



The importance of atopy on exhaled nitric oxide levels in African American children

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ABSTRACT

Background: For physicians to be maximally effective in managing asthma in minority populations, a better understanding of the factors that affect fractional exhaled nitric oxide (FeNO) measurements in African Americans is needed.

Objective: To examine demographic, environmental, and physiologic factors that influence FeNO measurements in African American children with and without asthma.

Methods: A cross-sectional study of 128 African American children aged 7 to 18 years (44% with asthma) was conducted. FeNO measurements, skin prick tests (as a measure of atopy), spirometry, and questionnaire data were obtained from all participants. Regression models were constructed after identifying factors significantly associated on univariate analysis.

Results: Among all study participants, the mean FeNO measurement at baseline was 24.4 ppb. Children with asthma had a higher level than those without (30.9 vs 19.3 ppb, $P = .002$). When examining all children through logistic regression analysis, an elevated FeNO level was significantly associated with atopy, lower spirometric values, and current asthma ($P < .05$ for all). Among asthmatic children, univariate analysis revealed that an elevated FeNO level was associated with inhaled corticosteroid use, recent respiratory infection, and atopy ($P < .05$ for all). However, only atopy remained significant after regression analysis. For asthmatic and nonasthmatic children, FeNO levels were directly correlated with the number of positive skin test results.

Conclusion: In African American children with and without asthma, FeNO levels are strongly influenced by atopy. Guidelines for FeNO measurements that incorporate atopic status are needed.

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Introduction

Fractional exhaled nitric oxide (FeNO) has emerged as a potential biomarker for eosinophilic airway inflammation. Eosinophils are thought to release cytokines and additional inflammatory mediators, which in turn stimulate epithelial cells to produce nitric oxide.^{1–3} Patients with eosinophilic asthma often have elevated FeNO levels during an exacerbation, and these levels may normalize after treatment with glucocorticoids.^{4–6} Compared with spirometry and peak expiratory flow readings, some studies have found that FeNO may be a better predictor of response to corticosteroid treatment.^{7,8} In addition, FeNO measurements are noninvasive and can be readily obtained in clinical practice.

Despite its potential advantages, appropriate clinical application of FeNO measurements remains ambiguous. The American Thoracic Society has recommended specific FeNO levels to guide patient care

in asthma management.⁹ Clinical use of exhaled nitric oxide, however, has yielded conflicting results. Although some studies have found no benefit in using FeNO measurements,^{10,11} another trial found that using an FeNO-based algorithm lowered exacerbation rates and mean dose of inhaled glucocorticoids.¹² Although varying study designs may have contributed to the inconsistent results, confounding factors likely influenced FeNO measurements and outcomes. Previous studies have suggested that age, atopy, cigarette smoking, air pollution exposure, and upper respiratory tract infections (URIs) may affect FeNO levels.¹³ Differences in race and ethnicity may also influence FeNO levels in both children and adults.^{14,15} Therefore, a better understanding of specific factors that influence FeNO levels is critical to enhance its clinical value.

Some authors have suggested that an incomplete understanding of airway pathophysiology and genetics contributes to inadequate, incorrect, and ineffective asthma treatment strategies.^{16–18} This knowledge gap amplifies the health disparities seen in asthma because minority populations may have different pathophysiologic properties and therapeutic responses.^{18–20} The prevalence rates for current asthma in the United States indicate that 9.3% of children have asthma, although this rate is 16.0% among African American

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Table 1
Characteristics of the study participants^a

Characteristic	All children (n = 128)	Asthmatic children (n = 56)	Nonasthmatic children (n = 72)	P value ^b
Age, mean (SD), y	11.8 (3.1)	11.5 (3.1)	12.1 (3.0)	.26
Female	66 (51.6)	19 (33.9)	47 (65.3)	<.001
BMI, mean (SD)	21.9 (5.9)	21.1 (5.4)	22.5 (6.2)	.21
Overweight or obese	33 (25.8)	11 (20.8)	22 (31.0)	.20
Allergies or hay fever	47 (36.7)	34 (60.7)	13 (18.1)	<.001
Eczema	44 (34.4)	28 (50.0)	16 (22.2)	.001
URI in 2 weeks	40 (31.3)	20 (35.7)	20 (27.8)	.34
Home smoke exposure	47 (36.7)	22 (39.3)	25 (34.7)	.60
Atopic sensitivity	79 (61.7)	43 (76.8)	36 (50)	.002
FEV ₁ , mean (SD), % predicted	97.4 (17.7)	95.7 (17.7)	98.7 (17.7)	.36
FEV ₁ /FVC, mean (SD)	87.3 (7.7)	86.3 (8.1)	88.0 (7.4)	.20
FeNO, mean (SD)	24.4 (20.7)	30.9 (26.0)	19.3 (13.0)	.002
Elevated FeNO	15 (11.7)	11 (21.2)	4 (6.0)	.01

Abbreviations: BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; URI, upper respiratory tract infection.

Data are presented as number (percentage) of children unless otherwise indicated.

P value is for comparison between those with and without asthma.

children.²¹ Unfortunately, severity and disease control are also significantly worse in this group. For example, the 2010 age-adjusted hospitalization rate among whites in Michigan was 11.2 per 10,000 people, whereas for blacks it was 45.1 per 10,000.²² A more complete understanding of the factors that influence FeNO measurements in African American children is needed for physicians to be maximally effective in its treatment. The goal of this study was to examine demographic, environmental, and physiologic factors that influence FeNO measurements in African American children and adolescents and specifically in those with asthma.

Methods

Participants and Protocol

Participants were self-identified African American children (with and without asthma) seen at a general pediatric clinic in Ypsilanti, Michigan (a city where one-third of the population is African American, and the median income is \$31,469). Children were 7 to 18 years old at the time of enrollment. Participants with any known cardiac or pulmonary condition other than asthma were excluded. Children and their parents or guardians were provided a questionnaire (see below) and underwent FeNO measurement, skin prick testing for common inhalant allergens, and spirometric testing. Participants were recruited through the use of flyers posted throughout the clinic. The entire study protocol was approved by the University of Michigan Institutional Review Board, and written informed consent was obtained from all participants.

Baseline Measurements

A questionnaire administered to all study participants assessed the following information: sex, home smoke exposure, weight, body mass index (BMI), URIs within the past 2 weeks, and physician diagnosis of allergy, asthma, or eczema. Patient with current asthma also provided asthma-specific information: current medications, prior history of intensive care unit stay or intubation for asthma, and hospitalization, emergency department, or urgent care visits in the previous year for an asthma exacerbation. Asthma quality of life was assessed with the Mini Pediatric Asthma Quality of Life Questionnaire (PAQLQ),²³ and asthma control was determined by the Asthma Control Questionnaire (ACQ).²⁴

All study patients with and without asthma performed spirometric measurements. The test was performed according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines.²⁵ Both the forced expiratory volume in 1 second (FEV₁) and the ratio of FEV₁ to forced vital capacity (FVC) were recorded as percent predicted for age, height, sex, and ethnic origin.

Skin prick testing was also performed for all study participants. This was accomplished using a panel of common allergens: house dust mite mix, grass mix, tree mix, weed mix, mold mix, and cockroach, cat, and dog epithelia. ComforTen lancets were used (Hollister-Stier Allergy, Spokane, Washington). The wheal diameter was recorded at 15 minutes, and the test result was interpreted positive if the wheal was at least 3 mm greater than the saline control.²⁶ Participants were classified as atopic if any of the 8 allergens were apparent on skin prick testing.²⁷

To obtain FeNO measurements, the online single-breath method was used with the NIOX MINO device (Aerocrine Inc, Morrisville, North Carolina), according to ATS/ERS guidelines.²⁸ This device uses a dynamic flow controller to ensure an exhalation flow rate of 50 mL/s. Each participant underwent coaching of the proper method before taking the measurements. As specified by the ATS guidelines, an FeNO measurement was considered elevated if the value was 35 ppb or more for children between the ages of 7 and 11 years and 50 ppb or more for children between the ages of 12 and 18 years.⁹

Statistical Analysis

Bivariate calculations for demographic information between those with and without asthma were obtained using a *t* test or Mann-Whitney test as appropriate. Next, associations with FeNO levels analyzed as a continuous variable were made using Pearson correlations or *t* tests for variables that were continuous or dichotomous, respectively. FeNO was also analyzed as a dichotomous outcome (elevated or normal), using a χ^2 test or *t* test for

Table 2
Asthma features

Feature	No (%) of asthmatic children (n = 56) ^a
Use of ICS	21 (37.5)
Use of ICS and LABA	7 (12.5)
Use of montelukast sodium	11 (19.6)
ACQ score, mean (SD)	1.3 (1.23)
PAQLQ, mean (SD)	5.4 (1.4)
History of ICU stay	7 (12.5)
History of intubation	5 (8.9)
Hospitalization, ED visit, or UC visit in past year	15 (26.8)
Has asthma action plan	37 (66.1)

Abbreviations: ACQ, Asthma Control Questionnaire; ED, emergency department; ICS, inhaled corticosteroid; ICU, intensive care unit; LABA, long-acting β -agonist; PAQLQ, Pediatric Asthma Quality of Life Questionnaire; UC, urgent care.

^aData are presented as number (percentage) of children unless otherwise indicated.

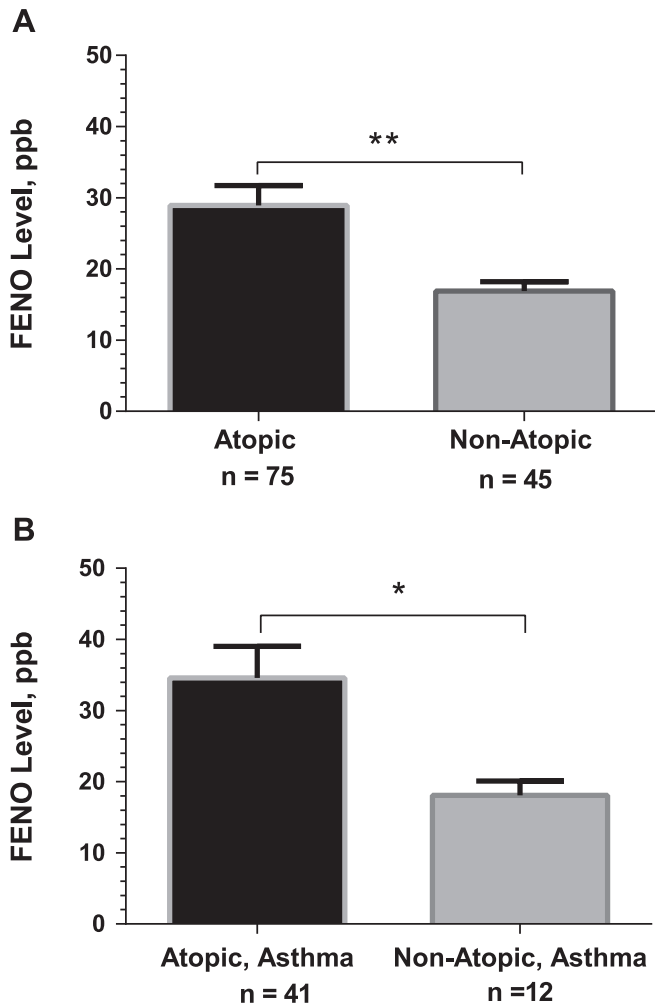


Figure 1. Comparison of fractional exhaled nitric oxide (FeNO) levels between atopic and nonatopic children (A) and between atopic asthmatic and nonatopic asthmatic children (B). Error bars indicate SEM. ** $P \leq .001$, * $P \leq .05$.

variables that were dichotomous or continuous, respectively. For variables that were not normally distributed, nonparametric analyses were used.

Logistic regression analyses with backward selection were next used to identify the odds ratios (ORs) for the effect of specific variables on an elevated FeNO level as defined by the ATS criteria. Multivariate linear regression was calculated for FeNO analyzed as a continuous variable. Independent variables included in both regression models were those found to be significant on bivariate analysis. Calculations were performed for all study participants and also only on those with asthma. Atopic skin test results were analyzed as both ordinal and dichotomous variables in separate models. Data were analyzed using a statistical software program (SPSS, version 19.0; SPSS Inc, Chicago, Illinois).

Sample size determination was based on previous cross-sectional studies that assessed factors associated with FeNO levels and consideration of the number of variables to be entered into the regression models. A sample of 110 was determined to be adequate for the purpose of this study.

Results

Baseline Characteristics

A total of 128 children aged 7 to 18 years were enrolled (Table 1). Of these, 56 children (44%) were under current physician care for

asthma. Compared with the children without asthma, asthmatic children were more likely to have allergic rhinitis or hay fever (60.7% vs 18.1%, $P < .001$), eczema (46.4% vs 13.9%, $P = .001$), male sex (66.1% vs 34.7%, $P < .001$), and atopic sensitization to at least one inhalant tested (76.8% vs 50%, $P = .002$). When examining FeNO levels, asthmatic children had a greater level than nonasthmatic children (30.9 vs 19.3 ppb, $P = .04$) and were more likely to have an FeNO level classified as elevated (21.2% vs. 6.0%, $P = .01$). As indicated in Table 1, there was no significant difference in terms of age, BMI, obesity, height, URI in the previous 2 weeks, or exposure to environmental smoke at home between asthmatic and nonasthmatic children. There was also no significant difference in FEV₁ percent predicted or FEV₁/FVC ratio between the 2 groups.

Table 2 lists features of children with current asthma ($n = 56$). More than a third of the asthmatic children were taking an inhaled corticosteroid (ICS), whereas 12.7% were taking a combination of an ICS and long-acting β -agonist (LABA). During the previous year, 15 (26.8%) of the asthmatic children had an emergency department visit, urgent care visit, or hospitalization for an asthma exacerbation. The mean ACQ score was 1.3, indicating asthma was not well controlled. The mean PAQLQ score was 5.4, indicating significant interference with quality of life. An asthma action plan was available for most children (66%). Of note, a significant number of children (12.7%) had a history of an intensive care unit stay for asthma exacerbation, and 8.9% of the asthmatic children had been intubated previously.

Correlation of FeNO level With Clinical Characteristics in All Children

Of the 128 children who attempted to provide FeNO measurements, 120 (93.8%) were able to do so successfully. Among these 120 children, an FeNO level in the elevated range (per ATS criteria) was positively correlated with a current diagnosis of asthma ($P = .01$) and atopy as detected by a positive skin prick test result ($P = .001$). An elevated FeNO level was negatively correlated with FEV₁/FVC percent predicted ($P = .001$). When FeNO was analyzed on a continuous scale, similar results were found. There was a negative correlation between FeNO and FEV₁/FVC ($P < .001$) and a positive correlation with a current diagnosis of asthma ($P = .002$), ever been diagnosed with asthma ($P = .007$) or eczema ($P = .03$), and atopy as detected by positive skin prick test results ($P < .001$). There was no association between FeNO and BMI, obesity, FEV₁ percent predicted, sex, home smoking exposure, or URI in the previous 2 weeks. As shown in Figure 1A, the FeNO levels of atopic children were significantly higher than those of nonatopic children (28.9 vs 16.9 ppb, $P = .002$).

A logistic regression analysis for all children ($n = 120$) was constructed (Table 3). Factors that remained significantly associated with an elevated FeNO included atopy, a lower percent predicted FEV₁/FVC, and a diagnosis of current asthma. Each additional positive skin test result conferred a 1.74-fold increased risk of having an elevated FeNO level.

Multivariate linear regression analysis was performed assessing FeNO levels as a continuous variable. FeNO levels were found to be

Table 3

Logistic regression analysis of factors associated with an elevated FeNO among all 120 children

Factor	OR (95% CI)	P value
Atopy	1.74 (1.25–2.43)	.001
FEV ₁ /FVC	0.898 (0.821–0.982)	.02
Asthma	4.50 (1.07–18.86)	.04

Abbreviations: CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; OR, odds ratio.

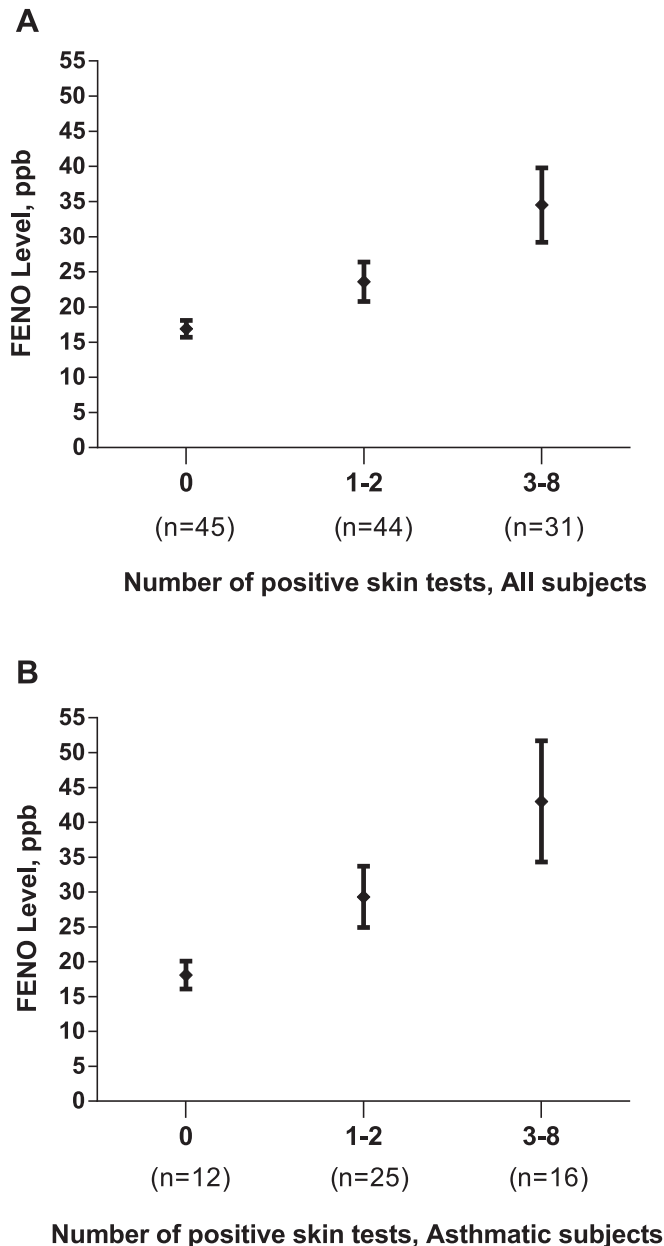


Figure 2. Comparisons of fractional exhaled nitric oxide (FeNO) levels based on the number of positive skin test results in all children (A) and in asthmatic children (B). Error bars indicate SEM. For both figures, $P \leq .05$ by analysis of variance.

associated with FEV₁/FVC (β -coefficient = -0.758 , $P = .001$), asthma diagnosis (β -coefficient = 6.713 , $P = .04$), and atopy (β -coefficient = 4.714 , $P < .001$). As shown in Figure 2A, FeNO levels were directly correlated with the number of positive skin test results. Among those with at least 1 positive skin test result ($n = 75$), the FeNO level was higher in asthmatic children compared with nonasthmatic children (34.6 vs 22.1 ppb, $P = .03$). However, among those who were nonatopic ($n = 45$), there was no difference in FeNO levels between those with and without asthma (18.1 vs 16.4 ppb, $P = .57$) (data not shown).

Correlation of FeNO Levels With Clinical Characteristics in Children With Asthma

Of the 56 children with asthma, 53 (94.6%) were able to provide an acceptable FeNO measurement. Among children with current asthma,

an elevated FeNO level was associated with use of an ICS or ICS-LABA combination ($P = .02$), having a URI in the past 2 weeks ($P = .03$), and atopy on skin testing ($P = .04$). When analyzing FeNO as a continuous value, associations were found with the FEV₁/FVC ratio ($P = .014$), cold in the previous 2 weeks ($P = .02$), ICS or ICS-LABA combination use ($P = .03$), and atopy on skin testing ($P < .001$). There was no association between FeNO and age, sex, BMI, FEV₁, home smoking exposure, eczema, ACQ, or PAQLQ. As shown in Figure 1B, the FeNO levels of atopic asthmatic children were significantly higher than those of nonatopic asthmatic children (34.6 vs 18.1 , $P = .05$).

Next, logistic regression analysis was performed to assess factors associated with an elevated FeNO level in asthmatic children. After controlling for confounding, a cold in the previous 2 weeks and ICS or ICS-LABA combination use no longer remained significant; atopy remained the only factor significantly associated with an elevated FeNO level. For each additional positive allergic skin test result, the likelihood of having an elevated FeNO level increased 1.68-fold ($P = .02$).

Linear regression analysis compared FeNO on a continuous scale with multiple independent predictors in asthmatic children. FeNO levels were negatively correlated with FEV₁/FVC (β -coefficient = -0.845 , $P = .03$) and were strongly correlated with atopy on skin testing (β -coefficient = 7.824 , $P < .001$). No other factors were significant. As shown in Figure 2B, FeNO levels were directly correlated with the number of positive skin test results among asthmatic children.

Discussion

Although FeNO measurements have the theoretical ability to improve asthma care for African Americans, results have been unimpressive to date. One recent study of urban minority children with asthma concluded that FeNO may not be a clinically useful predictor of asthma exacerbations, and another found that implementation of FeNO guideline-based care resulted in no additional benefit when combined with National Asthma Education and Prevention Program guidelines.^{29,30} This may be due to an incomplete understanding of the properties and characteristics of FeNO in African Americans. A search of the medical literature through PubMed identified only 9 articles when combining the search terms *exhaled nitric oxide with African American*.

When examining the African American children in our study, FeNO levels were greater than those reported in other races/ethnicities. For the entire cohort, the FeNO level was approximately 24 ppb, which is higher than levels seen in studies of participants of different ethnicities. The trend of an elevated FeNO levels among African American children has been previously noted, including evaluation of National Health and Nutrition Examination Survey data.¹⁴ In that study, the FeNO level of African American children aged 6 to 11 years was approximately 40% higher than that of white children aged 6 to 11 years. Therefore, the current ATS guidelines for elevated FeNO levels may be inappropriate for African Americans.

The use of FeNO has been proposed as a useful screening modality for asthma. Our study indicates this finding is true among African American children, even after controlling for other factors. However, this difference was primarily seen among atopic children; among nonatopic children, there was no difference in FeNO levels between asthmatic and nonasthmatic children.

Among those African American children with asthma, atopy was strongly associated with elevated FeNO levels. In fact, no nonatopic asthmatic children had an elevated FeNO level. Our results were consistent with studies in other ethnic populations, which have found that FeNO levels are significantly influenced by allergic sensitivity. For example, the Isle of Wight birth cohort study of

approximately 800 participants found no difference in FeNO levels between nonatopic asthmatic children and nonatopic non-asthmatic children.²⁷ In that study, the highest FeNO levels were observed in atopic asthmatic children, similar to the findings of this study. Similarly, a recent prospective study by Elmasri et al.³¹ found that atopic asthmatic adolescents consistently had the greatest FeNO level and that the FeNO level was higher among non-asthmatic atopic children than among nonatopic asthmatic children.

In contrast, some authors did not find an association between atopy and FeNO levels, including a study performed in a South American population.³² That study was performed exclusively during winter months, and it is possible that lack of allergen exposure may have influenced the findings. In addition, another study found that time of day can affect FeNO levels.³³ Finally, other pulmonary conditions, such as sarcoidosis, interstitial lung disease, and eosinophilic bronchitis, can be associated with elevated FeNO levels.⁹ These issues deserve further investigation among African American individuals.

In our study, asthma, atopy, and lung function influenced FeNO levels in African American children. Just as important were factors that were *not* associated with elevated FeNO levels. Age, BMI, environmental tobacco exposure, and sex did not appear to influence FeNO levels in African American children regardless of asthma status. Although other authors have found an association with these factors in different patient populations, many did not assess the role of atopy. Alternatively, specific genetic and epigenetic differences in African American individuals may influence FeNO levels in ways not observed among other race/ethnicities. In this study, a recent URI or the use of an ICS was no longer significant when accounting for atopy. Therefore, use of FeNO as a marker of controller adherence (which has been proposed)³⁴ may not be appropriate among asthmatic African American children if atopy is not considered.

In conclusion, FeNO levels of African American children are strongly influenced by atopy detected through skin prick testing. The significant influence of atopy on FeNO levels may explain the lack of positive results in trials of African American children when atopic status is not accounted for. FeNO levels may yet prove to be a useful screening and treatment tool for asthma in African American children. However, for FeNO to reach its full potential in asthmatic and nonasthmatic African American children, predictive models incorporating atopic status are needed.

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