Published in final edited form as:
J Allergy Clin Immunol. 2009 November ; 124(5): 949–953. doi:10.1016/j.jaci.2009.07.024.

Fractional Exhaled Nitric Oxide (FeNO) Measurements are Most Closely Associated with Allergic Sensitization in School Aged Children

Daniel J Jackson, MD[1,2], **Christine M Virnig, MD**[1,2], **Ronald E Gangnon, PhD**[3,4], **Michael D Evans, MS**[3], **Kathy A Roberg, BSN, MS**[1], **Elizabeth L Anderson, BSN, MA**[1], **Ryan M Burton, MS**[2], **Lisa P Salazar, BA**[1], **Douglas F DaSilva, BS**[1], **Kathleen M Shanovich, BA**[1], **Christopher J Tisler, MT**[1], **James E Gern, MD**[1], and **Robert F Lemanske Jr., MD**[1,2]

[1]Department of Pediatrics, University of Wisconsin-Madison

[2]Department of Medicine, University of Wisconsin-Madison

[3]Department of Biostatistics and Medical Informatics, University of Wisconsin-Madison

[4]Department of Population Health Sciences, University of Wisconsin-Madison

Abstract

Background—Factors affecting fractional exhaled nitric oxide (FeNO) in early childhood are incompletely understood.

Objective—To examine the relationships between FeNO and allergic sensitization, total IgE, atopic dermatitis, rhinitis, asthma, and lung function (spirometry) in children.

Methods—Children at high-risk of asthma and other allergic diseases due to parental history were enrolled at birth and followed prospectively. FeNO was measured by online technique at ages 6 and 8 years. Relationships among FeNO, various atopic characteristics, and asthma were evaluated.

Results—Reproducible FeNO measurements were obtained in 64% (135 of 210) of 6 year old and 93% (180 of 194) of 8 year old children. There was seasonal variability in FeNO. Children with aeroallergen sensitization at age 6 and 8 years had increased levels of FeNO compared to those not sensitized [geometric mean (6 years, 10.9 vs. 6.7 ppb, $p<0.0001$; 8 years, 14.6 vs. 7.1 ppb, $p<0.0001$)]. FeNO was higher in children with asthma than in those without asthma at 8 years, but not 6 years of age (6 years, 9.2 vs. 8.3 ppb, $p = 0.48$; 8 years, 11.5 vs. 9.2 ppb, $p = 0.03$). At 8 years of age, this difference was no longer significant in a multivariate model that included aeroallergen sensitization ($p=0.33$). There were no correlations between FeNO and spirometric indices at 6 or 8 years of age.

Conclusion—These findings underscore the importance of evaluating allergen sensitization status when FeNO is used as a potential biomarker in the diagnosis and/or monitoring of atopic diseases, particularly asthma.

Corresponding Author: Daniel J Jackson, MD, University of Wisconsin School of Medicine and Public Health 600 Highland Avenue K4/910, CSC Box 9988 Madison, WI 53792. djj@medicine.wisc.edu Fax: 608-263-3104 Phone: 608-263-6214.

Clinical Implications—When FeNO is utilized as a biomarker for the diagnosis and/or monitoring of atopic diseases such as asthma, the presence or absence of allergic sensitization should be carefully considered.

Capsule Summary—This pediatric cohort study evaluates the relationships between FeNO and various atopic characteristics. The results suggest that allergic sensitization should be evaluated when FeNO is used as a biomarker in clinical or research settings.

Keywords

fractional exhaled nitric oxide (FeNO); asthma; allergic sensitization; atopic dermatitis; lung function; children; seasonality; atopy

Introduction

Fractional exhaled nitric oxide (FeNO) is frequently measured in both research and clinical settings as a potential biomarker for the diagnosis and treatment of asthma. Exhaled nitric oxide is thought to be a sensitive marker of ongoing eosinophilic airway inflammation,(1;2) and FeNO levels decrease with anti-inflammatory therapy.(2) FeNO is particularly attractive for use in children, because it can be measured using noninvasive, standardized methods and yields reproducible, real-time results.(3-5) Indeed, FeNO measurement has shown potential promise as a non-invasive objective tool for use in the prediction of persistent wheezing (6) and diagnosis of asthma in preschool children. (7) Studies in both adults and children suggest that elevated FeNO can effectively predict response to inhaled corticosteroids.(5;8;9) Measurement of FeNO has also shown potential utility in guiding anti-inflammatory therapy in both adults (10;11) and children(12) with asthma, but its ability to do so has been recently demonstrated to not be superior to guideline-based strategies.(13)

Thus, while FeNO certainly has shown some promise as a biomarker in asthma diagnosis and therapy, many questions remain. Previous studies have consistently demonstrated strong correlations between elevated FeNO and atopy, (4;14-16) but there have been inconsistent results when comparing wheezing phenotypes and FeNO levels in young children.(6;14;17) Levels of FeNO in childhood are also known to increase with age,(3) but “normal values” in early school age have not been well established. Thus, a more complete understanding of the factors that affect FeNO levels in early school age children is critical to proper interpretation of its measurement.

Children enrolled in the Childhood Origins of ASThma (COAST) study, a birth cohort study designed to investigate the host and environmental factors involved in the development of asthma and allergic diseases in children at high risk due to parental history, were therefore evaluated to better delineate the relationship between FeNO and other markers of asthma and allergic disease. The longitudinal, observational nature of the study provides a means to examine the natural course of FeNO levels throughout childhood in relation to the onset, persistence, and remittance of various atopic phenotypic characteristics. The following report describes these relationships in this high-risk cohort of children 6 and 8 years of age.

Methods

Study Subjects

A total of 289 children were enrolled in the Childhood Origins of ASThma (COAST) study at birth as previously described,(18) and 254 were followed through age 8 years. To qualify, at least one parent was required to have a history of physician-diagnosed asthma and/or respiratory allergies, the latter being defined by one or more positive aeroallergen skin prick

tests. Informed consent was obtained from the parents and the Human Subjects Committee at the University of Wisconsin approved the study.

FeNO Measurement

Fractional exhaled nitric oxide (FeNO) was measured during scheduled study visits at 6 and 8 years of age using the NIOX system (Aerocrine, Stockholm, Sweden) according to ATS online measurement standards adapted for children.(19) The expiratory flow rate was 0.05 L/s. Exhalation times were at least 6 seconds with a 2 second analysis period. Children were required to have 3 measurements within 10% or 2 measurements within 5% for acceptability. Measurements were made prior to the performance of spirometry or impulse oscillometry.

Pulmonary Function Testing

Spirometry ($FEV_{0.5}$, FEV_1, and FEV_1/FVC) was performed at 6 and 8 years of age with the Jaeger Masterscope computer system (Jaeger-Toennies GmbH, Hoechberg, Germany) utilizing protocols described by the Childhood Asthma Research and Education (CARE) Network.(4) Since the ATS Standardization of Spirometry 1994 Update does not address recommendations for children specifically,(20) modified criteria published by Eigen et al were used to define standards for maneuver acceptability.(21)

Total IgE & Allergen-specific IgE

Blood was collected at 6 years of age and total IgE and specific IgE to dog, cat, cockroach, ragweed, birch, timothy grass, *Alternaria alternata*, *D. farinae*, *D. pteronyssinus*, peanut, and egg, were measured using automated fluoroenzyme immunoassays (Unicap® 100, Pharmacia and Upjohn Diagnostics, Kalamazoo, MI) (FEIA) as previously described.(22) Allergen-specific IgE values of 0.35 KU/L (Class I) or greater were considered positive, and the sensitivity for detection of total IgE was 2 KU/L.

Clinical Definitions

Atopic dermatitis (AD) was defined as “physician-diagnosed”, either documented by a health care provider in the medical record or by parental report of physician-diagnosed AD on historical questionnaires. As previously described, (23) current asthma was diagnosed at 6 and 8 years of age based on the documented presence of one or more of the following characteristics in the previous year: 1) MD diagnosis of asthma; 2) use of albuterol for coughing or wheezing episodes (prescribed by MD); 3) use of a daily controller medication; 4) step-up plan including use of albuterol or short-term use of ICS during illness; and 5) use of prednisone for asthma exacerbation. Rhinitis was defined as routinely or seasonally having frequent sneezes and/or itchy/runny nose, and was ascertained by parental report on historical questionnaires.

Statistical Analysis

Relationships between the years 6 and 8 FeNO outcomes (log-transformed) and season, gender, asthma, atopic dermatitis, total and specific IgE, SPT, peripheral blood eosinophils, and pulmonary function tests were examined using linear regression models. Because FeNO measurements were found to vary by the season of measurement, season was included as a covariate in these models. The strengths of association between FeNO and total IgE, peripheral blood eosinophils, and pulmonary function tests were summarized using the Pearson partial correlation coefficient adjusting for season. FeNO, total IgE, and eosinophil measurements were log-transformed for analysis, and FeNO levels were summarized using the geometric mean. A two-sided p-value of 0.05 was regarded as statistically significant.

Results

Reproducible FeNO measurements were obtained in 64% (135 of 210) of 6 year old children and 93% (180 of 194) of 8 year old children. There were no differences in gender, aeroallergen sensitization, food sensitization, asthma, rhinitis, or atopic dermatitis in children who performed reproducible FeNO versus those that did not. The geometric mean FeNO increased from 8.6 parts per biliion (ppb) at 6 years of age to 9.9 ppb at 8 years of age ($p = 0.01$). There were no differences in FeNO based on gender at either age (6 years, girls 8.4 vs. boys 8.7 ppb, $p = 0.80$; 8 years, girls 10.3 vs. boys 9.6 ppb, $p = 0.42$). However, there was seasonal variability in FeNO measurement at both 6 and 8 years of age, with higher FeNO in summer and fall, than winter and spring [Figure 1, (6 years, $p = 0.04$ & 8 years, $p = 0.01$)]. Therefore, all subsequent analyses adjust for season of FeNO measurement. This adjustment did not alter any of the relationships described, nor did adjustment for asthma controller medication use.

FeNO and Atopy

Children with aeroallergen sensitization, defined as at least 1 positive aeroallergen RAST at age 6 years, had increased levels of FeNO compared to those not sensitized to aeroallergens [Table 1, (6 years, 10.9 vs. 6.7 ppb, $p<0.0001$; 8 years, 14.6 vs. 7.1 ppb, $p<0.0001$)]. Similar results were obtained when aeroallergen sensitization was assessed at ages 1 and 3 years by RAST and age 5 years by skin prick testing (data not shown). Children sensitized to foods, defined as at least 1 positive food allergen RAST at age 6 years, also had higher levels of FeNO than those without food sensitization (Table 1, (6 years 10.9 vs. 8.0 ppb, $p = 0.02$; 8 years, 14.0 vs. 8.9 ppb, $p = 0.0001$).

There was a significant positive correlation between total IgE and FeNO (6 years, $r=+0.36$, $p<0.0001$; 8 years, $r=+0.46$, $p<0.0001$). There was also a weak positive correlation between peripheral blood eosinophils and FeNO (6 years, $r=+0.19$, $p = 0.04$; 8 years, $r=+0.23$, $p = 0.005$).

FeNO and Rhinitis

Children with current rhinitis had significantly higher FeNO levels compared to those without rhinitis at ages 6 and 8 years [Table 1, (6 years, 10.2 vs. 7.3 ppb, $p = 0.0006$; 8 years, 12.4 vs. 7.6 ppb, $p <0.0001$)] FeNO was highest in children with rhinitis who also demonstrated aeroallergen sensitization (Table 2).

FeNO and Atopic Dermatitis

Children with current atopic dermatitis had significantly higher FeNO levels than those without atopic dermatitis at 8 years, but not at 6 years of age [Table 1, (6 years, 9.5 vs. 8.1 ppb, $p = 0.13$; 8 years, 12.4 vs. 9.2 ppb, $p = 0.002$)]. However, this relationship was no longer significant after stratification by allergic sensitization (Table 2).

FeNO and Asthma

Similarly, children with current asthma had higher FeNO levels than those without asthma at age 8 years, but not at 6 years of age [Table 1, (6 years, 9.2 vs. 8.3 ppb, $p = 0.48$; 8 years, 11.5 vs. 9.2 ppb, $p = 0.03$). Once again, this relationship was no longer significant after stratification by allergic sensitization (Table 2).

FeNO and Spirometry

Reproducible spirometry measurements were obtained in 70% (95 of 135) of 6 year old children and 88% (158 of 180) of 8 year old children with reproducible FeNO measurements. There were no significant correlations between FeNO and any measure of pulmonary function ($FEV_{0.5}$, FEV_1, FEV_1 % predicted, FVC, FVC % predicted, $FEV_{0.5}$/FVC or FEV_1/FVC).

Discussion

Despite efforts over the past decade to better understand the relationships between FeNO and the development of asthma and allergic disease, “normal” FeNO levels in early school aged children are not well established. We report FeNO measurements obtained with on-line technique in a large cohort of children at 6 and 8 years of age, allowing for effective comparisons with previously published studies. We clearly show that in our high-risk birth cohort, FeNO was most significantly associated with atopic (the presence of allergic sensitization) status. In fact, FeNO was only elevated in children with asthma and atopic dermatitis who also demonstrated allergic sensitization. Interestingly, rhinitis without detectable allergic sensitization was significantly associated with elevations in FeNO at age 8 yrs, albeit less so than in children with both rhinitis and demonstrable allergic sensitization.

Our overall rates of obtaining successful FeNO measurements at 6 years of age (64%) and 8 years of age (93%) by on-line measurement were similar to previously published data.(3;24) Successful measurement in 2/3 of 6 year olds and more than 90% of 8 year olds confirms the appeal of FeNO measurement in this age group as a reliable, non-invasive test that yields real-time results.

Another important finding of this study is that FeNO measurements varied by season, with summer and fall yielding the highest FeNO measurements. This is similar to recent findings reported from another cohort in which FeNO was highest in fall.(25) One potential explanation for this finding could be greater exposure to allergens, such as dust mites and viruses (rhinovirus in particular), during the summer and fall, respectively. Importantly, controlling for season of measurement did not alter any of the relationships seen between atopic status and FeNO; however, season of measurement still should be considered when interpreting FeNO measurements in a clinical or research setting.

While Buchvald & Bisgaard reported no association between FeNO and atopy as measured by RAST testing in 2-5 year old children,(17) Brussee and colleagues, in a significantly larger cohort of 4 year old children, reported a small but statistically significant elevation of FeNO in atopic individuals as determined by RAST testing.(14) In this manuscript, we report greater differences in FeNO in atopic vs. non-atopic children at age 8 years compared to age 6 years. A significantly more pronounced elevation of FeNO in older atopic children has been demonstrated by many researchers, (3;26;27) which suggests that while normal FeNO values have previously been shown to increase with age, there also appears to be a larger discrepancy between “normal” and “abnormal” values as individuals progress through childhood. The small difference between “normal” and “abnormal” FeNO seen in early school age children makes it difficult to foresee widespread successful use of FeNO for diagnosis in this age group.

In this study, we found a significant relationship between FeNO and asthma only in those children with concomitant allergic sensitization. This is consistent with at least one pediatric (26) and one adult study,(16;26) but not with others.(14;28) This discrepancy may be secondary to the use of many different methods for classification of history of wheezing and asthma throughout the studies, in addition to the various ages of the populations studied, as a greater percentage of teenagers and young adults, compared to early school age children, have atopic asthma. Whether a stronger relationship between asthma and elevated levels of FeNO will develop over time in our cohort remains to be seen.

While there is much agreement that there is a strong relationship between elevated FeNO and atopy, there have been mixed results when comparing measurements of lung function and FeNO. Several groups have demonstrated a correlation between spirometric evidence of airway obstruction and elevated FeNO in children;(4) however, most studies have not shown any correlation between elevated FeNO and impairment of FEV_1 or FEV_1/FVC.(28;29) In this

study, we found no significant correlation between FeNO and any measurement of lung function at 6 or 8 years of age. This confirms the notion that FeNO measures a different aspect of atopic airway disease than spirometry, and is potentially a more sensitive test for allergic airway disease in this age group,(6;7;30) where the vast majority of asthmatic children have normal lung function.(31)

There are several limitations to our study. First, COAST is a cohort of children at high risk for the development of asthma and other allergic diseases, which could limit the generalizability of our results. However, despite the high risk status of the COAST cohort, the geometric mean FeNO measurements were comparable to those previously published in an unselected population of early school age children.(3) Second, due to the observational nature of COAST, treatment regimens varied amongst children. Some individuals with asthma were taking inhaled corticosteroids which are known to decrease FeNO. However, when adjusting for controller medication use, the relationship between asthma and FeNO did not change.

In summary, in this cohort of children at 6 and 8 years of age at high risk for the development of asthma and allergic disease, elevations of FeNO were strongly and significantly correlated with allergic sensitization. While this data adds to the growing evidence of a strong relationship between elevated FeNO and atopy in children, the relationship of FeNO and asthma in early school age is much less clear. These findings underscore the importance of evaluating allergen sensitization status when FeNO is used as a potential biomarker in the diagnosis and/or monitoring of atopic diseases, particularly asthma.

Acknowledgments

Supported by NIH grants R01 HL61879, P01 HL70831, and M01 RR03186 Word Count 2378

Abbreviations

COAST, Childhood Origins of ASThma; FeNO, Fractional Exhaled Nitric Oxide; ppb, Parts per billion; AD, Atopic dermatitis.

References

(1). Payne DN, Adcock IM, Wilson NM, Oates T, Scallan M, Bush A. Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone. Am J Respir Crit Care Med 2001;164(8):1376–81. [PubMed: 11704581]

(2). 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(5):738–43. [PubMed: 11549525]

(3). Buchvald F, Baraldi E, Carraro S, Gaston B, De Jongste J, Pijnenburg MW, et al. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. J Allergy Clin Immunol 2005;115(6): 1130–6. [PubMed: 15940124]

(4). Strunk RC, Szefler 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(5):883–92. [PubMed: 14610474]

(5). Zeiger RS, Szefler SJ, Phillips BR, Schatz M, Martinez FD, Chinchilli VM, et al. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. J Allergy Clin Immunol 2006;117(1):45–52. [PubMed: 16387583]

(6). Moeller A, Diefenbacher C, Lehmann A, Rochat M, Brooks-Wildhaber J, Hall GL, et al. Exhaled nitric oxide distinguishes between subgroups of preschool children with respiratory symptoms. J Allergy Clin Immunol 2008;121(3):705–9. [PubMed: 18177695]

(7). Malmberg LP, Pelkonen AS, Haahtela T, Turpeinen M. Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma. Thorax 2003;58(6):494–9. [PubMed: 12775859]

(8). Smith AD, Cowan JO, Brassett KP, Filsell S, McLachlan C, Monti-Sheehan G, et al. Exhaled nitric oxide: a predictor of steroid response. Am J Respir Crit Care Med 2005;172(4):453–9. [PubMed: 15901605]

(9). Szefler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF Jr. Strunk RC, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy Clin Immunol 2005;115(2):233–42. [PubMed: 15696076]

(10). 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(21):2163–73. [PubMed: 15914548]

(11). Shaw DE, Berry MA, Thomas M, Green RH, Brightling CE, Wardlaw AJ, et al. The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. Am J Respir Crit Care Med 2007;176(3):231–7. [PubMed: 17496226]

(12). 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(7):831–6. [PubMed: 15976380]

(13). Szefler 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(9643):1065–72. [PubMed: 18805335]

(14). Brussee JE, Smit HA, Kerkhof M, Koopman LP, Wijga AH, Postma DS, et al. Exhaled nitric oxide in 4-year-old children: relationship with asthma and atopy. Eur Respir J 2005;25(3):455–61. [PubMed: 15738288]

(15). Steerenberg PA, Janssen NA, de MG, Fischer PH, Nierkens S, van LH, et al. Relationship between exhaled NO, respiratory symptoms, lung function, bronchial hyperresponsiveness, and blood eosinophilia in school children. Thorax 2003;58(3):242–5. [PubMed: 12612304]

(16). van Asch CJ, Balemans WA, Rovers MM, Schilder AG, van der Ent CK. Atopic disease and exhaled nitric oxide in an unselected population of young adults. Ann Allergy Asthma Immunol 2008;100 (1):59–65. [PubMed: 18254484]

(17). Buchvald F, Bisgaard H. FeNO measured at fixed exhalation flow rate during controlled tidal breathing in children from the age of 2 yr. Am J Respir Crit Care Med 2001;163(3 Pt 1):699–704. [PubMed: 11254527]

(18). Lemanske RF Jr. The childhood origins of asthma (COAST) study. Pediatr Allergy Immunol 2002;13(Suppl 15):38–43. [PubMed: 12688623]

(19). Baraldi E, de Jongste JC. Measurement of exhaled nitric oxide in children, 2001. Eur Respir J 2002;20(1):223–37. [PubMed: 12166573]

(20). Medical Section of the American Lung Association. Standardization of spirometry. Am J Respir Crit Care Med 1994;152:1107–36.

(21). Eigen H, Bieler H, Grant D, Christoph K, Terrill D, Heilman DK, et al. Spirometric pulmonary function in healthy preschool children. Am J Respir Crit Care Med 2001;163(3):619–23. [PubMed: 11254514]

(22). Neaville WA, Tisler C, Bhattacharya A, Anklam K, Gilbertson-White S, Hamilton R, et al. Developmental cytokine response profiles and the clinical and immunologic expression of atopy during the first year of life. J Allergy Clin Immunol 2003;112(4):740–6. [PubMed: 14564354]

(23). Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med 2008;178(7):667–72. [PubMed: 18565953]

(24). Napier E, Turner SW. Methodological issues related to exhaled nitric oxide measurement in children aged four to six years. Pediatr Pulmonol 2005;40(2):97–104. [PubMed: 15965893]

(25). 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(6):576–83. [PubMed: 18429012]

(26). Franklin PJ, Turner SW, Le Souef PN, Stick SM. Exhaled nitric oxide and asthma: complex interactions between atopy, airway responsiveness, and symptoms in a community population of children. Thorax 2003;58(12):1048–52. [PubMed: 14645971]

(27). Barreto M, Villa MP, Monti F, Bohmerova Z, Martella S, Montesano M, et al. Additive effect of eosinophilia and atopy on exhaled nitric oxide levels in children with or without a history of respiratory symptoms. Pediatr Allergy Immunol 2005;16(1):52–8. [PubMed: 15693912]

(28). Nordvall SL, Janson C, Kalm-Stephens P, Foucard T, Toren K, Alving K. Exhaled nitric oxide in a population-based study of asthma and allergy in schoolchildren. Allergy 2005;60(4):469–75. [PubMed: 15727578]

(29). Jentzsch NS, le BM, de BJ, Scheinmann P, Waernessyckle S, Camargos PA. Nitric oxide in children with persistent asthma. J Pediatr (Rio J) 2006;82(3):193–6. [PubMed: 16683051]

(30). de MG, van Amsterdam JG, Janssen NA, Meijer E, Steerenberg PA, Brunekreef B. Exhaled nitric oxide predicts airway hyper-responsiveness to hypertonic saline in children that wheeze. Allergy 2005;60(12):1499–504. [PubMed: 16266381]

(31). Paull K, Covar R, Jain N, Gelfand EW, Spahn JD. Do NHLBI lung function criteria apply to children? A cross-sectional evaluation of childhood asthma at National Jewish Medical and Research Center, 1999-2002. Pediatr Pulmonol 2005;39(4):311–7. [PubMed: 15678505]

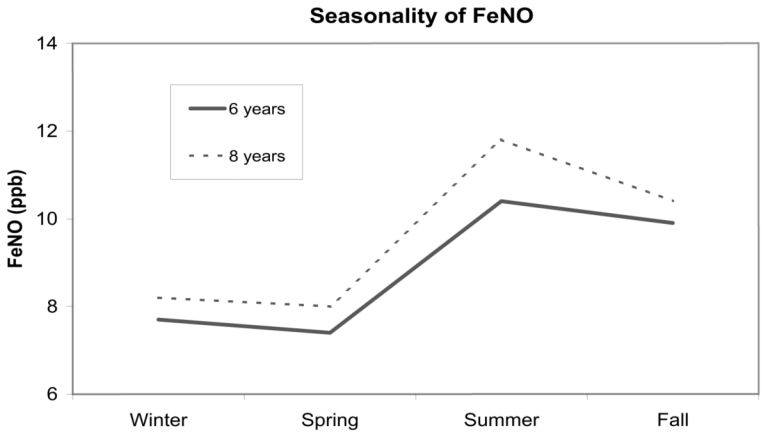

Figure 1.
Seasonality of FeNO measurement at 6 and 8 years of age. Geometric mean measurements were higher in summer and fall than in winter and spring (6 years, p = 0.04 & 8 years, p = 0.01).

Table 1

FeNO (geometric mean [25th, 75th percentile]) at 6 and 8 years of age in children of varying phenotypes.

		N	FeNO 6 years (ppb)	P-value	N	FeNO 8 years (ppb)	P-value
Aeroallergen RAST Age 6	−	63	6.7 [5.0, 9.0]	<0.0001	87	7.1 [5.3, 8.4]	<0.0001
	+	59	10.9 [6.7, 17.9]		70	14.6 [8.3, 27.1]	
Food RAST Age 6	−	95	8.0 [5.3, 10.1]	0.02	123	8.9 [6.1, 10.6]	0.0001
	+	26	10.9 [5.9, 14.8]		33	14.0 [7.1, 29.6]	
Current Rhinitis	−	70	7.3 [5.1, 9.3]	0.0006	84	7.6 [5.4, 9.1]	<0.0001
	+	65	10.2 [6.6, 14.8]		93	12.4 [7.5, 20.3]	
Current Atopic Dermatitis	−	91	8.1 [5.2, 10.8]	0.13	133	9.2 [6.0, 12.4]	0.002
	+	44	9.5 [6.2, 11.4]		47	12.4 [7.8, 20.8]	
Current Asthma	−	92	8.3 [5.6, 10.2]	0.48	115	9.2 [6.1, 11.3]	0.03
	+	43	9.2 [5.4, 13.6]		65	11.5 [7.4, 20.3]	

Table 2

Multivariable comparison of FeNO measurements (geometric mean [25th, 75th percentile]) at 6 and 8 years of age.

Allergic sensitization	Current Rhinitis	N	FeNO 6 years (ppb)	p-value	N	FeNO 8 years (ppb)	p-value
–	–	43	6.6 [5.0, 8.2]	Rhinitis:	53	6.7 [5.1, 8.2]	Rhinitis:
–	+	17	7.2 [4.1, 11.0]	0.054	28	7.5 [6.5, 9.1]	0.03
+	–	17	8.6 [5.1, 10.8]	RAST:	22	10.4 [7.0, 14.6]	RAST:
+	+	45	11.6 [7.4, 22.2]	0.001	52	16.0 [8.6, 29.9]	<0.0001

Allergic sensitization	Current Asthma	N	FeNO 6 years (ppb)	p-value	N	FeNO 8 years (ppb)	p-value
–	–	44	7.1 [5.3, 9.7]	Asthma:	59	6.9 [5.3, 8.3]	Asthma:
–	+	16	5.9 [4.3, 7.9]	0.88	23	7.3 [5.5, 8.6]	0.37
+	–	39	8.6 [6.7, 14.3]	RAST:	39	13.4 [7.3, 22.1]	RAST:
+	+	23	10.3 [6.8, 26.2]	<0.0001	36	15.0 [8.1, 28.1]	<0.0001

Allergic sensitization	Current AD	N	FeNO 6 years (ppb)	p-value	N	FeNO 8 years (ppb)	p-value
–	–	42	6.6 [4.7, 9.0]	AD:	67	6.9 [5.3, 8.3]	AD:
–	+	18	7.0 [5.6, 9.1]	0.21	15	7.7 [6.7, 8.5]	0.24
+	–	38	9.8 [6.1, 14.8]	RAST:	48	13.9 [7.5, 28.0]	RAST:
+	+	24	12.2 [7.4, 23.5]	<0.0001	27	14.6 [8.8, 22.6]	<0.0001