Associations of Fraction of Exhaled Nitric Oxide with Beta Agonist Use in Children with Asthma

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The fraction of exhaled nitric oxide (FeNO), a measure of airway inflammation, is a potential noninvasive tool to guide asthma management in children. It remains unclear, however, if FeNO adds any information beyond clinical assessment of asthma control. We evaluated the associations of FeNO level with short acting beta agonist use and compared it with other clinical asthma assessments. We examined a prospective cohort study of 225 tobacco-smoke-exposed children aged 6–12 years with doctor-diagnosed asthma, including measures of FeNO, reported days of short acting beta agonist use, and unscheduled asthma visits. FeNO was analyzed in relation to current and future (3 months later) short acting beta agonist use. Mean FeNO at baseline, 6, and 12 months was 15.5, 15.7, and 16.8 ppb. In multivariable analyses, higher FeNO level was associated with increased short acting beta agonist use but only among children who were not on inhaled corticosteroids. Among those not on an inhaled steroid, there was a 12% increase in current and 15% increase in future days of short acting beta agonist use for every 10 ppb increase in FeNO level. FeNO levels remained associated with current short acting beta agonist use even after adjusting for unscheduled asthma visits. FeNO levels remained associated with future short acting beta agonist use even after adjusting for current short acting beta agonist use or unscheduled asthma visits. We conclude that FeNO levels are associated with short acting beta agonist use but only among children who are not on an inhaled corticosteroid.

Introduction

ASTHMA IS A DISEASE characterized by chronic airway inflammation, but most primary care practitioners rely on reported medication use, symptoms, and quality of life measures to assess asthma control.^{1,2} These measures do not directly measure levels of inflammation. The fraction of exhaled nitric oxide (FeNO) is an FDA-approved tool for monitoring response to anti-inflammatory medications, but it is not currently indicated for monitoring asthma control.^{3,4}

FeNO levels correlate with markers of inflammation in children with asthma.^{5,6} FeNO levels are associated with percent eosinophils and eosinophil cationic protein in bronchoalveolar lavage fluid and peripheral blood eosinophils.^{5,6} FeNO levels rise after exposure to known asthma triggers, decrease in response to anti-inflammatory therapy, and rise after steroid withdrawal.^{7–13} Smokers have lower FeNO levels, but investigators report varied associations of passive smoke on FeNO levels ranging from no effect to

inverse association.^{14–16} In cross-sectional analyses, FeNO level is correlated with asthma control as measured by physician clinical assessment.^{17,18} In these studies, clinical control was defined by combining clinical parameters (peak flow, reported symptoms, activity limitation, and short acting beta agonist use). The creation of combined control measures may be less generalizable than singular measures. Thus, questions remain about whether FeNO levels predict asthma control based on single parameters or whether FeNO levels predict asthma control over time beyond currently used asthma clinical assessments.^{13,18,19}

Short acting beta agonist use is one simple measure that reflects asthma impairment. The frequency of short acting beta agonist use has been associated with emergency department visits and hospitalization.²⁰ Our objectives were to (1) examine whether FeNO levels were associated with current impairment as measured by short acting beta agonist use, (2) examine whether FeNO levels were associated with short acting beta agonist use at 3-month follow-up, and (3)

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explore whether FeNO levels provided any additional information about short acting beta agonist use after accounting for daily beta agonist use over the previous 2 weeks or unscheduled asthma visits.

Materials and Methods

We used data from the Cincinnati Asthma Prevention (CAP) study for this analysis. Briefly, the CAP study was a 12-month-long, randomized controlled trial to evaluate the efficacy of high efficiency particulate air cleaners in the homes of 225 children (age 6–12 years old) who had physician-diagnosed asthma and were exposed to tobacco smoke.⁷ This project and the CAP study were approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board. Trial Registration Name is Environmental Exposures, Genetics, and Exhaled Nitric Oxide in Pediatric Asthma, NCT00395096.

FeNO measurement

Research assistants collected exhaled air for FeNO analysis according to the offline technique at baseline, 6 months, and 12 months home visits.²¹ Briefly, children inhaled through a bacterial filter attached to the mouthpiece of a collecting tube that had a charcoal filter on the inspiratory end of the tube to remove nitric oxide from the inhaled ambient air (Deadspace Discard Kit; Sievers Instruments, Boulder, CO). The child exhaled slowly into the collecting tube maintaining a slow exhalation flow in the range of 50–80 mL/s. After discarding the first part of the exhaled breath, a valve was activated to direct the remainder of the breath into a Mylar balloon. We used the Model 280i nitric oxide analyzer (Sievers Instruments) according to the manufacturer's instructions for nitric oxide analyses.²¹ FeNO values were not communicated with providers and did not affect treatment decisions.

Asthma measures and covariates

We collected demographic information at baseline and surveyed the participant's guardian about the child's asthma symptoms and treatment by telephone or in person every 3 months (Table 1). The main outcome variable, short acting beta agonist use over the previous 2 weeks, was based on the parent's response to the question, "Over the last 2 weeks, how often has [Child] taken albuterol (or another short acting inhaled medicine to control asthma symptoms)?" Answer choices were converted into days of use over the 2 weeks ("every day" was coded 14, "≥3 days per week" was coded 9, "1–2 days per week" was coded 3, "< once a week" was coded 1, and "Not at all" was coded 0).

We defined a child as using an inhaled steroid only if it responded that an inhaled steroid was prescribed and that it uses their inhaled steroid daily (Table 1). We considered a child as having an oral steroid burst if it responded yes to the question of oral steroid burst (Table 1). We defined a child as having a recent asthma-related upper respiratory infection if it answered a little of the time or anything more frequent to the question of recent cold (Table 1). The measure, unscheduled asthma visits, was created by combining the responses to the questions (1) how many times in the past 3 months has [Child] stayed overnight in the hospital (separate hospitalizations), (2) how many times in the past 3 months was [Child] seen in the emergency department for asthma,

TABLE 1. KEY SURVEY QUESTIONS

Beta Agonist Use

Q: Over the last 2 weeks, how often has [Child] taken albuterol (or another short acting inhaled medicine to control asthma symptoms)?

A: Daily, ≥3 Days per week, 1–2 Days per week, < Once a week, Not at all, Don't know

Inhaled Steroid Use

Q: Is [Child] currently prescribed a long acting inhaled steroid medication to prevent asthma symptoms, such as Vanceril, Beclovent, Azmacort, Flovent, Q-Var, Aerobid, or Pulmicort?

A: Yes, No, Don't know

Q: Over the last 2 weeks, how often has [Child] taken this inhaled steroid (referring to previous question)?

A: Daily, ≥3 Days per week, 1–2 Days per week, < Once a week, Not at all, Don't know

Oral Steroid Burst in the Last 3 months

Q: In the last 3 months, did [Child] take prescription steroids for asthma, such as prednisone, predlone, pediaped, or oraped?

A: Yes, No, Don't know

Recent Upper Respiratory Infection

Q: During the past 2 weeks, how much of the time has [Child] had wheezing with a cold?

A: All of the time, Most of the time, Some of the time, A little of the time, None of the time, Don't know

and (3) how many times in the last 3 months was [Child] seen in a doctor's office or clinic for problems with asthma, for a visit scheduled <24 h in advance (separate visits).

We administered the Children's Health Survey for Asthma at baseline.²² This quality-of-life measure assessed the components included in the National Asthma Education and Prevention Program (NAEPP) asthma severity classification system except pulmonary function. We used reported daytime symptoms, nighttime symptoms, activity limitation, beta agonist use, and recent exacerbations to classify baseline child asthma severity according to the NAEPP.²³

We quantified tobacco exposure using hair and serum cotinine, biomarkers of tobacco exposure. We collected and assayed hair and serum using standard techniques at each home visit (liquid chromatography–tandem mass spectrometry).^{24–26} The lower detection limits for hair and serum cotinine were 0.005 ng/mg and 0.05 ng/mL respectively.

Data analysis

We used arithmetic means and 95% confidence intervals to describe central tendency and dispersion of key measures. We compared group with and without FeNO data using *t*-tests to test for differences in means and chi-square tests to test for differences in frequencies. We employed the standard 2-sided 5% level to determine statistical significance for analyses.

The outcome variable was days of short acting beta agonist use over the previous 2 weeks. This outcome was assessed every 3 months (at baseline, 3, 6, 9, and 12 months). The

TABLE 2. BASELINE CHARACTERISTICS OF STUDY PARTICIPANTS

	FeNO available	FeNO missing	P value
Number of participants, N (%)	203 (90.2)	22 (9.8)	N/A
Gender			
Female	73 (36.0)	13 (59.1)	0.04
Male	130 (64.0)	9 (40.9)	
Race			
African-American	112 (55.2)	13 (59.1)	0.82
Caucasian	86 (42.4)	9 (40.9)	
Other	5 (2.4)	0 (0)	
Income			
< \$20,000	89 (45.6)	5 (23.8)	0.01
\$20,000–\$40,000	63 (32.3)	5 (23.8)	
> \$40,000	43 (22.1)	11 (52.4)	
Sensitized to indoor allergens			
No	69 (34.7)	7 (31.8)	0.79
Yes	130 (65.3)	15 (68.2)	
Baseline age (years), mean $\pm$ standard deviation	8.6 $\pm$ 1.8	8.7 $\pm$ 2.0	0.82
Baseline NAEPP Classification			
Intermittent	41 (20.2)	5 (22.7)	0.93
Mild persistent	58 (28.6)	5 (22.7)	
Moderate persistent	41 (20.2)	5 (22.7)	
Severe persistent	63 (31.0)	7 (31.8)	
Season during baseline FeNO Collection			
Winter	55 (27.1)	N/A	N/A
Spring	58 (28.6)		
Summer	52 (25.6)		
Fall	38 (18.7)		
Not on an inhaled steroid	152 (75.3)	16 (72.7)	0.80
Baseline FeNO (ppb), mean $\pm$ standard deviation	15.5 $\pm$ 11.2	N/A	N/A

N/A, not applicable; FeNO, fraction of exhaled nitric oxide; NAEPP, National Asthma Education and Prevention Program.

primary independent variable of interest, FeNO levels, was obtained every 6 months (at baseline, 6, and 12 months). We used 2 analytic approaches. Both analyses were conducted separately with a repeated measures design using a general estimating equation model (Proc GenMod in SAS) with subjects (children) as a random effect and subject characteristics as fixed effects. We used a negative binomial distribution for our model as it offered the best fit based on deviance. In the first longitudinal analysis, referred to as the “current” model, FeNO levels were examined with concurrent short acting beta agonist use (at 0, 6, and 12 months). In the second longitudinal analysis, referred to as the “future” model, we tested whether baseline FeNO levels were associated with short acting beta agonist use at 3 months, and 6-month FeNO levels were associated with short acting beta agonist use at 9 months.

In both analyses, we first conducted bivariate analyses to evaluate the relationship between FeNO and short acting beta agonist use. Next, we developed a full multivariable model including environmental, demographic, and treatment covariates determined to be significant in earlier studies.^{7,27} We explored interactions of covariates with FeNO levels in these models. A primary interaction of interest was inhaled steroid use as it is associated with FeNO levels and asthma control.^{9,27} If the interactions were significant, we stratified the model by the interaction variable. After developing these adjusted models, we inserted other clinical measures of asthma status (daily beta agonist use over the previous 2 weeks and unscheduled asthma visits) individually into the models to determine the association of these factors with beta agonist use relative to the FeNO association. Although the intervention in the CAP study (air filters) did not affect FeNO levels, we included a group and a time variable in all models to account for potential design effects of intervention group assignment. SAS Version 9.2 (SAS Institute, Inc., Cary, NC) was used for all data analyses.

Results

The mean age of participants at baseline was 8.6 years, about two-thirds of children were male, and 42% were Caucasian (Table 2). FeNO levels were available from 90% of the participants at baseline, 89% at 6 months, and 89% at 12 months. Characteristics and outcomes of the participants from whom FeNO levels were available did not differ significantly from those from whom FeNO levels were unavailable, except for sex and income (Table 2). Arithmetic mean FeNO levels at baseline, 6, and 12 months were 15.5, 15.7, and 16.8 ppb, respectively. Means of the asthma measures varied little over the time period (Table 3).

Current short acting beta agonist use

In bivariate analysis, there was no association of FeNO level with current days of short acting beta agonist use ($\beta=0.003$, $P=0.41$). There was no association of any individual smoke exposure variable with current short acting beta agonist use except for serum cotinine ($P=0.024$). The inclusion of serum cotinine did not significantly affect the estimate of the coefficient for FeNO; it changed from 0.008 to 0.0079. Thus, we did not include measures of tobacco smoke exposure in the multivariable analysis of current short acting beta agonist use.

In the multivariable analysis, the FeNO relationship with days of short acting beta agonist use changed $\beta=0.003$ and $P=0.45$ with the addition of oral steroid burst in the previous 3 months, to $\beta=0.005$ and $P=0.17$ with the addition of baseline age, $\beta=0.007$ and $P=0.05$ with the addition of inhaled steroid use, and $\beta=0.004$ and $P=0.34$ with the addition of cold in the past 2 weeks. In multivariable analysis, higher FeNO level was associated with increased current days of

TABLE 3. FRACTION OF EXHALED NITRIC OXIDE LEVELS AND STUDY OUTCOMES OVER THE STUDY PERIOD, MEAN AND 95% CONFIDENCE INTERVAL

	Baseline	3 months	6 months	9 months	12 months
FeNO (ppb)	15.5 (13.9, 17.1)	—	15.7 (13.9, 17.4)	—	17.1 (15.2, 18.4)
Beta agonist use (number of days in previous 2 weeks)	5.8 (5.0, 6.5)	5.2 (4.4, 6.0)	4.6 (3.8, 5.4)	5.1 (4.3, 5.9)	4.3 (3.5, 5.1)

short acting beta agonist use (Table 4, $\beta=0.008$, $P=0.03$), adjusting for group, timing, baseline age, inhaled steroid use, recent oral steroid burst, and cold in the past 2 weeks.

There was an interaction of inhaled steroid use and FeNO level, so we stratified the analysis (Table 4, interaction term $P=0.04$). We found that higher FeNO levels were associated with increased current short acting beta agonist use among children, but only for those who were not on an inhaled steroid (Table 4).

Future short acting beta agonist use (3-month follow-up)

Higher FeNO levels were associated with increased short acting beta agonist use ($\beta=0.011$, $P=0.01$) at 3-month follow-up in bivariate analysis. There was no association of any of the smoke exposure variables with future short acting beta agonist use.

In multivariable analysis, higher FeNO levels were associated with increased short acting beta agonist use at 3-month follow-up (Table 4, $\beta=0.012$, $P=0.02$), adjusting for group, timing, race, inhaled steroid use, recent oral steroid burst, and a cold in the past 2 weeks.

There was an interaction of inhaled steroid use and FeNO level, so we stratified the analysis (Table 4, interaction term $P=0.06$). Higher FeNO levels were associated with increased short acting beta agonist use at 3-month follow-up, but only for those who were not on an inhaled steroid (Table 4).

FeNO level's value in comparison to other clinical control measures

Short acting beta agonist use could not be added to the analysis of current short acting beta agonist use because the predictor was also the outcome. When unscheduled asthma

visits was added to the analysis of current short acting beta agonist use, higher FeNO levels were still associated with increased current short acting beta agonist use ($\beta=0.008$, $P=0.03$).

Higher FeNO levels were still associated with increased short acting beta agonist use at 3-month follow-up when we adjusted for recent short acting beta agonist use at time of FeNO measurement ($\beta=0.010$, $P=0.03$) or recent unscheduled asthma visits ($\beta=0.013$, $P=0.01$). When we explored the adjustment for recent short acting beta agonist use and recent unscheduled asthma visits limited to children who were not on inhaled steroids, the associations were consistent with those for the whole group.

Discussion

We found that higher FeNO levels were associated with a modest increase in current short acting beta agonist use and short acting beta agonist at 3-month follow-up, but only among children who were not on an inhaled corticosteroid. The association of FeNO level with short acting beta agonist use remained significant even after accounting for other clinical asthma tools (reported short acting beta agonist use or unscheduled asthma visits), suggesting that FeNO level provides supplementary data about short acting beta agonist use in children who are not on an inhaled steroid.

The children in this study were all smoke exposed, two-thirds were male, over half were black, and a majority were from lower income families (Table 2). Among these children, we found that FeNO levels were associated with a modest increase in current and future (at 3-month follow-up) short acting beta agonist use, but this relationship was only present among children who were not on inhaled steroid therapy. Among those not on an inhaled steroid, there was a 12% increase in current days of short acting beta agonist use and 15% increase in days of short acting beta agonist at 3-month

TABLE 4. ADJUSTED ASSOCIATIONS OF FRACTION OF EXHALED NITRIC OXIDE LEVEL WITH BETA AGONIST USE

Model	Current beta agonist use ^a			Future beta agonist use ^b		
	Estimate (95% CI)	P value	Difference in days of use comparing 95th to 5th FeNO percentile (95% CI) ^c	Estimate	P value	Difference in days of use comparing 95th to 5th FeNO percentile (95% CI) ^c
FeNO (ppb)	0.008 (0.001, 0.014)	0.03	31% (1, 71)	0.012 (0.002, 0.024)	0.02	50% (8, 110)
Stratified by steroid use: ^d						
Not on inhaled steroids						
FeNO	0.011 (0.003, 0.019)	0.006	47% (12, 93)	0.014 (0.003, 0.026)	0.01	63% (8, 146)
On inhaled steroids						
FeNO	-0.008 (-0.024, 0.006)	0.29	-23% (-53, 28)	0.0001 (-0.014, 0.016)	0.99	0.3% (-39, 66)

^aAdjusted for group, time, baseline age, inhaled steroid use, oral steroid bursts in last 3 months, and recent upper respiratory tract infection.

^bAdjusted for group, time, race, inhaled steroid use, oral steroid bursts in last 3 months at FeNO measurement, and recent upper respiratory tract infection.

^cThis column represents the difference in days of use of beta agonist comparing a child in the 95th percentile of FeNO to a child in the 5th percentile of FeNO.

^dInteraction of FeNO level and inhaled steroid use; current beta agonist use $P=0.04$, future beta agonist use $P=0.06$. CI, confidence interval.

follow-up for every 10 ppb increase in FeNO level. This confirms what has been noted in another study citing a poor correlation of FeNO with sputum eosinophils among patients with oral steroid-dependent asthma.²⁸ FeNO levels have been shown to represent eosinophilic airway inflammation, and higher levels of inflammation (higher FeNO levels) are associated with restricted air flow and more frequent short acting beta agonist use.⁶ For a child on an inhaled steroid, FeNO values may not be useful for predicting short acting beta agonist use.

In the unadjusted analysis of current days of short acting beta agonist use, there was no association of FeNO level; however, after adjusting for inhaled steroid use the association was significant. Moreover, the association of FeNO levels with short acting beta agonist use was only present among children not on inhaled steroids. This finding suggests that FeNO levels may not reflect or predict short acting beta agonist use for children who are using inhaled steroids. Since inhaled steroids are an important component of asthma management, this finding might also help explain why several of the trials of the use of FeNO in the clinical management of asthma have been unsuccessful.²⁹⁻³¹ We found that FeNO does offer information about short acting beta agonist use in addition to that provided by other clinical tools that predict or reflect asthma status (days of short acting beta agonist use over the previous 2 weeks and unscheduled asthma visits). In the analysis of predictors of short acting beta agonist use at 3-month follow-up, both FeNO level and current short acting beta agonist use were associated with future short acting beta agonist. Therefore, while FeNO provides additional information for children not on an inhaled steroid, the relatively modest contribution of this information and the cost of the measurement may limit its value.

According to the American Thoracic Society and European Respiratory Society, there is no clear definition of asthma control.³² The term "asthma control" implies a global assessment of symptoms, use of short acting beta agonists, pulmonary function, and exacerbation frequency.³² We chose to focus on a single factor, reported beta agonist use, because it is a proximal measure of asthma control.²⁰ Furthermore, short acting beta agonist use is a key component of many asthma clinical tools, including the Asthma Control Test, the Asthma Control Questionnaire, and Global Initiative for Asthma Guidelines.^{23,33-35} We have shown that for children not on an inhaled steroid, FeNO levels reflect current short acting beta agonist use and predict short acting beta agonist use at 3-month follow-up. Investigators have explored the correlation of FeNO levels with other measures of asthma control, but most of these studies were cross-sectional.^{8,17,18,33} There have been a few trials of the use of FeNO in the clinical management of children with asthma, but there has been little focus on whether FeNO levels are associated with asthma status over time.^{13,30,31,36,37}

There are some limitations to this analysis. First, we relied on parental report of short acting beta agonist use. While this is a limitation, it does represent data that is typically obtained in the clinic setting. Additionally, there is evidence to suggest that parents are relatively accurate in their report of medication use.³⁸ Second, the cohort was limited to children who were exposed to household tobacco smoke. Still, according to National Health and Nutrition Examination Survey data (2007-2008), over half of nonsmoking children age 3-18 years have detectable second-hand smoke exposure, and 18% of children

lived with someone who reportedly smoked inside the home.³⁹ Thus, these results are important for a large fraction of children with asthma. Third, smoke exposure is associated with neutrophilic inflammation, and may have attenuated associations of FeNO levels with asthma symptoms. Fourth, there is no gold standard tool for assessment of asthma control; most guidelines rely on medication use to define asthma control and as an outcome. For this reason we chose to focus on short acting beta agonist use, a factor that is common to most questionnaires designed for assessment of asthma.

We have shown that FeNO levels reflect current short acting beta agonist use and predict short acting beta agonist use at 3-month follow-up. FeNO levels also provide information about asthma control in children that may supplement other clinical tools (short acting beta agonist use or unscheduled asthma visits). However, the modest association of FeNO level with short acting beta agonist use is limited to children who are not on an inhaled steroid. Thus, the utility of FeNO may be limited because most patients with moderate to severe asthma are or should be on an inhaled steroid.

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References

- McIvor RA, Chapman KR. The coming of age of asthma guidelines. *Lancet* 2008;372:1021-1022.
- Horner SD, Kieckhefer GM, Fouladi RT. Measuring asthma severity: instrument refinement. *J Asthma* 2006;43:533-538.
- Gandhi RK, Blaiss MS. What are the best estimates of pediatric asthma control? *Curr Opin Allergy Clin Immunol* 2006;6:106-112.
- Silkoff PE, Carlson M, Bourke T, Katial R, Ogren E, Szeffler SJ. The Aerocrine exhaled nitric oxide monitoring system NIOX is cleared by the US Food and Drug Administration for monitoring therapy in asthma. *J Allergy Clin Immunol* 2004;114:1241-1256.
- Strunk RC, Szeffler SJ, Phillips BR, Zeiger RS, Chinchilli VM, Larsen G, et al. Relationship of exhaled nitric oxide to clinical and inflammatory markers of persistent asthma in children. *J Allergy Clin Immunol* 2003;112:883-892.
- Warke TJ, Fitch PS, Brown V, Taylor R, Lyons JD, Ennis M, et al. Exhaled nitric oxide correlates with airway eosinophils in childhood asthma. *Thorax* 2002;57:383-387.
- Spanier AJ, Hornung R, Lierl M, Lanphear BP. Environmental exposures and exhaled nitric oxide in children with asthma. *J Pediatr* 2006;149:220-226.

8. Covar RA, Szeffler SJ, Martin RJ, Sundstrom DA, Silkoff PE, Murphy J, et al. Relations between exhaled nitric oxide and measures of disease activity among children with mild-to-moderate asthma. *J Pediatr* 2003;142:469–475.
9. Beck-Ripp J, Griese M, Arenz S, Koring C, Pasqualoni B, Bufler P. Changes of exhaled nitric oxide during steroid treatment of childhood asthma. *Eur Respir J* 2002;19:1015–1019.
10. Langley SJ, Goldthorpe S, Craven M, Morris J, Woodcock A, Custovic A. Exposure and sensitization to indoor allergens: association with lung function, bronchial reactivity, and exhaled nitric oxide measures in asthma. *J Allergy Clin Immunol* 2003;112:362–368.
11. Roberts G, Hurley C, Bush A, Lack G. Longitudinal study of grass pollen exposure, symptoms, and exhaled nitric oxide in childhood seasonal allergic asthma. *Thorax* 2004;59:752–756.
12. Pijnenburg MW, Hofhuis W, Hop WC, De Jongste JC. Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. *Thorax* 2005;60:215–218.
13. Jones SL, Kittelson J, Cowan JO, Flannery EM, Hancox RJ, McLachlan CR, et al. The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. *Am J Respir Crit Care Med* 2001;164:738–743.
14. Spanier AJ, Kahn RS, Hornung RW, Wang N, Sun G, Lierl MB, et al. Environmental exposures, nitric oxide synthase genes, and exhaled nitric oxide in asthmatic children. *Pediatr Pulmonol* 2009;44:812–819.
15. Dinakar C, Lapuente M, Barnes C, Garg U. Real-life environmental tobacco exposure does not affect exhaled nitric oxide levels in asthmatic children. *J Asthma* 2005;42:113–118.
16. Barreto M, Villa MP, Martella S, Ronchetti F, Darder MT, Falasca C, et al. Exhaled nitric oxide in asthmatic and non-asthmatic children: influence of type of allergen sensitization and exposure to tobacco smoke. *Pediatr Allergy Immunol* 2001;12:247–256.
17. Delgado-Corcoran C, Kissoon N, Murphy SP, Duckworth LJ. Exhaled nitric oxide reflects asthma severity and asthma control. *Pediatr Crit Care Med* 2004;5:48–52.
18. Meyts I, Proesmans M, De Boeck K. Exhaled nitric oxide corresponds with office evaluation of asthma control. *Pediatr Pulmonol* 2003;36:283–289.
19. Fitzpatrick A, Teague WG. Severe asthma in children: insights from the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *Pediatr Allergy, Immunol Pulmonol* 2010;23:131–138.
20. Paris J, Peterson EL, Wells K, Pladevall M, Burchard EG, Choudhry S, et al. Relationship between recent short-acting beta-agonist use and subsequent asthma exacerbations. *Ann Allergy Asthma Immunol* 2008;101:482–487.
21. Sievers Nitric Oxide Analyzer (NOA) 280i Homepage Manual. Available at www.ionicsinstruments.com/ionics/index.cfm?product_code=NitricOxideAnalyzer&category_code=NOA (accessed December 2009).
22. Asmussen L, Olson LM, Grant EN, Fagan J, Weiss KB. Reliability and validity of the Children's Health Survey for Asthma. *Pediatrics* 1999;104:e71.
23. Committee. NAEAPPC. National Asthma Education and Prevention Program Expert Panel Report 3 Guidelines for the Diagnosis and Management of Asthma. Available at www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm 2007.
24. Bernert JT, Jr., Turner WE, Pirkle JL, Sosnoff CS, Akins JR, Waldrep MK, et al. Development and validation of sensitive method for determination of serum cotinine in smokers and nonsmokers by liquid chromatography/atmospheric pressure ionization tandem mass spectrometry. *Clin Chem* 1997;43:2281–2291.
25. Eliopoulos C, Klein J, Koren G. Validation of self-reported smoking by analysis of hair for nicotine and cotinine. *Ther Drug Monit* 1996;18:532–536.
26. Bernert JT, Jr., McGuffey JE, Morrison MA, Pirkle JL. Comparison of serum and salivary cotinine measurements by a sensitive high-performance liquid chromatography-tandem mass spectrometry method as an indicator of exposure to tobacco smoke among smokers and nonsmokers. *J Anal Toxicol* 2000;24:333–339.
27. Spanier AJ, Hornung RW, Kahn RS, Lierl MB, Lanphear BP. Seasonal variation and environmental predictors of exhaled nitric oxide in children with asthma. *Pediatr Pulmonol* 2008;43:576–583.
28. Nair P, Kjarsgaard M, Armstrong S, Efthimiadis A, O'Byrne PM, Hargreave FE. Nitric oxide in exhaled breath is poorly correlated to sputum eosinophils in patients with prednisone-dependent asthma. *J Allergy Clin Immunol* 2010;126:404–406.
29. Pijnenburg MW, Bakker EM, Hop WC, De Jongste JC. Titrating steroids on exhaled nitric oxide in children with asthma: a randomized controlled trial. *Am J Respir Crit Care Med* 2005;172:831–836.
30. Szeffler SJ, Mitchell H, Sorkness CA, Gergen PJ, O'Connor GT, Morgan WJ, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet* 2008;372:1065–1072.
31. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005;352:2163–2173.
32. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59–99.
33. Khalili B, Boggs PB, Shi R, Bahna SL. Discrepancy between clinical asthma control assessment tools and fractional exhaled nitric oxide. *Ann Allergy Asthma Immunol* 2008;101:124–129.
34. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004;113:59–65.
35. Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med* 2006;100:616–621.
36. Rosias PP, Dompeling E, Dentener MA, Pennings HJ, Hendriks HJ, Van Iersel MP, et al. Childhood asthma: exhaled markers of airway inflammation, asthma control score, and lung function tests. *Pediatr Pulmonol* 2004;38:107–114.
37. Zacharasiewicz A, Wilson N, Lex C, Erin EM, Li AM, Hansel T, et al. Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. *Am J Respir Crit Care Med* 2005;171:1077–1082.
38. Tisnado DM, Adams JL, Liu H, Damberg CL, Chen WP, Hu FA, et al. What is the concordance between the medical record and patient self-report as data sources for ambulatory care? *Med Care* 2006;44:132–140.
39. Centers for Disease Control and Prevention (U.S.). Vital signs: nonsmokers' exposure to secondhand smoke—United States, 1999–2008. *MMWR Morb Mortal Wkly Rep* 2010;59:1141–1146.

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