or merely a failure of delivery of adequate doses of bronchodilator distally is unclear.^{33–35}

Our study has several limitations that need to be taken into account when interpreting our findings. The main inclusion criterion for wheezers was physician-diagnosed recurrent wheeze before age 3 years because we also wanted to explore whether pulmonary function would be abnormal in those without symptoms for more than 12 months. Unfortunately, this led to an imbalance in the final subgroupings. Nonetheless, our *a priori* sample size for comparison between episodic (viral) and multiple-trigger wheezers was met. Physicians usually rely on parental reports of wheeze, and it is known that parental interpretation of wheeze can vary from that of physicians.^{36,37} However, the accuracy of reporting wheeze increased with increasing frequency and severity of wheeze,³⁷ and all wheezers in this study had recurrent wheeze. In addition, in our study a physician previously confirmed wheeze during an acute episode in nearly all wheezers (94%). A further weakness is that late-onset wheezers (wheeze onset after age 3 years) were excluded, and pulmonary function in this subgroup was not determined. A significant number of wheezers were receiving ICSs (53%), which might influence the results, particularly FeNO values. However, because current multiple-trigger, currently symptomatic, and atopic wheezers were more likely to receive ICSs, this should have masked the differences rather than *vice versa*. The main outcome of interest was ventilation inhomogeneity, and significant differences were found between all wheezers and healthy control subjects and between episodic (viral) and multiple-trigger wheezers, irrespective of atopic status, current wheeze, or steroid therapy status. It might be argued that the study was not adequately powered to detect differences in FeNO and sR_{aw} values between episodic (viral) and multiple-trigger wheezers, but the *a priori* sample size calculation based on MBW as the primary outcome was met. However, we cannot exclude the possibility that a larger study might have detected differences in FeNO and sR_{aw} values. We only assessed acute BDR and hence could not determine

whether the wheezers had reached their best possible pulmonary function. (This might have necessitated treatment with systemic steroids,^{38,39} which is not ethically feasible in this preschool cohort.) Moreover, BDR was assessed after 200 µg of salbutamol, and this dose might be inadequate. There is no current consensus on the ideal dose of salbutamol to be used to assess BDR in preschool children. Bearing in mind these children were asymptomatic, it would have been difficult ethically to justify the use of very large doses of salbutamol. Nevertheless, studies in older children and adults with stable asthma have demonstrated up to 20% improvement in forced expiratory volumes on spirometry with salbutamol doses of 100 µg⁴⁰ and 200 µg,^{41,42} and the latter is the dose generally used in clinical practice.

Several studies have shown that wheezing associated with poor airway function in the late preschool years tracks with age and is associated with asthma in adulthood.^{5,43} If these findings are extended to our study, it would suggest that multiple-trigger wheezers are likely to persist in having abnormal pulmonary function and become future asthmatic subjects. If the differences between symptom-pattern phenotypes persist in this cohort on follow-up and pulmonary function abnormalities continue in multiple-trigger wheezers irrespective of atopic or current wheeze status, then this group might respond to disease-modifying therapy, if such was found. However, these are cross-sectional data, and the long-term clinical significance of our findings awaits further longitudinal follow-up.

In summary, this study externally validates the symptom-pattern phenotype of episodic (viral) and multiple-trigger wheeze in preschool children and indicates that multiple-trigger wheeze is the most influential characteristic associated with significant pulmonary function abnormalities independent of atopic or current wheeze status. Conductive airways ventilation inhomogeneity is the most sensitive indicator of abnormal pulmonary function in wheezers, particularly those with multiple-trigger wheeze. Preschool multiple-trigger wheezers at a median age of 4.9 years already have conducting airways disease, which is only partly reversible, at least acutely. These results suggest that multiple-trigger wheezers might be the target group on which to focus for potential disease-modifying strategies.

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Key messages

- The symptom-pattern phenotype of preschool multiple-trigger wheeze is the patient characteristic factor most significantly associated with abnormal pulmonary function independent of atopic and current symptom status.
- S_{cond} derived from MBW analysis is more sensitive than sR_{aw} at detecting abnormal pulmonary function in preschool multiple-trigger wheezers.

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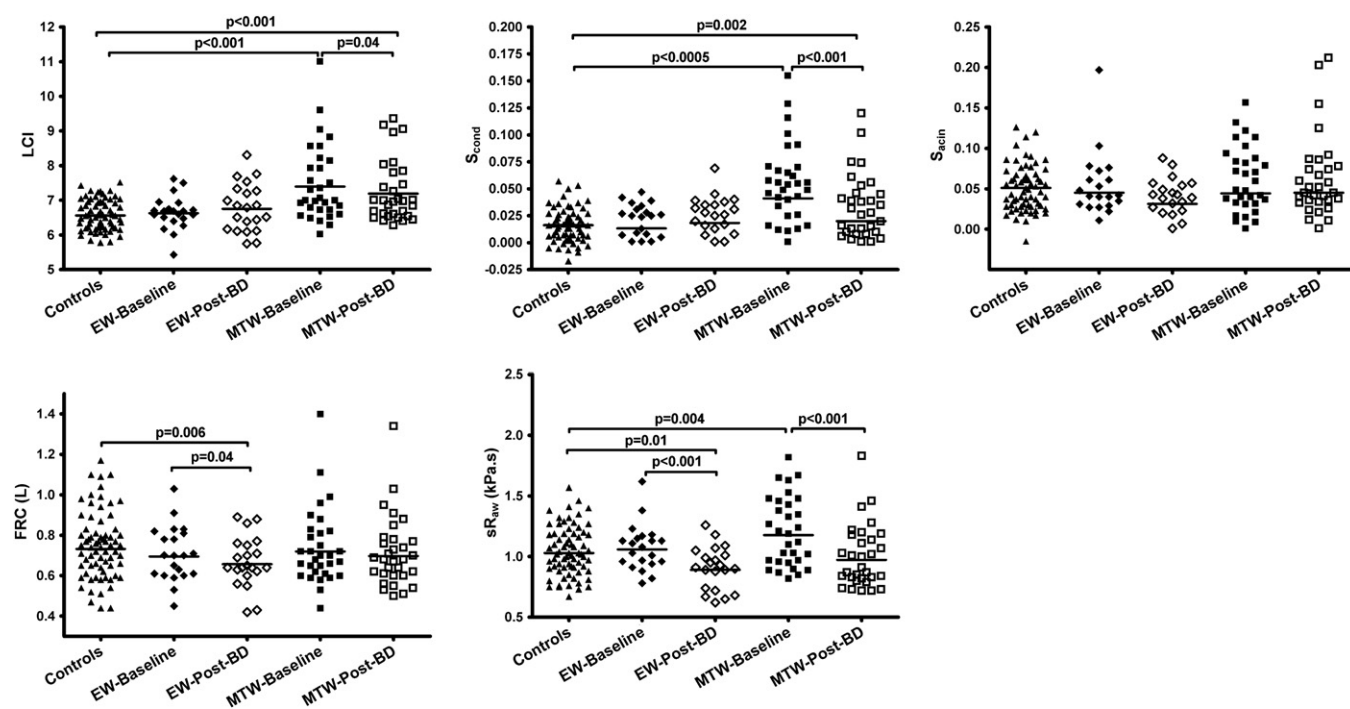


FIG E1. Baseline and postbronchodilator (*post-BD*) pulmonary function in episodic (viral) wheezers (*EW*) and multiple-trigger wheezers (*MTW*) compared with healthy control subjects.

TABLE E1. Baseline characteristics of the study participants

Variable	Healthy control subjects (n = 72)	All wheezers (n = 62)	P value
Age (y)	5.5 (5.1-6.2)	4.9 (4.6-5.7)	.001
Weight (kg)	19.4 (17.7-22.3)	18.5 (17.2-21.2)	.21
Height (cm)	112 (108.3-118.2)	109.6 (105.7-114)	.04
Sex (male/female)	37/35	39/23	.18
Gestation (wk)	40 (39-40)	40 (39-40)	.44
Birth weight (kg)	3.24 (2.9-3.57)	3.07 (2.83-3.54)	.43
Ethnic origin (white/Asian/others)	36/31/5	31/28/3	.48
Atopy, no. (%)	15 (21)	39 (63)	<.001

Subjects' characteristics are presented as medians (interquartile ranges).

TABLE E2. FeNO and pulmonary function values in healthy control subjects and wheezers

Pulmonary function	No.	Healthy control subjects	No.	All wheezers	Mean difference (95% CI)	P value
FeNO (ppb)	63	4.8 (4 to 5.8)	52	8.1 (6.4 to 10.2)	4.9 (1.8 to 8.1)	.001
LCI	70	6.6 (6.5 to 6.7)	62	7.1 (6.9 to 7.3)	0.6 (0.3 to 0.8)	.001
S _{cond}	65	0.010 (0.007 to 0.014)	60	0.026 (0.020 to 0.035)	0.023 (0.014 to 0.032)	<.001
S _{acin}	65	0.042 (0.035 to 0.051)	60	0.048 (0.039 to 0.060)	0.010 (−0.001 to 0.022)	.35
FRC (L)	70	0.73 (0.70 to 0.77)	62	0.71 (0.67 to 0.75)	−0.02 (−0.08 to 0.03)	.37
sR _{aw} (kPa/s)	70	1.03 (0.98 to 1.08)	62	1.14 (1.07 to 1.21)	0.12 (0.04 to 0.21)	.002

Pulmonary function data are presented as geometric means (95% CIs).

TABLE E3. Subjects' characteristics and FeNO and pulmonary function values in nonatopic and atopic wheezers

Parameter	Healthy control subjects (n = 72)	Nonatopic (n = 23)	Atopic (n = 39)	Kruskal-Wallis P value
Age (y)	5.5 (5.1-6.2)	5.1 (4.2-6.8)	4.9 (4.1-6.9)	.002
Weight (kg)	19.4 (17.7-22.3)	18.9 (15.8-33.3)	18.4 (14.6-39.6)	.28
Height (cm)	112 (108.3-118.2)	110.7 (101.4-130.9)	109.4 (102.3-127.7)	.11
Sex (male/female)	37/35	11/12	28/11	.07
Gestation (wk)	40 (39-40)	40 (36-42)	40 (36-42)	.51
Birth weight (kg)	3.24 (2.9-3.57)	3.1 (2.37-4.02)	3.04 (2.57-4.04)	.52
Current ICS treatment, no. (%)	NA	13 (57)	20 (51)	NA
FeNO (ppb)	4.8 (4-5.8)	6.7 (4.4-10.2)	8.9 (6.7-12.1)	.002
LCI	6.6 (6.5-6.7)	6.9 (6.6-7.3)	7.2 (6.8-7.5)	<.001
S _{cond}	0.010 (0.007-0.014)	0.019 (0.009-0.035)	0.032 (0.023-0.044)	<.001
S _{acin}	0.042 (0.035-0.051)	0.046 (0.034-0.061)	0.049 (0.037-0.068)	.29
FRC (L)	0.73 (0.70-0.77)	0.71 (0.64-0.79)	0.71 (0.66-0.75)	.60
sR _{aw} (kPa/s)	1.03 (0.98-1.08)	1.05 (0.78-1.63)	1.2 (0.82-1.98)	.09

Subjects' characteristics are presented as medians (ranges). FeNO and pulmonary function values are presented as geometric means (95% CIs).

TABLE E4. Subjects' characteristics and FeNO and pulmonary function values in current asymptomatic and symptomatic wheezers

Parameter	Healthy control subjects (n = 72)	Asymptomatic (n = 10)	Symptomatic (n = 52)	Kruskal-Wallis P value
Age (y)	5.5 (5.1-6.2)	4.4 (4.1-6.6)	5.07 (4.2-6.9)	<.005
Weight (kg)	19.4 (17.7-22.3)	19.5 (15.8-33.3)	18.5 (14.6-39.6)	.22
Height (cm)	112 (108.3-118.2)	109.3 (103.4-130.9)	109.6 (101.4-127.7)	.12
Sex (male/female)	37/35	6/4	33/19	.40
Gestation (wk)	40 (39-40)	40 (36-41)	40 (36-42)	.64
Birth weight (kg)	3.24 (2.9-3.57)	3.53 (2.6-4.02)	3.04 (2.57-4.04)	.42
FeNO (ppb)	4.8 (4-5.8)	4.3 (2.0-9.4)	8.9 (7.0-11.4)	<.005
LCI	6.6 (6.5-6.7)	7.1 (6.4-7.8)	7.1 (6.8-7.3)	<.005
S _{cond}	0.010 (0.007-0.014)	0.026 (0.017-0.042)	0.026 (0.019-0.037)	<.001
S _{acin}	0.042 (0.035-0.051)	0.075 (0.059-0.095)	0.044 (0.035-0.057)	.03
FRC (L)	0.73 (0.70-0.77)	0.70 (0.60-0.84)	0.71 (0.67-0.75)	.60
sRaw (kPa/s)	1.03 (0.98-1.08)	1.19 (0.94-1.51)	1.13 (1.06-1.2)	.10

Subjects' characteristics are presented as medians (ranges). FeNO and pulmonary function values are presented as geometric means (95% CIs).

TABLE E5. Sensitivity, specificity, and area under the receiver operating characteristic curve (AUC_{ROC}) for LCI, S_{cond} , and sR_{aw} when wheeze is the outcome variable

Parameter	Sensitivity	Specificity	AUC_{ROC}	<i>P</i> value
LCI	26%	97%	0.678	<.005
S_{cond}	37%	95%	0.740	<.0005
sR_{aw}	19%	97%	0.606	<.05

Sensitivity and specificity defined by cutoffs of greater than 1.96 *z* scores for LCI (7.42), S_{cond} (0.045), and sR_{aw} (1.44 kPa/s). An AUC_{ROC} (SE) of 1.0 represents perfect discrimination, and an area of 0.5 represents no discrimination. The *P* value tests the null hypothesis that AUC_{ROC} is equal to 0.5. Note that S_{cond} was significantly more sensitive than LCI and sR_{aw} at discriminating wheezers from healthy control subjects.

TABLE E6. Sensitivity, specificity, and area under the receiver operating characteristic (AUC_{ROC}) curve for LCI, S_{cond} , and sR_{aw} when multiple-trigger wheeze is the outcome variable among wheezers

Parameter	Sensitivity	Specificity	AUC_{ROC} (SE)	<i>P</i> value
LCI	39%	95%	0.752 (0.07)	.003
S_{cond}	68%	96%	0.825 (0.06)	<.0005
sR_{aw}	26%	96%	0.629 (0.08)	.123

Sensitivity and specificity defined by cutoffs of greater than 1.96 *z* scores for LCI (7.42), S_{cond} (0.045), and sR_{aw} (1.44 kPa/s). An AUC_{ROC} (SE) of 1.0 represents perfect discrimination, and an area of 0.5 represents no discrimination. The *P* value tests the null hypothesis that AUC_{ROC} is equal to 0.5. Note that S_{cond} was significantly more sensitive than LCI and sR_{aw} at discriminating multiple-trigger from episodic (viral) wheezers.