

Letter to the Editor

Symptom-based classification of wheeze: How does it work in infants?

To the Editor:

Wheezing in early childhood is a common but heterogeneous condition.¹ Asthma predictive indices have been created to evaluate the prognosis of wheezing.² Nonetheless, there are unanswered questions with regard to the clinical definition of different phenotypes of wheezing, appropriate treatment, and need for follow-up.

For treatment purposes, the European Respiratory Society proposed a new symptom-based classification of wheeze into episodic viral and multiple-trigger wheeze.³ There is very limited experimental evidence to support the new symptom-based classification, especially with regard to children aged less than 3 years. The only report comparing pulmonary function in multiple-trigger and episodic viral wheezers involved children aged 4 to 6 years.⁴ In addition, the clinical usefulness of the symptom-based classification has been questioned because of its transient value.⁵

In the present study we aimed to clarify whether infants and toddlers with multiple-trigger or episodic viral wheeze differ in their atopic traits, lung function, airway responsiveness, and/or fraction of exhaled nitric oxide (FENO) level.

The study subjects included 160 full-term, steroid-free, infection-free children aged 4 to 26 months who were referred to a tertiary hospital for investigation of recurrent lower respiratory tract symptoms and who successfully underwent lung function testing, a dosimetric methacholine challenge test, and FENO measurement as part of the recruitment phase of an intervention study of infant asthma conducted in 2004-2008. Fifty-eight (36%) children had atopic manifestations, 65 (41%) had a parental history of asthma, and 50 (31%) were exposed to environmental tobacco smoke. One hundred twenty-nine (81%) had at least 1 episode of wheezing confirmed by a physician. Details of lung function testing and the dosimetric methacholine test have been presented elsewhere.⁶ For more information on FENO measurements, see the [Methods](#) section of this article's Online Repository (available at www.jacionline.org).

All the tests were performed after receiving informed consent from the parents. In addition, the parents of the children were asked to provide written consent to allow the use of lung function and methacholine challenge test results, FENO measurements, skin prick test results, and related clinical data for research purposes. The study was approved by the local ethics committee.

The baseline lung function values were expressed as *z* scores based on height- and sex-corrected reference values⁷ or weight-corrected reference values.⁸ Lung function parameters, which were regarded as abnormal, were a functional residual capacity (FRC) *z* score of 2 or more and a forced expiratory flow at FRC ($V'_{\max, \text{FRC}}$) *z* score of -2 or less.⁶ The provocative dose of methacholine causing a 40% decrease in $V'_{\max, \text{FRC}}$ of 0.90 mg or less was defined as increased airway responsiveness.⁶ FENO levels of 27 ppb or greater (ie, the highest quartile) were considered increased.

The clinical data were collected prospectively by interviewing the parents and by reviewing the medical records of the children,

as described earlier.⁶ On the basis of parental reports of symptoms, children with at least 1 episode of wheezing confirmed by a physician were classified as multiple-trigger wheezers or episodic viral wheezers, according to the recommendations of the European Respiratory Society.³ Children with recurrent lower respiratory tract symptoms but no wheezing confirmed by a physician were designated as nonwheezers.

The data were analyzed with SPSS 17.0 software for Windows (SPSS, Inc, Chicago, Ill). Fisher exact or χ^2 tests for dichotomous variables and Mann-Whitney *U* or Kruskal-Wallis tests for continuous or ordinal variables were used to evaluate the statistical differences between the groups. Bonferroni correction (multiplying the *P* values by 3) was applied in paired analyses. *P* values of less than .05 were considered statistically significant.

There were 96 multiple-trigger wheezers, 33 episodic viral wheezers, and 31 nonwheezers. Age, sex, a parental history of asthma, occurrence of atopic eczema, skin prick test response positivity, exposure to environmental tobacco smoke, and FRC and FENO levels did not differ between the study groups (see [Table E1](#) in this article's Online Repository at www.jacionline.org). Parentally reported respiratory symptoms differed only with respect to shortness of breath that was reported merely by parents of wheezers (see [Table E1](#)). $V'_{\max, \text{FRC}}$ values were lower ([Fig 1, A](#)) and increased airway responsiveness was more common ([Fig 1, B](#)) in multiple-trigger wheezers than in nonwheezers. No such differences were found between the 2 wheezing groups.

It was found in the present study that lung function was significantly lower and increased airway responsiveness more common in multiple-trigger wheezers than in nonwheezers. Multiple-trigger and episodic viral wheezers did not significantly differ in their baseline characteristics or in any other objective measures. Since 2008, the European Respiratory Society has recommended the use of a symptom-based classification of wheeze for treatment purposes,³ although experimental evidence to support this type of classification is scanty, especially with respect to infants who wheeze. It has been claimed that episodic viral wheezers are more commonly nonatopic, with their condition rarely progressing to asthma, whereas multiple-trigger wheezers are assumed to have become sensitized to various allergens early in life and are at risk for a decrease in lung function.⁹

Is this really so? Do these symptom-based wheezers represent 2 distinct conditions? In a recently published study, multiple-trigger preschool wheezers did have lower lung function than episodic viral wheezers and nonwheezers.⁴ However, there were no differences in any other features between the 2 wheezing groups,⁴ which is consistent with our findings of similar prevalences of atopy, exposure to environmental tobacco smoke, increased airway responsiveness, and equal FENO levels. Moreover, the symptom-based classification of wheeze is likely to change significantly within a single calendar year.⁵ At least in infants, the symptom-based classification of wheeze is not supported by the cross-sectional data on lung function, increased airway responsiveness, or FENO levels. It could be argued that one way to improve the clinical usefulness of the classification would be to include some elements from asthma predictive

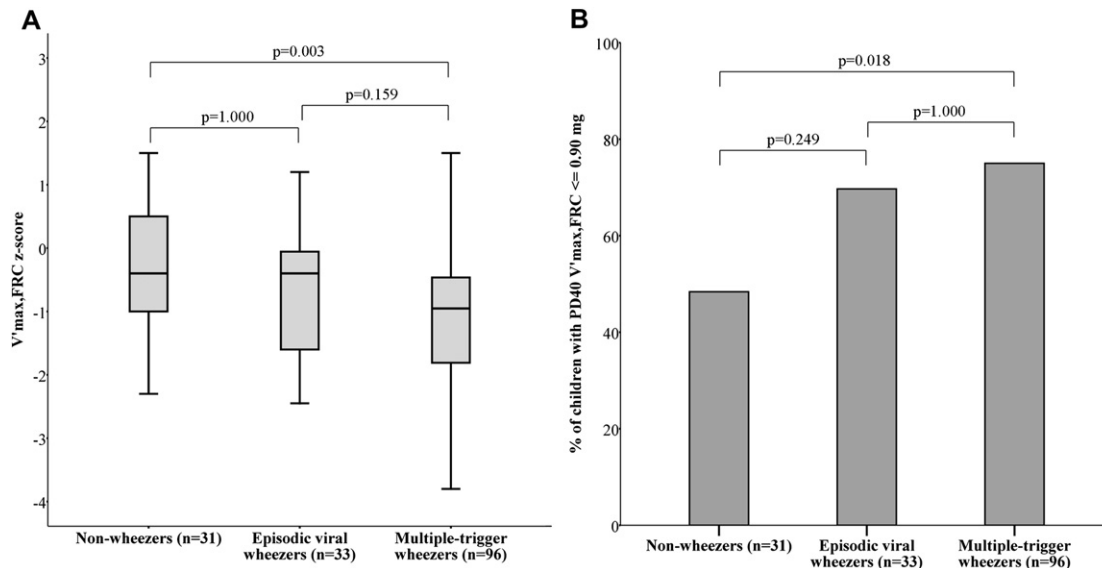


FIG 1. A, Forced expiratory flow at functional residual capacity ($V'_{max,FRC}$) in multiple-trigger wheezers was significantly lower than that seen in nonwheezers. B, Increased airway responsiveness (ie, the provocative dose of methacholine causing a 40% decrease in $V'_{max,FRC}$ [$PD_{40} V'_{max,FRC}$]) of 0.90 mg or less was significantly more common in multiple-trigger wheezers than in nonwheezers.

indices into the definitions of episodic viral and multiple-trigger wheeze.

In conclusion, infants and toddlers with physician-confirmed wheeze, especially multiple-trigger wheeze, differ from non-wheezers with respect to lung function and airway responsiveness. On the other hand, it seems that a parentally reported symptom-based classification of early childhood wheeze cannot reliably identify those wheezers with lung function abnormalities, increased airway responsiveness, or increased FENO levels. New approaches are needed for early identification of those wheezers requiring treatment and follow-up.

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METHODS

FENO measurement

FENO levels were assessed with a modification of the online single-breath measurement.^{E1} During sedation, the babies spontaneously breathed room air through a mask to which a pneumotach was attached. A rapid thoracoabdominal compression technique was applied to generate forced expiration starting from end-inspiration. By using the shutter mechanism of the pneumotach and a 3-way valve, the expired air was led to a chemiluminescence analyzer (NIOX; Aerocrine, Solna, Sweden) through a dynamic resistor that restricted the expiratory flow to 50 mL/s. Sampling of the exhaled air occurred in the proximity of the 3-way valve, with a dead space, including the mask and valve/shutter system, of about 25 mL. FENO levels were measured from the end-expiratory sample by using the plateau phase of the nitric oxide profile.

Repeated exhalations were performed to obtain 3 reproducible FENO measurements (variation <10% or 5 ppb). The mean value of these measurements was recorded, as well as the ambient nitric oxide level during the test. Only measurements with an ambient nitric oxide level of 5 ppb or less were included in the analyses. The majority (>80%) of all tested children fulfilled these strict criteria for an acceptable FENO measurement. FENO levels of 27 ppb or more (ie, the highest quartile) were considered increased.

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TABLE E1. Wheezing phenotypes with regard to baseline characteristics, lung function, airway responsiveness, and fractional concentration of exhaled nitric oxide

Characteristics and parameters	Nonwheezers (n = 31)	Episodic viral	Multiple-trigger	P value
		Wheezers (n = 33)	Wheezers (n = 96)	
Age (mo)	15.3 (6.6; 26.3)	17.6 (8.8; 25.9)	16.5 (4.0; 26.7)	.714
Age ≥12 mo	19 (61%)	24 (73%)	66 (69%)	.605
Gender (male/female)	17/14 (55%/45%)	25/8 (76%/24%)	73/23 (76%/24%)	.063
Parental history of asthma	16 (52%)	12 (36%)	37 (39%)	.373
Parentally reported main respiratory symptom				
Cough	20 (65%)	14 (42%)	50 (52%)	.208
Wheeze	2 (6%)	7 (21%)	14 (15%)	.232
Shortness of breath	0 (0%)	6 (18%)	19 (20%)	.011
Sputum production	9 (29%)	6 (18%)	13 (14%)	.142
Atopic eczema	7 (23%)	8 (24%)	24 (25%)	.963
Skin prick test positivity	8/30 (27%)	8 (24%)	24/95 (25%)	.976
Exposure to environmental tobacco smoke	11 (37%)	7 (21%)	32 (33%)	.343
FRC z score	0.7 (−2.2; 3.1)	0.7 (−1.1; 4.2)	0.7 (−1.5; 4.8)	.884
FRC z score ≥ 2	3/30 (10%)	8/32 (25%)	20 (21%)	.296
V' max,FRC z score	−0.4 (−2.3; 1.5)	−0.4 (−2.4; 1.2)	−1.0 (−3.8; 1.5)	.003
V' max,FRC z score ≤ −2	1 (3%)	5 (15%)	21 (22%)	.052
PD ₄₀ V' max,FRC (mg)	0.91 (<0.10; 3.60)	0.52 (<0.10; 3.60)	0.50 (<0.10; 3.60)	.217
PD ₄₀ V' max,FRC ≤0.90 mg	15 (48%)	23 (70%)	72 (75%)	.021
FENO (ppb)	18.0 (2.0; 45.3)	19.4 (6.5; 58.7)	19.3 (2.3; 59.9)	.878
FENO ≥ 27 ppb	6 (19%)	6/26 (23%)	20/79 (25%)	.789

Results are presented as number of cases (%), or as median (range).

FENO, Fractional concentration of exhaled nitric oxide; FRC, functional residual capacity; PD₄₀ V' max,FRC, provocative dose of methacholine causing a 40% fall in forced expiratory flow at functional residual capacity; V' max,FRC, forced expiratory flow at functional residual capacity.