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Association of fractional exhaled nitric oxide with asthma morbidity in urban minority children

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ABSTRACT

Objective: Fractional exhaled nitric oxide (FeNO) is a well-established measure of allergic airway inflammation and possible useful adjunct disease management tool. We investigated the association of baseline and follow-up FeNO measurements with disease burden in minority children with persistent asthma.

Methods: A retrospective chart review was conducted on 352 African American and Hispanic children seen at an urban Asthma Center in Bronx, NY. Demographic, clinical characteristics, and pulmonary function tests (PFTs) were compared between children with low, intermediate, and high baseline FeNO levels. Among 95 children with subsequent follow up visits, associations of change in FeNO with demographics, clinical characteristics, and PFTs were examined using mixed effects linear regression models.

Results: A higher proportion of children with intermediate (54%) and high FeNO (58%) levels had lower airways obstruction compared to those with low FeNO levels (33%). Children with intermediate FeNO levels had more annual hospitalizations (2.8 ± 6.2) compared to those with low and high FeNO levels (1.3 ± 2.8 and 1.3 ± 2.5). These associations did not differ between ethnicities. An increase in FeNO over time was associated with higher BMI z-scores ($\beta = 6.2$, 95% CI: 1.0 to 11.4) and two or more hospitalizations in the past year ($\beta = 16.1$, 95% CI: 1.5 to 30.8).

Conclusions: Intermediate and high FeNO levels are associated with lower airways obstruction and hospitalizations. Initial and serial FeNO measurements can be a useful adjunctive tool in identifying asthma-related morbidity in urban African American and Hispanic children.

Abbreviations: ACT: asthma control test; ANOVA: analysis of variance; ATS: American Thoracic Society; BMI: body mass index; BTS: British Thoracic Society; CI: confidence interval; EMR: electronic medical records; ER: emergency room; ERV: expiratory reserve volume; FEF_{25-75%}: forced expiratory flow at 25-75%; FeNO: fractional exhaled nitric oxide; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; GE: gastroesophageal; ICS: inhaled corticosteroids; LABA: long acting beta agonist; NHLBI: National Heart Lung and Blood Institute; NICE: National Institute for Health and Care Excellence; OR: odds ratio; PFTs: pulmonary function tests; RAST: radioallergosorbent; RV: residual volume; SD: standard deviation; SPT: skin prick test; TLC: total lung capacity

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Introduction

Asthma affects 8.4% of children in the United States, and is more prevalent among minorities, including non-Hispanic African Americans and Hispanics, relative to non-Hispanic Whites (1). Pulmonary function (PFTs) testing is an integral part of asthma severity classification, asthma control, and can help guide

disease management (2). Fractional exhaled nitric oxide (FeNO), is a quick, easy and noninvasive measurement of allergic airway inflammation that provides adjunctive information for disease phenotyping and management by supporting the contribution of allergic inflammation to pulmonary function deficits (3). It is a test that can be used in a wide age range in

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children, as well as in high and low income countries (4). Although FeNO quantification has been standardized, there are few reference guidelines for health care providers on its optimal use in diagnosing and monitoring pediatric asthma, including in minority populations, a limitation highlighted in the recent National Heart Lung and Blood Institute (NHLBI) Asthma Expert Panel Report 4 (EPR-4) (3,5,6).

Pediatric studies on FeNO support its diagnostic value in steroid naïve asthmatics and in nonsmokers, but not in other populations (5). Low baseline FeNO levels are consistent with nonatopic as well as well controlled atopic asthma with corticosteroid adherence, while intermediate levels must be interpreted with caution, and high levels are consistent with allergic airway inflammation (6). Subsequent or serial FeNO measurements aid in monitoring medication adherence, especially to inhaled corticosteroids (ICS), where a decrease in FeNO of 10 parts per billion (ppb), or by 20%, is deemed clinically relevant (3). Higher FeNO levels have also been linked to increased risk of future asthma exacerbations and poorer asthma control (7,8). Persistently elevated levels could be secondary to inadequate inhaled corticosteroid dose, poor adherence, environmental exposures, changes, or lack of medication responsiveness (6,9).

Apart from disease, demographic factors also contribute to variability in FeNO values. While FeNO increases with age and height (10), it varies by ethnicity (11–15). Healthy non-Hispanic African Americans and Hispanic children have been reported to have higher FeNO levels than non-Hispanic White children (13–15), which may be due to differences in atopy, societal influences, or genetics. However, there is a paucity of studies investigating the role of FeNO in asthma management in these populations, which limits our understanding of the contribution of these factors on FeNO levels in these populations (11,13,16–19). Currently, the contribution of FeNO measurement to the management of pediatric moderate to severe asthma, particularly among minority ethnicities and those not medication naïve at the time of clinical evaluation, is highlighted by NHLBI EPR-4 as an area with low level of evidence (6).

To address these gaps in knowledge, we aimed to study and compare the association of FeNO with asthma burden, defined as asthma severity, control, school days missed, emergency room and hospital visits related to asthma, along with medication use, and pulmonary function tests in urban non-Hispanic African American and Hispanic children with persistent asthma. We wanted to understand the relationship of how baseline FeNO levels relate to these

factors, in addition to how the change in FeNO over time may be associated with these variables. Our sub aim was to elucidate the utility of intermediate FeNO levels in this population, since intermediate range of FeNO is not defined as normal or elevated in the ATS, British Thoracic Society (BTS), and National Institute for health and Care Excellence (NICE) recommendations (3,20,21) yet may be influenced by both disease as well as ethnicity in this population (1,11–15). We hypothesized that baseline and serial measures of FeNO serve as a marker of asthma severity and control, pulmonary function test deficits, and medication need among urban non-Hispanic African American and Hispanic children with asthma, independent of ethnicity.

Materials and methods

Study population

A retrospective chart review was conducted on 352 children with asthma, ages 7–20 years, who were seen at the Asthma Center at the Children's Hospital at Montefiore in the Bronx, NY between September 2015 and March 2017 who were able to perform FeNO testing. Asthma was defined based on the presence of a physician diagnosis with evidence of respiratory distress with bronchospasm that was responsive to short-acting bronchodilator administration, with or without systemic corticosteroids. The Center serves children with high disease burden referred by their primary care provider for poor disease control or from the hospital if a child has had frequent ED or hospitalization visits due to asthma. Visits to the Center are scheduled at least four weeks following an ED visit or hospitalization. Twenty-nine patients were excluded due to co-morbid conditions that affect FeNO levels, including eosinophilic esophagitis ($n=2$), primary ciliary dyskinesia ($n=1$), sickle cell disease ($n=18$), autoimmune disorders ($n=4$), immunodeficiencies ($n=3$), and Churg Strauss syndrome ($n=1$) (Figure 1). Of the 323 children retained in the analysis, longitudinal data was available on 95 patients who returned to the clinic for at least one follow-up visit (Figure 1). The Institutional Review Board at Montefiore Medical Center and Albert Einstein College of Medicine, NY, approved this study (IRB #2016-7026).

FeNO quantification and classification

FeNO was quantified by a PFT laboratory technician using NIOXVERO® Airway Inflammation Monitor.

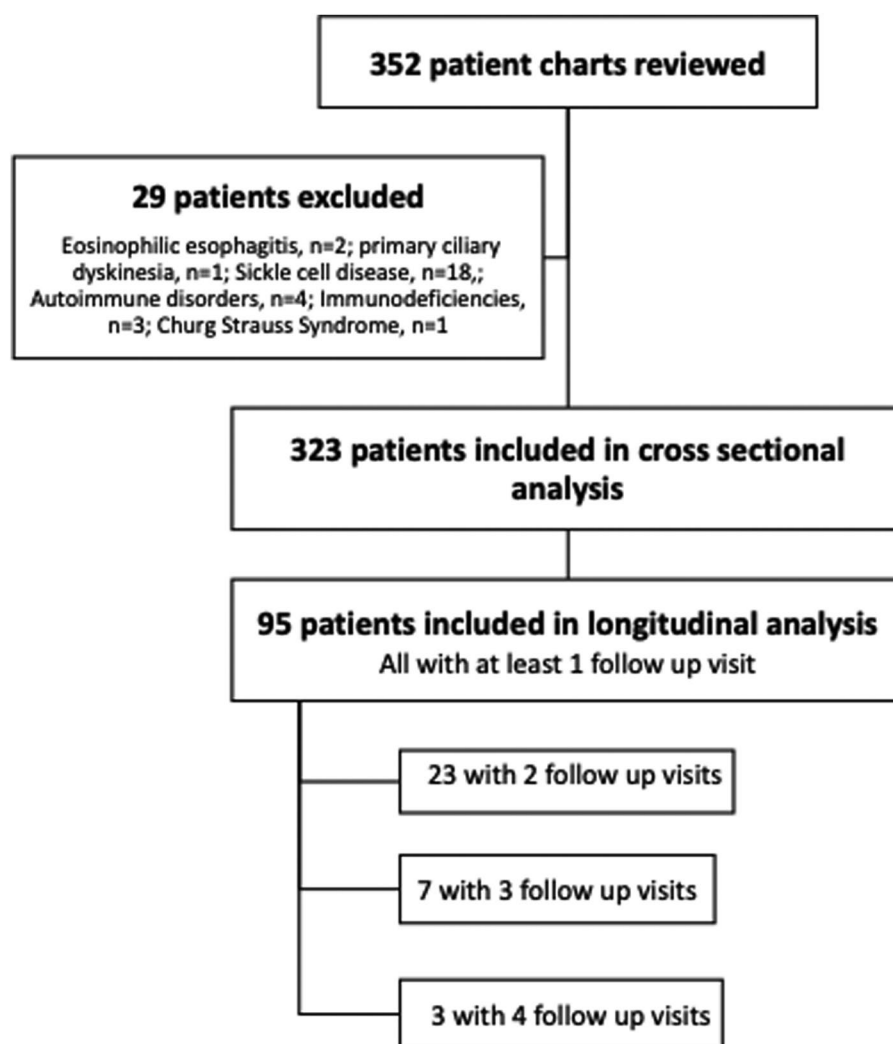


Figure 1. Flow diagram of patients included in study.

Patients were given up to five attempts for a reliable FeNO measurement. Baseline and subsequent FeNO levels were abstracted from electronic medical records (EMR). Based on the American Thoracic Society (ATS) criteria (3), FeNO levels were categorized as low or normal (<20 ppb in children 7-11 years or <25 ppb in children ≥ 12 years), intermediate (20-35 ppb in children 7-11 years or 25-50 ppb in children ≥ 12 years), or high (> 35 ppb in children 7-11 years or >50 ppb in children ≥ 12 years) (3). Baseline FeNO levels reflect the first time patients underwent FeNO testing in clinic.

Demographic and clinical co-variables

Demographic and anthropometric variables, asthma characteristics, co-existent co-morbidities, environmental exposures, season, and PFTs at the time of baseline and subsequent FeNO measurement were abstracted from the EMR to investigate their

association with FeNO categories. Demographic and anthropometric data included age, sex, self-reported ethnicity and race, height, weight, and BMI percentile. Asthma data included severity classified by providers using the National Heart Lung and Blood Institute (NHLBI) guidelines, as well as number of school days missed, ER visits, and hospitalizations due to asthma in the past 12 months. Asthma symptom control was based on the Asthma Control Test (ACT) (asthma controlled defined as ≥ 20 using either ACT in children 4-11 years old or 12 years old and older). Medication use was based on medical provider documentation of use of ICS, ICS with a long-acting beta agonist (ICS/LABA), leukotriene receptor antagonist (e.g. Montelukast), oral anti-histamines, and nasal anti-allergy (including steroids and anti-histamine) medications.

Co-morbidities included eczema, gastroesophageal (GE) reflux, allergic rhinitis, sleep disordered breathing, and atopy. Atopy was defined as one or more

positive radioallergosorbent (RAST) tests or skin prick tests (SPT) to common environmental allergens in the northeast coast. Environmental exposures included presence of a humidifier, rugs, curtains, mold, cockroaches, mice, rats, dogs, cats, stuffed toys, and secondhand smoke obtained from parental and/or patient history.

PFTs included spirometry and lung volumes, which were conducted as per ATS guidelines (22,23) on the same clinic visit day as FeNO measurements. For spirometry, percent predicted forced vital capacity (FVC), forced expiratory volume in on second (FEV₁), FEV₁/FVC and mid-expiratory flow rates, forced expiratory flow at 25–75% (FEF_{25-75%}), based on the National Health and Nutrition Examination Survey (NHANES) reference values (24) and for lung volumes, percent predicted functional residual capacity (FRC), expiratory reserve volume (ERV), residual volume (RV) and total lung capacity (TLC) as well as the RV/TLC ratio, calculated using equations developed by the ATS workshop (25), were included in the analysis. Lower airways obstruction was defined as FEV₁/FVC <80% (26).

Statistical analysis

In the cross sectional analysis, the primary aim was to examine association of the three FeNO categories with asthma morbidity (including severity, control, school days missed, ED visits, hospitalizations, pulmonary function, and asthma and allergy-related medication use). In addition, demographic variables, co-morbidities, and environmental exposures were compared between the three FeNO categories. The association of continuous variables with the FeNO categories were analyzed using Analysis of Variance (ANOVA), while categorical variables were analyzed using χ^2 test; all tests were two sided with significance level $\alpha=0.05$. Based on results from bivariate analyses, we used multinomial logistic regression analysis to examine association between baseline FeNO categories and variables that were independent predictors of outcomes, including measures of asthma morbidity (27).

For longitudinal analysis, we included 95 children who had at least one follow-up visit; $n=23$ (24%) of them had two follow-up visits. The change in FeNO was defined as the difference in FeNO measurements between baseline and follow-up visits; the distribution of outcome did not violate normality assumptions. The average time to follow up were categorized as 1-3 months or more than 3 months based on clinical practices and to account for the time needed for

medication modification to take effect. We used mixed effects linear regression models to examine associations between change in FeNO with demographic and clinical variables (as fixed effects), whereas the patient was modeled as random effect to account for correlations that existed between repeated measurements in the same person over time. Variables that showed an association with change in FeNO in the univariate analysis with a p values of <0.1 were included in the multivariate model that also included demographic factors such as age, sex, ethnicity, race, and baseline FeNO category. The study had 80% statistical power to detect associations (ORs) of 2-fold or higher with exposure prevalence of 10% or higher (with a type I error rate of $\alpha=5\%$; 2-sided). All data analyses were performed using IBM SPSS Statistics version 25 and Stata version 15 (StataCorp LP, College Station, TX).

Results

Demographics of the study cohort

The average age of the 323 children in the study cohort was 11.8 years (SD = 3.4), 50% were female, 33% were African-American, and 53% were Hispanic. The mean FeNO level for the entire cohort was 34.5 ppb (SD = 35.1), while the median FeNO level was 20 ppb (IQR 25%-75%: 10-46). There was no difference in baseline demographic characteristics between the three FeNO categories (low, intermediate, and high FeNO levels), other than atopy, which was present in a higher proportion of children in intermediate (79.1%) and high (78%) compared to low FeNO (54.5%) categories (Table 1).

Cross sectional association of FeNO with asthma morbidity

Asthma characteristics differed between the three FeNO categories (Table 2). While 16.5% of children with high FeNO were classified as severe asthmatics, only 6.1% in the low, and 9% in the intermediate FeNO categories, fell under this classification. Mean hospitalizations in the past year were highest in the intermediate FeNO category (2.8 ± 6.2) compared to the low (1.3 ± 2.8) and high (1.3 ± 2.5) FeNO categories (Table 2). Asthma controller and anti-allergic medication use (Table 2) as well as co-morbidities or environmental exposures (Supplemental Table S1) did not differ between the three FeNO categories.

PFTs also differed between the FeNO categories. Children in intermediate and high FeNO categories had lower mean percent-predicted FEV₁ (88.4 ± 16 and

Table 1. Baseline demographic characteristics stratified by FeNO category.

Variable ^a	All (n=323)	Low FeNO (n=165)	Intermediate FeNO (n=67)	High FeNO (n=91)	P-value
Age, mean $\pm$ SD	11.8 $\pm$ 3.4	11.5 $\pm$ 3.4	12.1 $\pm$ 3.5	12.2 $\pm$ 3.4	0.2
Sex, n (%)					
Male	162 (50.2)	81 (49.1)	33 (49.3)	48 (52.7)	0.84
Female	161 (49.8)	84 (50.9)	34 (50.7)	43 (47.3)	
Ethnicity, n (%)					
Non-Hispanic	128 (39.6)	56 (33.9)	30 (44.8)	42 (46.2)	0.12
Hispanic	172 (53.3)	96 (58.2)	31 (46.3)	45 (49.5)	
Race, n (%)					
African American	107 (33.1)	46 (27.9)	23 (34.3)	38 (41.8)	0.2
White	24 (7.4)	15 (9.1)	4 (6.0)	5 (5.5)	
Asian, American Indian/Alaskan	5 (1.5)	2 (1.2)	1 (1.5)	5 (5.5)	
Other/Mixed ^b	151 (46.7)	88 (53.3)	26 (38.8)	37 (40.7)	
Height, cm mean $\pm$ SD	148.7 $\pm$ 15	147.1 $\pm$ 15.3	148.3 $\pm$ 13.7	151.8 $\pm$ 15.2	0.06
Weight, kg mean $\pm$ SD	56.2 $\pm$ 26.8	54.9 $\pm$ 27.9	57.2 $\pm$ 26.3	57.9 $\pm$ 25.2	0.66
BMI Z-score, mean $\pm$ SD	1.2 $\pm$ 1.5	1.1 $\pm$ 1.1	1.2 $\pm$ 1.1	1.3 $\pm$ 2.3	0.67
Obese, n (%)	133 (41.2)	68 (41.2)	31 (46.3)	34 (37.4)	0.53
Atopic ^c , n (%)	214 (66.3)	90 (54.5)	53 (79.1)	71 (78)	<0.001
Season FeNO collected, n (%)					
Spring	85 (26.3)	51 (30.9)	15 (22.4)	19 (20.9)	0.23
Summer	39 (12.1)	22 (13.3)	10 (14.9)	7 (7.7)	
Fall	66 (20.4)	30 (18.2)	12 (17.9)	23 (25.2)	
Winter	133 (41.2)	62 (37.6)	30 (44.8)	41 (45.1)	

a: The number of children on whom race and ethnicity data was available are: ethnicity, $n=300$; race, $n=287$.

b: Of these Other/Mixed race, 131 (86%) out of the 151 patients identified as Hispanic patients.

c: Atopy was classified as a positive reaction to one or more allergens on skin prick testing and/or radioallergosorbent testing.

FeNO: Fractional exhaled Nitric Oxide.

SD: Standard Deviation.

BMI: Body Mass Index.

Table 2. Baseline asthma morbidity characteristics stratified by FeNO category.

Variable ^a	All (n=323)	Low FeNO (n=165)	Intermediate FeNO (n=67)	High FeNO (n=91)	P-value
Severity, n (%)					
Intermittent	37 (11.5)	26 (15.8)	6 (9.0)	5 (5.5)	0.04
Mild Persistent	92 (28.5)	43 (26.1)	21 (31.3)	28 (30.8)	
Moderate Persistent	160 (49.5)	84 (50.9)	33 (49.3)	43 (47.3)	
Severe Persistent	31 (9.6)	10 (6.1)	6 (9.0)	15 (16.5)	
Asthma Controlled, n (%)	123 (38)	56 (33.9)	30 (44.8)	37 (40.7)	0.29
Markers of morbidity					
School days missed in past year, mean $\pm$ SD	10 $\pm$ 13.4	11 $\pm$ 14.5	6.9 $\pm$ 9.8	12.1 $\pm$ 15.1	0.55
ER visits in past year, mean $\pm$ SD	3.9 $\pm$ 6.2	4.0 $\pm$ 6.7	4.1 $\pm$ 7.1	3.6 $\pm$ 4.1	0.91
Hospitalizations in past year, mean $\pm$ SD	1.6 $\pm$ 3.7	1.3 $\pm$ 2.8	2.8 $\pm$ 6.2	1.3 $\pm$ 2.5	0.03
Medications					
Inhaled corticosteroids, n (%)	151 (46.7)	77 (46.7)	32 (47.8)	42 (46.2)	0.74
ICS/LABA, n (%)	110 (34.1)	50 (30.3)	21 (31.3)	39 (42.9)	0.26
Montelukast, n (%)	197 (61.0)	90 (54.5)	42 (62.7)	65 (71.4)	0.15
Oral anti-histamines, n (%)	177 (54.8)	88 (53.3)	35 (52.2)	54 (59.3)	0.09
Nasal anti-allergic medications, n(%)	144 (44.6)	77 (46.7)	28 (41.8)	39 (42.9)	0.87
PFT Indices					
FEV1% pred, mean $\pm$ SD	89.5 $\pm$ 15.5	91.5 $\pm$ 14.3	88.4 $\pm$ 16	86.5 $\pm$ 16.8	0.04
FVC% pred, mean $\pm$ SD	97.8 $\pm$ 14.4	97.4 $\pm$ 14.1	98 $\pm$ 14.2	98.1 $\pm$ 15.4	0.92
FEV1/FVC, mean $\pm$ SD	80.6 $\pm$ 8.5	82.8 $\pm$ 7.4	79.7 $\pm$ 8.8	77.4 $\pm$ 8.9	<0.001
FEV1/FVC < 80% predicted	143 (44.3)	54 (32.7)	36 (53.7)	53 (58.2)	<0.001
FEF25-75% pred, mean $\pm$ SD	73.8 $\pm$ 24.7	79.2 $\pm$ 23.4	71.1 $\pm$ 26.5	66 $\pm$ 23.6	<0.001
FRC% pred, mean $\pm$ SD	84 $\pm$ 16.3	84.9 $\pm$ 16.6	85.2 $\pm$ 16.1	80.6 $\pm$ 16.9	0.77
TLC% pred, mean $\pm$ SD	93.2 $\pm$ 12.2	93.6 $\pm$ 10.9	92.5 $\pm$ 16.6	92.9 $\pm$ 10.5	0.97
RV% pred, mean $\pm$ SD	97.3 $\pm$ 32.4	93.8 $\pm$ 32.1	96.5 $\pm$ 42	106.1 $\pm$ 20.3	0.62
RV/TLC, mean $\pm$ SD	23.9 $\pm$ 7.1	23.0 $\pm$ 7.5	23.8 $\pm$ 8.1	26.4 $\pm$ 3.8	0.41
ERV% pred, mean $\pm$ SD	72.8 $\pm$ 22.3	79.1 $\pm$ 20.5	74.1 $\pm$ 24.8	56.2 $\pm$ 16	0.02

a: The number of children on whom data was available is as follows: asthma severity, $n=320$; asthma control, $n=227$; inhaled corticosteroids, ICS/LABA, and Montelukast, $n=292$; oral anti-histamines and nasal anti-allergic medications, $n=243$; spirometry volumes, $n=323$; lung volumes, $n=45$. ER: Emergency room.

ICS/LABA: Inhaled corticosteroid/long acting beta agonist.

PFT: Pulmonary function test.

86.5 $\pm$ 16.8) compared to children in the low FeNO category (91.5 $\pm$ 14.3) (Table 2). There was no difference in percent-predicted FVC between the categories.

Mean FEV₁/FVC ratio was lower among children in the intermediate and high FeNO categories, corresponding to a higher percentage of children with

Table 3. Multifactorial analysis of FeNO and asthma morbidity.

Covariates	Intermediate FeNO ^a		High FeNO ^a	
	β (95% CI)	P-value	β (95% CI)	P-value
FEV ₁ /FVC	0.95 (0.9–0.99)	0.02	0.92 (0.88–0.96)	<0.001
Hospitalizations	1.12 (1.01–1.24)	0.03	1.0 (0.88–1.13)	0.97
Atopy	6.0 (1.85–19.76)	0.003	5.2 (1.8–14.78)	0.002
Asthma Severity				
Intermittent	Ref		Ref	
Mild Persistent	0.46 (0.13–1.63)	0.23	0.32 (0.11–0.99)	0.048
Moderate Persistent	0.53 (0.91–3.12)	0.49	0.14 (0.02–0.9)	0.04
Severe Persistent	1.22 (0.33–4.53)	0.76	0.14 (0.02–0.9)	0.46

a. Reference category is low/normal FeNO.

Ref: reference category.

lower airway obstruction (FEV₁/FVC ratio <80%) in these two categories, relative to those in low FeNO category. Mid expiratory flow rates (FEF_{25–75%}) were also lower in intermediate and high FeNO categories.

Although only 45 (13%) patients had lung volumes in the cohort, the distribution of this subset in the three FeNO groups was similar to the whole cohort. Mean percent-predicted ERV was lowest in the high FeNO category (56.2 ± 16 vs 79.1 ± 20.5 and 74.1 ± 24.8 in the low and intermediate groups) and was the only index that was significantly different between the three FeNO categories. While mean percent-predicted RV was 12% higher in the high FeNO category relative to the normal FeNO category, this difference did not reach statistical significance.

Multivariate analysis of baseline FeNO based on FeNO category, using low FeNO as the reference category (Table 3), revealed that lower FEV₁/FVC (OR = 0.95, 95%CI: 0.90 to 0.99), higher hospitalizations (OR = 1.12, 95%CI: 1.01 to 1.24), and atopy (OR = 6.0, 95%CI: 1.85 to 19.76) remained statistically significant in their independent association with the intermediate FeNO group. Lower FEV₁/FVC (OR = 0.92, 95%CI: 0.88 to 0.96) and atopy (OR = 5.2, 95%CI: 1.82 to 14.78) were also independently associated with high FeNO levels. In addition, patients with intermittent (OR = 0.32, 95%CI: 0.11 to 0.99) and mild persistent asthma (OR = 0.14, 95%CI: 0.02 to 0.90) were less likely to have high FeNO levels. The association of FeNO categories with asthma severity, hospitalizations, and pulmonary function testing were not independently influenced by race or ethnicity.

Longitudinal association of FeNO with asthma morbidity

Among 95 children who had at least one follow up visit, 23 (24%) of them had two follow up visits, with a median of 126 days (IQR 64–231 days) between the visits. The distribution of absolute change in FeNO

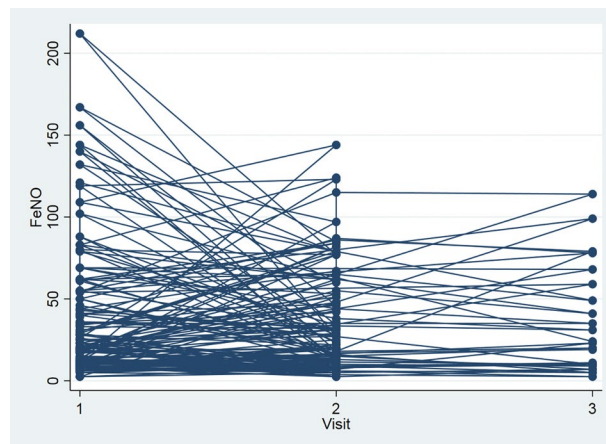


Figure 2. Changes in absolute Fractional exhaled nitric oxide (FeNO) during first two follow up visits.

during the follow up visits is seen in Figure 2. Compared to low baseline FeNO group, children within the highest baseline FeNO group had the largest decrease in FeNO over time ($\beta = -31.6$, 95%CI: -45.5 to -17.8) (Table 4 and Figure 3). Eighteen of the 95 children (19%) had persistently high FeNO, of which 7 showed increase in FeNO over time. An increase in FeNO was associated with two or more hospitalizations in the past year ($\beta = 17.9$, 95%CI: 2.2–33.6), and with baseline obese status ($\beta = 15.6$, 95%CI: 2.6–28.6) as well as with weight gain (higher BMI z-scores) between visits ($\beta = 8.8$, 95% CI: 3.7 to 13.8) (Table 4). In addition, FeNO tended to increase in children with average follow up time period of more than 3 months ($\beta = 33$, 95% CI: 9.7–56.2) compared to those followed up within 1–3 months ($\beta = 26.2$, 95%CI: 0.2 to 52.1) (Table 4). To ensure that the increase in FeNO was not due to lack of appropriate change in medication, we compared change in FeNO over time to change in medication regimen and found no difference in medication modification patterns among those with decreasing or stable FeNO to those with increase in FeNO over time (Supplemental Table S2).

Table 4. Association of demographic and clinical characteristics with longitudinal change in FeNO from baseline to follow-up visits.

Variable (n = 95)	Bivariate analysis β (95% CI)	P-value	Multivariate analysis ^a β (95% CI)	P-value
FeNO Category				
Low	ref		ref	
Intermediate	−4.3 (−20.2 to 11.5)	0.59	−5.4 (−22.1 to 11.4)	0.52
High	−31.6 (−45.5 to −17.8)	<0.001	−28.4 (−43.8 to −15)	<0.001
Demographic variables				
Age ^b	−0.6 (−2.6 to 1.5)	0.58	−0.02 (−2.0 to 1.9)	0.98
Time between visits ^c				
<30 days	ref		ref	
30–89 days	26.2 (0.2 to 52.1)	0.048	21.2 (−2.5 to 44.8)	0.08
90+ days	33.0 (9.7 to 56.2)	0.006	29.8 (8.6 to 50.9)	0.006
Female vs. male	3.9 (−9.3 to 17.1)	0.56	−2.0 (−14.1 to 10)	0.74
Hispanic vs. non-Hispanic	−3.8 (−17.9 to 10.3)	0.59	−14.7 (−41.8 to 12.4)	0.28
Race				
African American vs. Non-African American ^d	−1.9 (−15.9 to 12.1)	0.79	−6.4 (−32.6 to 19.7)	0.62
Height	−0.2 (−0.6 to 0.2)	0.34		
Weight	0.2 (−0.1 to 0.4)	0.20		
BMI Z-score	8.8 (3.7 to 13.8)	<0.001	6.2 (1.0 to 11.4)	0.02
Obese	15.6 (2.6–28.6)	0.02		
Atopy	0.4 (−17.3 to 18.1)	0.97		
Season FeNO collected				
Winter	ref		ref	
Spring	−1.2 (−17.1 to 14.7)	0.88	−16.7 (−32.6 to −0.8)	0.04
Summer	10.1 (−10.8 to 31)	0.34	−0.6 (−20.5 to 19.3)	0.95
Fall	−19.5 (−36.8 to −2.2)	0.047	−14.3 (−29.9 to 1.2)	0.07
Asthma Severity				
Intermittent	ref			
Mild Persistent	−0.9 (−32.3 to 30.5)	0.96		
Moderate Persistent	10.1 (−20.4 to 40.6)	0.51		
Severe Persistent	5.0 (−28.2 to 38.1)	0.77		
Asthma Control	−1.3 (−2.8–0.2)	0.08		
Markers of Morbidity				
ER visits	ref (none)			
1 visit in the past year	29 (−10.3 to 68.2)	0.15		
2+ visits in the past year	4.7 (−13.6 to 23.1)	0.61		
Hospitalizations	ref (none)			
1 visit in the past year	18.1 (−2.8 to 39.1)	0.09	12.3 (−7.9 to 32.5)	0.23
2+ visits in the past year	17.9 (2.2 to 33.6)	0.03	16.1 (1.5 to 30.8)	0.03
Medications				
Inhaled corticosteroids	2.8 (−10.9 to 16.5)	0.54		
ICS/LABA	0.4 (−13.5 to 14.2)	0.58		
Montelukast	6.9 (−8.6 to 22.4)	0.42		
Oral anti-histamines	−4.5 (−23.7 to 14.7)	0.85		
Nasal anti-histamines	−6.6 (−21.4 to 8.2)	0.37		
PFT indices				
FEV1% pred	0.05 (−0.37 to 0.48)	0.80		
FVC% pred	0.07 (−0.4 to 0.5)	0.78		
FEV1/FVC	0.2 (−0.5 to 0.9)	0.61		
FEV1/FVC < 80% pred	−3.3 (−16.5 to 9.9)	0.62		
FEF25–75% < 75% pred	0.02 (−0.3 to 0.3)	0.90		

a: Variables that were adjusted for in the final longitudinal multivariate analysis included associations found in the univariate analysis and also demographic factors such as age, sex, ethnicity, race, and FeNO category.

b: There was no difference in change in FeNO among children <12 years of age compared to those 12 years and older.

c: There was no difference in change in FeNO and number of follow up visits.

d: Includes White, Asian, American Indian/Alaskan, mixed race.

Ref: reference category.

CI: Confidence Interval.

BMI: Body mass index.

Pred: Predicted.

ICS: Inhaled corticosteroids.

LABA: Long acting beta agonist.

PFT: Pulmonary function testing.

In the multivariate analysis of longitudinal change in FeNO over time, persistently higher FeNO, average follow up time of over three months, weight gain, and two or more hospitalizations in the past year,

remained significantly associated with change in FeNO over time (Table 4). Predictors of asthma morbidity including multiple hospitalizations and lower airways obstruction were also analyzed for children with

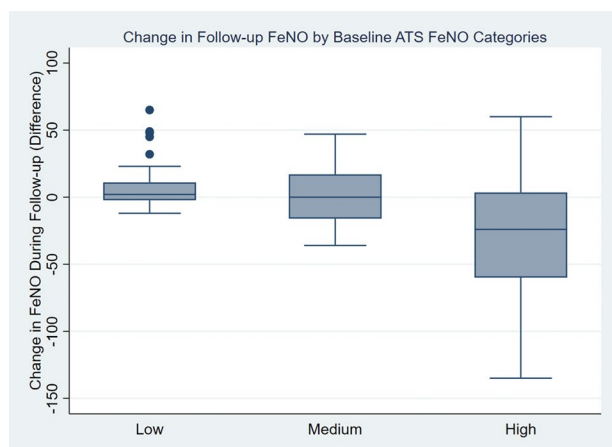


Figure 3. Absolute change in FeNO by baseline ATS FeNO category.

longitudinal data. Inhaled corticosteroid use was found to be a predictor of lower airways obstruction (OR = 0.33 (95% CI: 0.12-0.87)) while change in FeNO and moderate and severe persistent asthma approached statistical significance as predictors of hospitalization (Supplemental Table S2).

Discussion

This study investigated the cross sectional and longitudinal association of FeNO with asthma morbidity in a population of urban minority children with high asthma burden. The mean baseline FeNO in our entire cohort was similar to that reported in the healthy African American children (15), supporting existing literature that FeNO levels in minority children trend higher than the normal cutoff of <20ppb included in ATS guidelines (3). Baseline intermediate FeNO levels was associated with more asthma hospitalizations as well as lower airways obstruction, which was more common than what has been reported in non-Hispanic White children (28). Our study highlights the importance of intermediate FeNO as a marker of poorly controlled asthma present in our cohort, independent of race and ethnicity. From the perspective of longitudinal change, the greatest decline in FeNO over time occurred in children with high baseline FeNO levels, suggesting that medication responsiveness is present among children with high disease burden. However, this comparison also identified a subset of children with persistently high or rising serial FeNO measurements that were associated with weight gain and more hospitalizations, suggesting that rising FeNO may accompany obesity and is a marker of poor disease control.

Our study is one of the few pediatric studies with a large number of African American and Hispanic children that investigated the association of FeNO

levels with a history of hospitalization in the past 12 months. We extend findings from prior adult studies that demonstrated that FeNO predicts asthma exacerbations and/or asthma-related ER visits (29,30). Moreover, we highlight the clinical relevance of intermediate FeNO category, given that it is not classified as normal or elevated by the current guidelines, yet was associated with prior hospitalizations in our cohort. Drawing from an older study on high risk urban children from minority population (17), the NHLBI EPR-4 report highlights that FeNO levels do not necessarily predict future exacerbations in children at risk for higher asthma severity in urban minority populations (6). In contrast, our study showed that baseline and rising FeNO levels may be associated with asthma exacerbations as it relates to hospitalizations. Although the lack of access to a non-minority cohort with similar disease severity limits our ability to make direct comparisons between minority and non-minority racial groups, these findings are particularly relevant since they support the association of higher FeNO with asthma disease burden, rather than ethnicity, among non-Hispanic African American and Hispanic children that tend to have higher FeNO levels as compared to non-Hispanic White children (13–15).

ICS or ICS/LABA use did not differ between the FeNO categories and was not associated with change in FeNO over time. We therefore speculate that children with baseline intermediate FeNO levels were either less adherent or less responsive to controller medications, compared to those in the high FeNO group, and thereby had more poorly controlled difficult-to-treat asthma. It is possible that environmental factors impacting medication uptake may have influenced FeNO levels as well. Literature published on FeNO suppression in the setting of asthma medication adherence further supports this point, as almost a third of patients adherent to their controllers were found to have corticosteroid-resistant elevations in FeNO (31). While we have included only minority children due to the location of our hospital, our findings are in keeping with patterns observed in non-Hispanic White adults (31). Together, our findings suggest that lack of FeNO responsiveness to medications is present but may not be unique to those of Hispanic and non-Hispanic African American descent, supporting FeNO as a tool to identify non-responders in addition to those non-adherent to controller therapy (31). Further research is needed to understand the mechanisms underlying lack of FeNO response despite objective evidence of medication adherence. Our longitudinal findings of an association between rise in FeNO and poor disease control, based

on prior hospitalizations, together with a recent meta-analysis that linked FeNO monitoring in children with lower asthma exacerbations and therefore better disease control (32), additionally support the use of FeNO as a prognostic tool in children. FeNO has also been shown to be a cost-effective and cost-saving way of monitoring and treating children with asthma (33,34).

Several studies have investigated the additive benefit of FeNO to spirometry and symptom monitoring to guide asthma treatment (35–37). The inverse relationship seen between lower airways obstruction and intermediate and high FeNO levels are consistent with findings from a prior pediatric analysis of the 2007–2012 NHANES survey (19). These findings support prior reports of a beneficial role of combining FeNO with spirometry in stratifying asthma severity and control (30,38), sometimes with symptom questionnaires (28), but differ from others that found little predictive value of FeNO for lower airways obstruction (39,40). Our opposing findings are likely due to differences in outcomes of interest; the prior studies used change in FEV_1 , as compared to $FEV_1/FVC < 80\%$, which we retained as a more sensitive, stringent and standard marker of airways obstruction (39). In a study from the UK, where half of the children were from an inner city region, airflow obstruction was observed in 12% of children with FeNO more than 35 ppb (28) while we observed it in 54–58% of children with FeNO in intermediate and high levels respectively. Taken together, our findings, suggest that baseline FeNO may indeed serve as a more sensitive indicator of pulmonary function deficits in our patient population of Hispanic and African American children. Improvement in FEV_1/FVC ratio with decrease in FeNO further validates this speculation. Our longitudinal analysis did not support the same relationship between FEV_1/FVC ratio with decrease in FeNO, when adjusted for covariate, but are in keeping with a meta-analysis conducted in children that found no association between $\%FEV_1$ change and $\%$ change in FeNO (41). Since our smaller sample size of those with serial FeNO measurements may have influenced our observation, our findings highlight the need for future studies powered to detect the association of change in FeNO with measures of airways obstruction in urban minority children with asthma.

Our study is one of the few pediatric FeNO studies (42–44) to additionally investigate the relationship of FeNO with lung volume indices. Prior studies have not shown a trend in FeNO levels with differing lung volume indices (42,44). While our findings are limited by the relatively small proportion of children who

underwent lung volume quantification, we found an association of higher FeNO levels with lower ERV. There was over 10% higher RV in high versus normal FeNO groups. Since elevated RV due to air trapping is a marker of disease severity when associated with airways obstruction (45), our observations further support FeNO as an important adjunctive testing to lung volumes in children with asthma and identify a need for future studies with a larger cohort size with lung volumes.

On longitudinal multivariate analysis, change in FeNO directly correlated with BMI Z-scores. This supports a prior cross-sectional study in an NHANES cohort that found that obesity may worsen control in early-onset allergic asthma when a correlation was identified between FeNO levels and worsening adiposity among children with eosinophilic airway inflammation (46). Our longitudinal findings of higher FeNO with two or more hospitalizations and higher BMI Z-scores underscore the utility of FeNO as a valuable biomarker to delineate non-allergic asthma from poorly controlled allergic asthma due to concurrent weight gain (47,48). Although factors such as prenatal exposures, lack of physical activity, sleep disturbances, and insulin and leptin resistance may explain the obesity-asthma link (47), our findings identify a need for mechanistic longitudinal studies into the links between atopy, obesity and asthma in children (46). Moreover, although oral corticosteroid use due to poor disease control may have contributed to the association of weight gain with high FeNO, these children with persistently high FeNO are a subset that need further investigation.

Our study has certain limitations. Our cohort was primarily comprised of minority children, so we are unable to comment on the association of FeNO in non-minority groups. However, the limited number of studies in minority children (11,13,16–19,46,49) despite their high disease burden adds clinical relevance to our findings. We do not have details on the age of asthma onset, additional measures of atopy, such as blood eosinophils, doses of controller medications, or medication compliance, the latter being a limitation described in prior retrospective studies examining the role of FeNO in asthma, where it was not always feasible to quantify controller adherence (50,51). In addition, self-reports of compliance frequently overestimate adherence (52) and traditional measurements of temporal patterns of non-adherence to asthma controller medications have been challenged with the introduction of electronic medication monitoring (52), which is not yet part of routine asthma care, limiting our ability to confidently quantify compliance in a routine clinical setting. Time since the

most recent asthma exacerbation requiring oral steroids and dose of inhaled steroids, which may also possibly impact FeNO, were not accounted for. However, given the referral format of our Asthma Center, we are confident that the four-week interval between the exacerbation and outpatient visit allowed for FeNO to return to its baseline (53,54). Timing of follow up FeNO measurements was dependent on the health care provider, rather than a structured research-based approach. Although these are important aspects of research on FeNO, these factors are inherent to every real-world clinical setting, a key aspect of our study design and reporting.

Conclusion

Our study is one of the few real-world studies in urban minority children with persistent asthma to compare the association of guidelines-based FeNO categories with demographics, asthma morbidity, and pulmonary function testing. We demonstrated that baseline intermediate and high FeNO is associated with lower airway obstruction, potentially as a measure of eosinophilic airway inflammation, in both African American and Hispanic children, independent of ethnicity, supporting FeNO use in conjunction with spirometry to improve asthma control in this patient population. The association of intermediate FeNO category with more hospitalizations and lower airways obstruction makes it a clinically relevant category in urban minority children. The longitudinal relationship between obesity, atopy, FeNO levels, and asthma identifies an area for further mechanistic exploration to further support FeNO use in guiding asthma treatment in obese atopic children with asthma. Since these associations were driven by disease severity rather than ethnicity, our study highlights the importance of inclusion of FeNO as part of routine management of urban minority children with persistent asthma.

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Contributors' statement

Dr. Chen contributed substantially to the acquisition, analysis, interpretation of data for the work, and drafting of the manuscript.

Dr. Agalliu contributed substantially to the design of the work, analysis and interpretation of data, drafting of the manuscript, and critically revising the work for important intellectual content.

Dr. Roth contributed substantially to the acquisition of data and critically revising the manuscript for important intellectual content.

Dr. Rastogi conceptualized and designed the study, coordinated and supervised data collection, analyzed and interpreted data, reviewed and revised the manuscript for important intellectual content.

All authors have provided final approval of the version of this manuscript to be submitted.

Declarations of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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