



Letter

Association between allergic sensitization and exhaled nitric oxide in children in the School Inner-City Asthma Study

Fractional exhaled nitric oxide (FeNO) is increased in children with asthma and is thought to reflect eosinophilic lung inflammation.^{1,2} It is not known whether sensitization to 1 particular allergen is more strongly associated with worsened lung inflammation over any other particular allergen. Our aim was to determine whether children with asthma and allergic sensitization have higher levels of lung inflammation as measured by FeNO compared with children without allergic sensitization, and whether sensitization to 1 specific allergen was most predictive of elevated FeNO in a school-based setting.

We studied 128 children consecutively enrolled in the School Inner-City Asthma Study (SICAS) from 2008 through 2012 from whom we obtained skin prick testing results for indoor allergens, outdoor allergens, and FeNO (NIOX TM System, Aerocrine, Sweden). Further details regarding SICAS methods have been previously reported.³ The FeNO was obtained at the same time as the skin prick test results using standard methods,³ and a wheal size larger than 3 mm compared with a saline control was used to define a positive sensitization reaction. FeNO was collected according to standard American Thoracic Society procedures.⁴ The primary outcome was FeNO, and the logarithmic value of FeNO was used to obtain an approximately normal distribution. We performed an independent *t* test of the mean FeNO (logarithmically transformed) between sensitized and unsensitized children, and the Mann-Whitney *U* test was used to compare untransformed FeNO levels in sensitized vs unsensitized children. Univariate regression was used to determine the relation between sensitization to allergens and FeNO (logarithmically transformed). In the multiple regression model, we adjusted for age, sex, inhaled corticosteroid use, and multiple sensitizations, variables that were significantly associated with model outcome. Analyses were conducted using SPSS 19 (SPSS, Inc, Chicago, Illinois) and SAS 9.2 (SAS Institute, Cary, North Carolina).

The mean FeNO level was 24.75 ppb, and the median was 15 ppb (range 5–143 ppb) for the 128 children studied (eTable 1). Only 6% of children were white, and 40.6% and 28.1% of children were black

and Hispanic, respectively. The mean age at the time of FeNO measurement was 8.8 years. More than 70% of children in the SICAS were sensitized to more than 1 allergen, and more than 60% were sensitized to more than 2 allergens. The most common allergens to which children were sensitized were cat (40.6%), dust mite (35%), tree pollen (32%), mouse (37.5%), cockroach (24.2%), grass (25%), rat (25.8%), and ragweed (20.3%).

We found that logarithmically transformed FeNO significantly increased as the number of positive skin prick test reactions per child increased. Mean FeNO levels (parts per billion) were significantly different between those children with no sensitization and those children with 1 to 3, 4 to 5, and at least 6 positive skin prick test reactions. When comparing FeNO levels between children with and without sensitization to specific indoor allergens, we found that for cat, mouse, dust mite, rat, and cockroach, the FeNO levels were significantly higher in children who were sensitized to that specific allergen compared with those who were not.

Sensitizations to cat, rat, mouse, tree pollen, dust mite, and cockroach were significant predictors of increased FeNO in the univariate model (Table 1). When adjusted for age, sex, inhaled corticosteroid use, asthma control, and multiple sensitizations (>1 positive skin prick test reaction), sensitizations to cat and rat allergens were significant predictors of increased FeNO ($P < .01$ and $P = .016$, respectively).

Our study focused on the relation between allergic sensitization and FeNO levels, an objective measurement of lung inflammation in children with asthma. Children enrolled in the SICAS were strongly allergic, with more than 70% being sensitized to more than 1 allergen. This high degree of allergic sensitization translated to higher FeNO levels compared with unsensitized children. The mean FeNO for our cohort was higher than 20 ppb (24.75 ppb), indicating

Table 1

Predictors of fractional exhaled nitric oxide by multivariate regression^a

Allergic sensitization	Univariate regression			Multiple regression		
	β Coefficient	SE	<i>P</i> value	β Coefficient	SE	<i>P</i> value
Intercept						
Cat	0.785	0.122	<.0001	0.401	0.153	.01
Rat	0.738	0.143	<.0001	0.440	0.183	.016
Mouse	0.641	0.130	<.0001	−0.105	0.178	.557
Multiple sensitizations ^b	0.370 ^b	0.052	<.0001			
1–3				0.402	0.147	.006
4–5				0.357	0.216	.099
≥6				0.608	0.226	.007

^aOutcome is the natural logarithmic value of fractional exhaled nitric oxide. Adjusted for age, sex, inhaled corticosteroid use, and asthma control.

^bSensitizations were categorized as 0, 1 to 3, 4 to 5, or at least 6 positive skin test reactions and used as a single predictor in univariate analysis.

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that significant eosinophilic airway inflammation likely was present.⁵ In attempting to identify which allergens contribute most to elevated FeNO levels, we found sensitization to cat and rat and multiple sensitizations to be significant independent predictors of increased FeNO after adjusting for age, sex, and inhaled corticosteroid use. To our knowledge, no other studies have shown sensitization to rat allergen to be a significant independent predictor of increased FeNO levels after adjusting for other factors. There could be unique characteristics of this allergen that correlate with allergic airway inflammation.

In our multiple regression model, sensitization to at least 6 allergens carried the strongest β coefficient of 0.608. This is in contrast to some studies that have demonstrated that sensitization to specific allergens such as dust mite are major determinants of increased FeNO in children.⁶ Our study highlights the importance of rat allergen sensitization and the dose–response relation of polysensitization and airway inflammation.

Other studies have demonstrated that sensitization to multiple specific allergens is associated with elevated FeNO levels,^{7–9} and our study adds to this body of literature by confirming this relation in a population that is more diverse compared with other communities that have been studied. Therefore, our results are generalizable to other diverse, urban populations with a large proportion of nonwhite ethnicities.

The clinical implications of our results are important. A study from the National Cooperative Inner City Asthma Study showed that children with asthma who were exposed and sensitized to rat allergen had higher rates of hospitalization and unscheduled doctor visits.¹⁰ Our study adds to these findings by showing that sensitization to rat allergy also predicts airway inflammation. Finding that rat and multiple sensitizations predict high FeNO levels is important because FeNO levels have been shown to be predictive of asthma exacerbations.¹¹

We acknowledge that this study is limited by sample size in that limited resources allowed us to obtain FeNO in a subset of children.

In this school-based cohort of ethnically diverse, highly allergic children, we found that FeNO levels were predicted by cat and rat sensitization and most strongly by having multiple sensitizations. Future studies should be aimed at decreasing cat and rat allergen exposure and assessing the effect on asthma morbidity and markers of airway inflammation.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2014.12.004>.

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eTable 1

Demographics

Characteristic	
Boys, % (n)	52.3 (67)
Age, mean (range)	8.8 (5–13)
Race, % (n)	
White	6.3 (8)
Black	40.6 (52)
Hispanic	28.1 (36)
Haitian/creole	1.6 (2)
Asian	1.6 (2)
Mixed/other	17.2 (22)
ICS use, % (n)	50.8 (65)
FeNO (n = 128)	
Mean $\pm$ SD (range)	24.75 $\pm$ 23.5 (5–143)
Median	15
Allergen (n = 128), % (n with SPT ⁺)	
≥ 1 SPT ⁺	72.7 (93)
≥ 2 SPT ⁺	61.7 (79)
Cat	40.6 (52)
Dust mite	35 (45)
Tree pollen	32 (41)
Mouse	37.5 (48)
Cockroach	24.2 (31)
Grass	25 (32)
Rat	25.8 (33)
Ragweed	20.3 (26)

Abbreviations: FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; SPT⁺, positive skin prick test reaction.