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Office-based exhaled nitric oxide measurement in children 4 years of age and older

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ABSTRACT

Background: Fractional exhaled nitric oxide (FENO) is increasingly being used in the office-based management of asthma, but data in children are limited.

Objectives: To report FENO values in 4- to 7-year-old children with suspected asthma and characterize their relation to clinical variables and describe the relation among FENO levels, age, and sex in 4- to 18-year-old children with suspected asthma.

Methods: Retrospective data in 4- to 18-year-old children (n = 825) who underwent FENO testing using the NIOX MINO device were collected and analyzed. Chart reviews were performed for the 4- to 7-year-old children (n = 75).

Results: FENO values ranged from less than or equal to 5 to 89 ppb in 75 4- to 7-year-old children and less than or equal to 5 to 300 ppb in 750 > 7 to 18-year-old children. Approximately one tenth of 4- to 7-year-old children and one third of > 7 to 18-year-old children had FENO values indicative of eosinophilic/allergic inflammation (>35 ppb). In regression analysis of the 4- to 7-year-old children, increasing age (P = .03) and asthma severity (P = .01) were associated with higher FENO levels. Atopic dermatitis was significantly associated (P = .03), whereas allergic rhinitis was marginally associated (P = .06), with higher FENO levels. Inhaled corticosteroid use was associated with lower FENO levels (P = .02).

Conclusion: This study characterizes the largest cohort of 4- to 7-year-old children to undergo FENO testing in ambulatory asthma management. Correlations between FENO levels and clinical variables were consistent with established findings in older children. This preliminary real-world study suggests that FENO assessment may be feasible and useful in the office-based asthma management of children as young as 4 years.

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Introduction

Nitric oxide (NO) is an endogenously produced gas that functions as a signaling molecule, with regulatory effects on multiple physiologic and pathologic processes. NO is produced by respiratory epithelial cells and was first measured in exhaled breath in 1991.¹ Numerous studies have established that levels of fractional exhaled NO (FENO) are elevated in patients with asthma,^{2–4} can predict impending exacerbations,^{5,6} and decrease after inhaled or systemic steroid use.^{2–4,7} Recognizing FENO as an important biomarker of inflammation (“inflammometer”), guidelines were recently issued on the clinical interpretation of FENO values relating to the diagnosis, treatment, monitoring, and assessment of

adherence in asthma.^{8,9} In May 2003, the US Food and Drug Administration cleared NIOX (Aerocrine AB, Solna, Sweden), a chemiluminescence-based FENO monitoring system, for clinical use.¹⁰ In March 2008, Aerocrine introduced a hand-held device, the NIOX MINO, for use in adults and children older than 7 years, with multiple studies validating its use.^{11–15} However, there are sparse data on FENO values in children measured during routine clinical care of asthma, particularly in those younger than 7 years.

In young children, objective evaluation of asthma can be challenging. Difficulty with reliable performance of spirometry and mismatch between symptoms and lung function have been reported.^{16–18} The 2007 National Heart, Lung, and Blood Institute (NHLBI) guidelines state that spirometry is generally valuable in children older than 5 years, although some children may not adequately conduct the maneuver until 7 years of age.¹⁹ The guidelines also acknowledge that recent publications have shown that preschool and school-age children have difficulty meeting some of the quality-control criteria outlined in the American Thoracic Society (ATS) and European Respiratory Society guidelines and

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recommend the development and use of modified criteria for pre-schoolers.^{20–23} In contrast, FENO testing uses a different respiratory maneuver and presumably can be performed relatively easily by school-age children.¹⁸ FENO measurement is particularly attractive because it adds information to a hitherto immeasurable dimension of asthma, namely inflammation, and yields reproducible real-time results.^{24,25} Clinical use of this tool in children younger than 7 years would enable office-based objective evaluation of asthma in this elusive-to-evaluate age group. The authors have been measuring FENO levels in children with asthma at their center since 2006 and have experience with the chemiluminescence analyzer and the hand-held device.

The primary objectives of this study were to report FENO values in patients 4 to 7 years of age with suspected or diagnosed asthma and describe the association of FENO with important clinical characteristics. The secondary objective was to examine the relation among FENO levels, age, and sex in a larger group of patients 4 to 18 years of age.

Methods

Study Subjects and FENO Measurement

A retrospective chart review of patients 4 to 7 years of age (specifically 4 years 0 month to 7 years 0 month) who underwent routine FENO testing using the NIOX MINO device as part of their asthma evaluation in pediatric asthma/allergy clinics from June 1, 2010 through April 30, 2012 was completed after institutional review board approval. Informed consent was waived by the institutional review board. In addition, data on FENO values, age, and sex were obtained during the same period for a group of patients > 7 to 18 years of age (specifically 7 years 1 month to 18 years 0 month).

Single-breath FENO testing was performed using the NIOX MINO device, using a 10-second exhalation time and measured in parts per billion.²⁰ For subjects unable to perform this maneuver, a 6-second exhalation time was used.^{26,27} FENO testing at the authors' center is typically performed in all children older than 7 years presenting with suspected asthma and attempted in younger children depending on the clinician's assessment of the child's ability to perform respiratory maneuvers. FENO testing is usually performed before spirometry or after a 30-minute interval after spirometry.

Clinical Definitions

Asthma severity and asthma control were determined based on provider assessment using the 2007 NHLBI asthma guidelines and/or validated Childhood Asthma Control Test (C-ACT) score (ACT score ≤19 indicating inadequate control).^{19,28} Asthma severity was assigned a numerical value of 0 (no asthma), 1 (intermittent asthma), 2 (mild persistent asthma), 3 (moderate persistent asthma), or 4 (severe persistent asthma). Asthma control was assigned a numerical value of 0 (no asthma), 1 (well-controlled asthma), 2 (not well-controlled asthma), or 3 (poorly controlled asthma). The presence of allergic rhinitis or atopic dermatitis was determined by provider assessment. Use of inhaled corticosteroids (ICSs) or leukotriene receptor antagonists (LTRAs) was determined by documented parental report on the day of the visit.

Allergic sensitization was defined as a positive skin prick test result with a wheal larger than 3 mm and flare larger than 5 mm compared with the negative control (saline) or a specific IgE to at least 1 allergen of at least 0.35 kU/L using the ImmunoCap (Thermo Fisher, Waltham, Massachusetts) specific IgE blood test. Serum specific IgE testing was performed using the ImmunoCap method to a set of allergens, including tree pollen mix, grass pollen mix, weed pollen mix, molds (*Alternaria*, *Cladosporium*, *Aspergillus*, and *Penicillium* species), cat dander, dog dander, *Dermatophagoides*

farinae, and cockroach. Skin testing was performed to a similar panel of allergens. Additional allergens (eg, rat, mouse, horse, or foods) were added as indicated by the clinical history.

Data Analyses

Natural logarithmically transformed values of FENO (LFENO) were needed to properly model relations. Comparisons of the associations between LFENO and clinical characteristics were completed using Pearson product correlation analysis (hereafter, correlation) and general linear models. Statistical significance was assumed with a 2-tailed *P* value less than or equal to .05.

Results

Descriptive Analysis

Children 4 to 7 years old

Seventy-five children 4 to 7 years of age underwent FENO testing during the study period. Table 1 presents their demographic and clinical characteristics. Seventy-one subjects were diagnosed with asthma, and the remainder were diagnosed with chronic cough (*n* = 2) or postnasal drip (*n* = 2). FENO values ranged from less than or equal to 5 to 89 ppb (mean 18.4, median 12, interquartile range 8–24). Seven of 75 FENO measurements (9%) were lower than 5 ppb (lower limit of sensitivity), 51 measurements (68%) were in the normal range (5–25 ppb), 8 measurements (11%) were 26 to 34 ppb, 4 measurements (5%) were 35 to 50 ppb (strongly suggestive of eosinophilic allergic inflammation in children <12 years old), and 5 measurements (7%) were higher than 50 ppb (strongly suggestive of eosinophilic allergic inflammation in children >12 years old).⁸ Figure 1 shows the distribution of FENO measurements in the 4- to 7-year and > 7 to 18-year age groups.

Table 1

Characteristics of patients 4 to 7 years of age (*n* = 75)

Boys	39 (52%)
Age (y), mean (range)	6.4 (4.75–7)
Height (cm), mean (range)	120.8 (107–140)
Weight (kg), mean (range)	24.8 (16.5–44.5)
BMI (kg/m ²), mean (range)	16.9 (12.2–28.4)
Public insurance (Medicaid)	37 (49%)
Ethnic background	
Caucasian	54 (72%)
Black	14 (19%)
Hispanic	3 (4%)
Other	4 (5%)
Atopic dermatitis	25 (33%)
Allergic rhinitis	53 (71%)
Using ICS	31 (41%)
Using LTRA (montelukast)	33 (44%)
Using ICS and LTRA	16 (21%)
Asthma severity	
No asthma (ie, PND or chronic cough)	4 (5%)
Intermittents	23 (31%)
Mild persistent	30 (40%)
Moderate persistent	15 (20%)
Severe persistent	3 (4%)
Asthma control	
No asthma (ie, PND or chronic cough)	4 (5%)
Well controlled	44 (59%)
Not well controlled	17 (23%)
Very poorly controlled	10 (13%)
Smoke exposure (<i>n</i> = 55)	18 (33%)
Allergy testing (<i>n</i> = 48)	
Positive skin prick test result	20 (42%)
Positive blood test result	17 (35%)
Spirometry (<i>n</i> = 36)	
FEV ₁ /FVC <85% predicted	8 (22%)
FEV ₁ <80% predicted	4 (11%)
FEV ₁ /FVC <85% and FEV ₁ <80%	1 (3%)

Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; PND, postnasal drip.

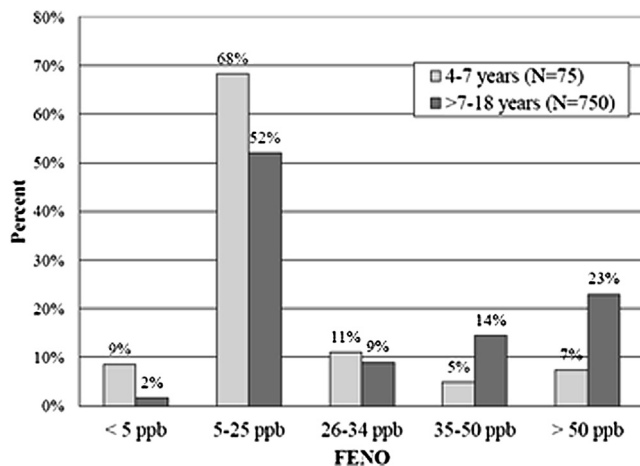


Figure 1. Distribution of fractional exhaled nitric oxide (FENO) values by age group. Normal, 5 to 25 ppb; upper limit of normal, 26 to 34; 35 to 50, strongly suggestive of eosinophilic/allergic inflammation in children younger than 12 years; >50, strongly suggestive in children older than 12 years.⁸

Thirty-six children (48%) performed spirometry in addition to FENO testing. The forced expiratory volume in 1 second (FEV₁) percentage predicted and the ratio of FEV₁ to forced vital capacity (FVC) percentage predicted are reported in concordance with the 2007 NHLBI guideline criteria for classification of asthma severity and control.¹⁹ The mean FEV₁ percentage predicted was 102 (median 97, standard deviation 20.1). Mean FEV₁/FVC percentage predicted was 91 (92–9.2) and mean forced expiratory flow between 25% and 75% predicted was 101 (92–52.9). Only 1 subject met spirometric criteria for persistent asthma as recommended by the 2007 NHLBI guidelines (FEV₁ <80% predicted and FEV₁/FVC ratio <85% predicted)²³; that subject's FENO level was 80 ppb. The FEV₁/FVC ratio was lower than 85% predicted in 8 of 36 observations and 3 of these had elevated FENO levels (41, 49, and 80 ppb). Four subjects had FEV₁ less than 80% predicted and 3 of them had elevated FENO values (53, 56, and 80 ppb). The correlation between FEV₁/FVC percentage predicted and LFENO was not statistically significant ($r = -0.24$, $P = .16$). Correlation between these spirometric parameters and LFENO values yielded insignificant correlations between FEV₁ percentage predicted ($r = -0.29$, $P = .09$) and forced expiratory flow between 25% and 75% predicted ($r = -0.31$, $P = .06$). The correlation between FEV₁/FVC percentage predicted and LFENO was not significant ($r = -0.27$, $P = .11$).

Asthma control was determined by provider assessment in accordance with recommendations made in the 2007 NHLBI guidelines and given a numerical value as indicated in the "Methods" section. There was a statistically significant correlation between asthma control and LFENO ($r = 0.25$, $P < .03$), with worsening asthma control associated with higher FENO levels. Forty-three children had a C-ACT score assigned as part of their asthma control assessment. The range of C-ACT scores was 4 to 27 (mean 17.9, median 17, standard deviation 5.9). Sixteen children (37%) had a C-ACT score higher than or equal to 20 (adequate control) and 27 children (63%) had a score lower than or equal to 19 (inadequate control). Correlation analysis between C-ACT scores and LFENO values and between the natural logarithm of C-ACT scores and LFENO values yielded no significant correlations.

The correlation between asthma severity and LFENO was marginally insignificant ($r = 0.22$, $P < .06$). However, as presented in Table 2, asthma severity was strongly related to LFENO, with a standardized regression coefficient (β) equal to 0.32 ($P \leq .01$), when included in regression analysis with other clinical variables.

Forty-eight patients had allergy testing performed, with 37 having results indicative of allergic sensitization. There was a statistically

Table 2

Relation between LFENO and clinical variables in patients 4 to 7 years old^a

Summary ($F = 4.14$, $P < .001$, $R^2 = 0.268$)	Coefficients				95% CI for β	
	β	SE	P value	Standardized β^b	Lower bound	Upper bound
Age ^c	2.7	1.23	.03	0.23	0.24	5.15
Asthma severity	0.28	0.10	.01	0.32	0.07	0.48
Allergic rhinitis	0.32	0.16	.06	0.20	−0.01	0.64
Atopic dermatitis	0.41	0.18	.03	0.23	0.04	0.77
Inhaled corticosteroid	−0.45	0.19	.02	−0.27	−0.84	−0.06
LTRA	−0.26	0.18	.15	−0.16	−0.60	0.09

Abbreviations: CI, confidence interval; LFENO, natural logarithm of fractional exhaled nitric oxide; LTRA, leukotriene receptor antagonist; SE, standard error.

^aDependent variable is LFENO.

^bStandardized regression coefficients.

^cNatural logarithms of age.

significant correlation between positive allergy test results and LFENO ($r = 0.32$, $P < .03$). Patients with atopic dermatitis were more likely to have a positive skin test result than patients without atopic dermatitis ($P = .02$). There was no statistically significant difference between the 2 groups in regard to positive blood test results ($P = .12$). Sample sizes were 28 and 22, respectively. Only 8 patients had a positive skin or blood allergy test result to a food allergen.

For all 75 patients, there was no statistically significant correlation between LFENO and height, insurance status, smoke exposure, or race. Body mass index and weight were found to be significantly correlated with LFENO ($r = 0.31$, $P < .01$; $r = 0.35$, $P < .01$).

Children > 7 to 18 years old

Data on FENO values, age, and sex were collected for 750 children > 7 to 18 years of age. The range of FENO values was less than or equal to 5 to 300 ppb (mean 34.3, median 22, interquartile range 12–47). Fifty-eight percent of patients were boys and the mean age was 11.5 years. Thirteen of 750 FENO measurements (2%) were less than 5 ppb (lower limit of sensitivity), 392 measurements (52%) were in the normal range (5–25 ppb), 71 measurements (9%) were 26 to 34 ppb, 102 measurements (14%) were 35 to 50 ppb (strongly suggestive of eosinophilic allergic inflammation in children <12 years old), and 172 measurements (23%) were higher than 50 ppb (strongly suggestive of eosinophilic allergic inflammation in children >12 years old).⁸

General Linear Models

Children 4 to 7 years old

General linear models were fitted to the 4- to 7-year-old group and included the following variables: age, asthma severity, allergic rhinitis, atopic dermatitis, use of ICSs, and use of LTRAs (Table 2). The standardized regression coefficients (Table 2) allow for assessment of the overall impact of each variable on FENO. Asthma severity had the greatest impact on FENO (0.32), followed by ICS (−0.27), atopic dermatitis and age (each 0.23), allergic rhinitis (0.20), and LTRAs (−0.16).

When controlling for other variables, each 1-month increase in age was associated with a 4.8% increase in FENO ($P = .03$). As shown by its standardized coefficient, asthma severity had the greatest impact on FENO; each 1-unit increase (ie, from 1, intermittent, to 2, mild persistent) was associated with a 32% increase in FENO, and a 2-unit increase compounded to a 74% increase (ie, a 32% increase of 32%) in FENO ($P = .01$). Children with allergic rhinitis had a 37% higher FENO level than children without allergic rhinitis, with a marginal statistical insignificance ($P = .06$). Children with atopic dermatitis had a 50% higher FENO level than children without atopic dermatitis ($P = .03$). Use of ICSs was associated with a 36% lower FENO ($P = .02$). Use of LTRAs was associated with a 22% lower FENO, but was not statistically significant ($P = .15$).

The variables included in this relation were found to be independent of each other (ie, orthogonal); thus, the inclusion or exclusion of any independent variable had no statistical impact on the magnitude or significance of the remaining coefficients.

Children 4 to 18 years old

Regression analysis was performed using sex and natural logarithms of age in the entire group of children (4 to 18 years old). When controlling for age, girls had a 10% lower FENO ($P < .05$). When controlling for sex, FENO increased by 11% with each 1-year increase in age ($P < .001$). Figure 2 shows the mean and median FENO and mean LFENO levels with 95% confidence intervals by age for the entire group of 4- to 18-year-old children.

Discussion

To the authors' knowledge, this is the first US study describing the use of the NIOX MINO device in the routine clinical care of asthma in children 4 to 7 years of age. In this study, most children 4 to 7 years of age (88%) had FENO values from lower than 5 to 34 ppb. The mean FENO in the present study was 18.4 ppb, lower than the range reported by other researchers (Kalliola et al,¹² 7.8 ppb; Ito et al,³¹ 28.9 ppb) and within 1 standard deviation of the means reported by Ito et al³¹ and Jones et al⁵ (9.3 ppb). Twelve percent of children had a FENO value higher than 35 ppb, the recommended cutoff value consistent with the phenotypic profile of eosinophilic allergic inflammation, and in whom FENO testing had been shown to aid in management.⁸ Some investigators have attempted to study FENO levels in young children using older technology in various regions of the world. These preliminary studies differed from the present study in being limited in sample size, particularly of children younger than 7 years, and in the use of older, outdated technology. In addition, these studies were not designed to evaluate factors relating to the use of FENO in ambulatory asthma management. Kalliola et al¹² evaluated 55 children in Finland with a mean age of 5.7 years (range 3.9–8.5) using the NIOX MINO and an older model called the NIOX. They reported a 73% success rate using the NIOX MINO in this age group, but noted relatively poor

accuracy at low FENO levels. Chawes et al²⁹ evaluated 38 7-year-old children in Denmark with rhinitis using the older, online technique and found elevated FENO levels in those with allergic rhinitis. Similarly, Jackson et al³⁰ reported that children enrolled in the Childhood Origins of Asthma study (289 patients) with aero-allergen sensitization at 6 and 8 years of age had increased FENO, as measured by the online technique. Ito et al³¹ measured FENO using the NIOX MINO in 258 Japanese children 5 to 11 years of age (median age 9 years) with asthma in an attempt to correlate the C-ACT with objective parameters of asthma control, but found no correlation. Thus, the present study reports on the largest group of children 4 to 7 years of age to perform FENO measurements successfully using the NIOX MINO device as part of "real-world" ambulatory management of asthma.

Measurement of pulmonary function parameters using office-based spirometry is recommended for the diagnosis and ongoing assessment of asthma.¹⁹ However, performance of spirometric maneuvers that meet ATS standards is challenging for children 4 to 7 years old.^{8,20–23} Compared with older children and adults, young children have small absolute lung volumes and large airways relative to their lung volume. Forced expiration is therefore completed in a shorter period (certainly more quickly than the 6 seconds recommended for adults) and sometimes in less than 1 second. Recommended methodology to obtain reliable and reproducible spirometry results in preschoolers includes a short period of training before data collection and recording a minimum of 3 maneuvers.²² For some children, it may be helpful to allow at least 10 attempts if technique improves with successive maneuvers and be wary of exhausting the child or inducing bronchospasm.²⁰ In addition, interpretation of pulmonary function parameters in the context of childhood asthma can be tricky, as reported in a cross-sectional evaluation of childhood asthma at a leading center.³² The investigators observed that most asthmatic children had FEV₁ values within the normal range, and with increasing age, the increase in FEV₁ lagged behind that of nonasthmatics. Furthermore, no useful FEV₁ cutoff could be generated to subclassify severity, and cutoff values did not appear to accurately stratify pediatric asthma. In the present study, about one half of children 4 to 7 years of age

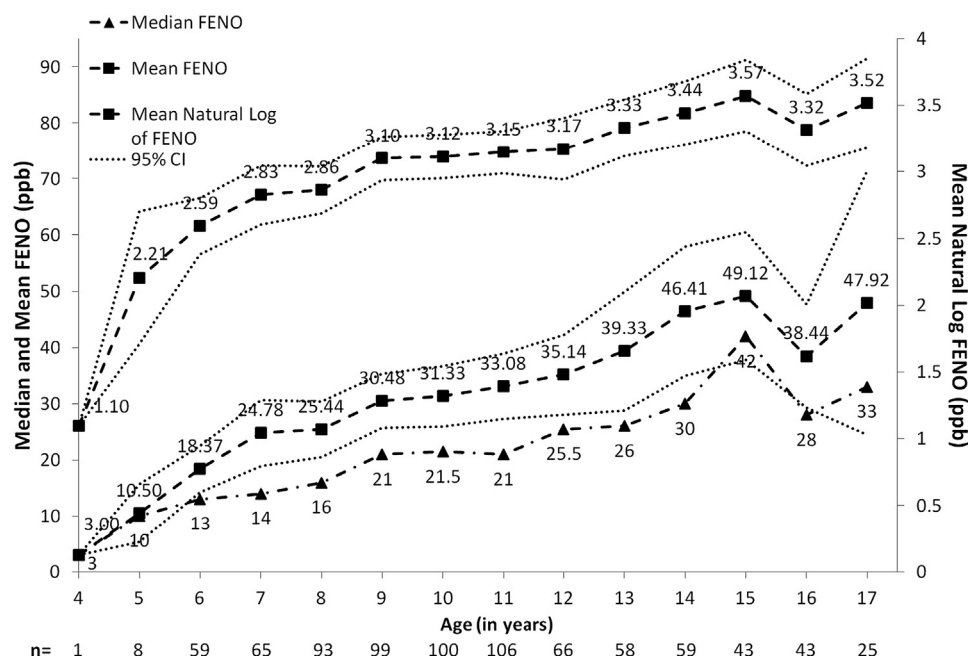


Figure 2. Median and mean fractional exhaled nitric oxide (FENO) and mean natural logarithm of fractional exhaled nitric oxide with 95% confidence intervals (CI) by age 4 to 18 years (N = 825).

performed spirometry and 89% of them had an FEV₁ in the normal range. Only 1 child met established criteria for asthma (FEV₁ <80% predicted and FEV₁/FVC ratio <85% predicted).¹⁹ Despite interpretive criteria being different for preschoolers than for children and adults, and regardless of adherence to established standards, most spirometers will accept any attempt and a read-out will be possible. However, FENO testing uses a different respiratory maneuver, namely exhaling in a steady manner, and the NIOX MINO device will accept only read-out maneuvers that conform to recommended ATS standards. The variation in technique and individual ability to perform these tests and the differential information accrued regarding lung function parameters may have been anecdotal factors contributing to preference in using FENO testing over spirometry at the authors' center in the 4- to 7-year-old group.

The degree of asthma severity was significantly associated with FENO in this study when controlling for other variables. Worsening asthma control correlated with increasing FENO but was not included in regression analysis, because asthma control is a variable that changes over time. In this study, 64% of children 4 to 7 years old had no asthma diagnosis or well-controlled asthma. The children in the present study with poorly controlled asthma may have been less successful at performing FENO testing, which may have affected the proportion of children assessed as having no or well-controlled asthma. Studies on the relation between asthma severity and control and FENO levels have been conflicting, with 1 study reporting an increase in FENO levels before moderate exacerbations (loss of control) and another observing that use of FENO alone did not predict asthma control.^{6,33} Pifferi et al³³ used a model combining spirometry and FENO levels to discriminate between levels of asthma control, whereas Sardon-Prado et al⁷ found no agreement between FENO and other instruments used in assessing asthma control in pediatric patients. The limitation of relying on a single instrument in the assessment of this complex and heterogeneous disorder is well recognized, and FENO assessment in conjunction with other measures likely provides the best value.

A positive skin or blood allergy test result, indicative of allergic sensitization, was associated with an increase in FENO levels in the present population, which is consistent with previous reports of this relation in older children.^{30,34,35} Sordillo et al³⁵ specifically reported higher FENO levels in children with sensitization to indoor allergens (dog, cat, dust mite), and Cano-Garcinuno et al³⁶ found that the main determinant of FENO level was sensitization to house dust mite. The presence of allergic rhinitis has been associated with elevated FENO levels in older children; however, the present results showed only a marginally significant association in the 4- to 7-year-old children, even after controlling for asthma severity.^{29,37} Atopic dermatitis has allergic and nonallergic components and was found to correlate with higher FENO levels in the present study. Previous studies have reported varying results. A study by Xu et al³⁸ found no association between atopic dermatitis and FENO levels; however, a study by Dinakar et al³⁹ found higher FENO levels in children younger than 3 years with atopic dermatitis compared with healthy controls. Thus, it is important to evaluate for the presence of allergic sensitization and atopy when using FENO as a biomarker in the diagnosis and management of asthma.

The well-described association between ICSs and lower FENO levels in older children with asthma was supported in the present study of patients 4 to 7 years of age.^{2–4,7,11,24,40–42} In a study assessing the predictive accuracy of FENO to identify steroid response (inhaled fluticasone) in 52 patients presenting with undiagnosed respiratory symptoms, FENO predicted response to steroid (defined as >12% improvement in FEV₁ after 4 weeks of therapy with ICSs) better than other conventional predictors, such as peak flow, spirometry, bronchodilator response, and airway hyperresponsiveness measured at baseline.⁴³ Another study evaluated the onset of anti-inflammatory action of low and high doses

of a fixed combination of extra-fine beclomethasone dipropionate/formoterol. A clear dose response to the ICS was found for FENO within 2 days of treatment.⁴⁴ Use of LTRAs lacked a significant association with FENO levels in the present study, consistent with other studies showing that higher FENO levels are associated with a greater pulmonary response to ICSs over LTRAs in children.^{45,46} As described earlier, numerous publications recognize that FENO levels provide a measurement of T-helper type 2 cells/allergic inflammation, a key component that suggests persistence and severity of asthma. FENO levels correlate well with the likelihood of responsiveness to inhaled steroids and can be a marker of response to therapy.⁸ The present study was not designed to explore or quantify the role of FENO in clinical decision making. Nevertheless, the authors believe their findings that increasing FENO levels in children 4 to 7 years of age correlate with worsening asthma severity and with responsiveness to ICSs has the potential to supplement and enhance the management of asthma in this challenging age group.

With 825 children 4 to 18 years of age, the present study is also one of the largest reported samples of children undergoing office-based measurement of FENO as part of their ongoing care of asthma. The present analysis of this group supports previously reported findings of increasing FENO values with age and lower FENO values in girls.^{25,47} This study also enables a comparison of FENO levels across 2 groups (4 to 7 and > 7 to 18 years). The mean FENO was higher in the older group (34.3 vs 18.4 ppb), and the range of FENO values was much wider (<5–300 vs <5–89 ppb). In addition, a larger proportion of children in the older group had a FENO value higher than 35 ppb (37% vs 12%), the recommended cutoff value consistent with the phenotypic profile of eosinophilic allergic inflammation, as noted earlier.⁸

This study highlights unique and interesting facets of the use of this relatively new tool in the assessment and management of childhood asthma, although there are limitations. First, this is a retrospective, cross-sectional assessment of patients presenting to the authors' center for initial evaluation or follow-up of asthma, and these results may be limited by the small sample. Second, there was no comparison group of children without asthma. Third, the authors cannot comment on the ability of 4- to 7-year-old children to successfully perform FENO testing because they do not have information on the number of children who unsuccessfully attempted the maneuver and cannot compare the relative success rate of performance of FENO vs spirometry. Fourth, although the authors correlated FENO values with clinical variables using this dataset and verified the reported coefficients and significances with bootstrap analyses ($n = 10,000$), the possibility of over-fitting exists, with only 75 observations and 6 independent variables; however, the authors do not believe this to be the case. Although cognizant of the limitations of this study, the authors intentionally focused on patients younger than 7 years, because there are sparse existing data on this age group using the NIOX MINO device in the routine clinical care of asthma. There is substantial published literature in children > 7 to 18 years of age; therefore, this group was included in the present study for comparative purposes and to establish that the present sample population was similar to that of previous reports.

In conclusion, this study characterizes a relatively large group of children 4 to 7 years of age who underwent FENO testing as part of routine clinical evaluation of asthma using the NIOX MINO device. The relation between FENO values and important clinical characteristics in 4- to 7-year-old children receiving care for asthma appears to be similar to that in their older counterparts. In addition, analysis of a significant number of children 4 to 18 years old confirmed previously reported findings that FENO increases with age and is lower in girls. This preliminary study suggests that FENO testing may be feasible and useful in the ambulatory asthma

management of children as young as 4 years. Prospective, large-scale, randomized, control trials are needed to better characterize and understand the role of FENO in the clinical care of young children with asthma.

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