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Allergen exposure modifies the relation of sensitization to FENO levels in children at risk for allergy and asthma

Joanne E Sordillo, ScD[1,2], **Tara Webb, BS**[1], **Doris Kwan, BS**, **Jimmy Kamel, BA**[1], **Elaine Hoffman, PhD**[3], **Donald K Milton, MD, DrPH**[4], and **Diane R Gold, MD, MPH**[1,2]

[1]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital

[2]Harvard Medical School, Boston, Massachusetts, USA

[3]Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, USA

[4]University of Maryland, College Park, Maryland, USA

Abstract

Background—Studies on airway inflammation, measured as fraction exhaled nitric oxide (FENO), have focused on its relation to control of asthma, but the contribution of allergen exposure to elevation of FENO is unknown.

Objective—We evaluated (1) whether FENO was elevated in children with allergic sensitization or asthma; (2) whether specific allergen exposure increased FENO levels in sensitized, but not in unsensitized children; and (3) whether sedentary behavior increased FENO, independent of allergen exposures.

Methods—At age 12, in a birth cohort of children with parental history of allergy or asthma, we measured bed dust allergen (dust mite, cat, cockroach) by ELISA; specific allergic sensitization primarily by specific IgE ; and respiratory disease (current asthma, rhinitis, and wheeze) and hours of TV viewing/video game playing by questionnaire. Children performed spirometry maneuvers before and after bronchodilator responses, and had FENO measured using electrochemical detection methods (NIOX MINO).

Results—FENO was elevated in children with current asthma (32.2 ppb), wheeze (27.0 ppb), or rhinitis (23.2ppb) as compared to individuals without these respective symptoms/diagnoses (16.4 ppb to 16.6 ppb, $p < 0.005$ for all comparisons). Allergic sensitization to indoor allergens (cat, dog, dust mite) predicted higher levels of FENO, and explained one third of the variability of FENO. FENO levels were highest in children both sensitized and exposed to dust mite. Greater than 10 hours of weekday TV viewing was associated with a 0.64 log increase in FENO, after controlling indoor allergen exposure, BMI and allergic sensitization.

Conclusion—Allergen exposures and sedentary behavior (TV viewing/ video game playing), may increase airway inflammation, measured as FENO.

Corresponding Author: Joanne E Sordillo, rejoa@channing.harvard.edu, 181 Longwood Ave., Boston, MA 02115, Office Phone: (617) 525-2113.

Keywords

Asthma; dust mite; cat; allergens; exhaled NO; allergic sensitization; home environment

Introduction

Fraction exhaled nitric oxide (FENO) has been used in epidemiological studies of allergic disease, and in clinical practice as a supplemental tool for monitoring exacerbations and treatment efficacy in asthmatic patients[1-3]. FENO serves as a biomarker of airway inflammation that often correlates with the presence of sputum eosinophils[4, 5]. The increase in FENO observed in allergic disease is most likely driven by an upregulation of inducible nitric oxide synthase (iNOS) by cytokines released during airway inflammation[6, 7]. In addition to established reports of increased FENO in asthmatic patients, studies have shown elevated FENO levels in subjects with allergic rhinitis and asymptomatic allergic sensitization[1, 8-11]. Over the past decade, the majority of studies on FENO have sought to relate this inflammatory biomarker with clinical diagnoses or symptom status in allergic disease. Although environmental factors may play a significant role in airway inflammation, few investigators have examined their impact on FENO levels. Most studies accounting for the environmental contribution to this inflammatory biomarker are conducted solely in asthmatics. A cross sectional analysis in an asthmatic cohort showed an interaction between environmental allergen exposure and allergic sensitization, with the highest production of FENO in sensitized asthmatics exposed to elevated home allergen levels[12]. Allergen challenge studies in asthmatics demonstrate increases in FENO with in the short term period (1-7 days) following administration of the inhaled allergen [10, 13].

In other literature, lifestyle factors, such as sedentary behavior (ie. watching TV) have been associated with asthma and wheezing[14, 15], but have not been evaluated as potential predictors of increased FENO. Sedentary behavior may reflect a constellation of lifestyle choices capable of promoting airway inflammation and asthma, including decreased physical activity, increased caloric intake and low fruit and vegetable consumption.

We have previously demonstrated the relationship between early life allergen exposure and the onset of asthma and atopy in our birth cohort of children at high risk for allergies and asthma[16][17]. In the present work, we show the impact of current allergen exposure on airway inflammation in sensitized vs. unsensitized individuals (both with and without asthma or rhinitis). We also investigate the relationship between sedentary behavior (TV watching/video game playing) and FENO levels.

Methods

Study Cohort

Study participants were recruited between September 1994 and August 1996. The screening and recruitment of families have been described in detail elsewhere.[18] In brief, eligibility criteria included residence in the Boston metropolitan area; maternal age ≥ 18 years; and history of hay fever, asthma, or allergies in at least 1 of the child's parents. Families were not screened if the newborn was hospitalized in the intensive care unit, if his/her gestational age was < 36 weeks, or if he/she had a congenital anomaly. After written informed consent was obtained from the child's primary caretaker, a series of home visits were made (at age 2-3 months, age 7 and age 12), and a questionnaire regarding demographics, home characteristics, environmental exposures, tobacco use, and health outcomes was administered by trained research assistants at each home visit. Over the course of follow-up, a telephone questionnaire (modified from the American Thoracic Society-Division of Lung

Diseases questionnaire) was administered by trained research assistants to the child's primary caretaker every 6 months. Of the 505 children enrolled in the study, 430 (85%) were followed until age 12. Of the children followed until age 12, 283 had FENO measurements, and 250 had both FENO and allergen exposure assessment at age 12. The study was approved by the Institutional Review Board of Brigham and Women's Hospital.

Home visit and dust sample collection

Index children in the cohort ranged from 11 to 13.9 years (average 11.8 years) at this home visit to assess current allergen exposure. The methods used for collection of dust samples at the home visit and for measurement of dust mite, cat and cockroach allergen have been described previously[18]. Briefly, to collect bed dust, we used a Eureka Mighty-Mite vacuum cleaner (Model 3621; Eureka Co., Bloomington IN) modified to hold 19 × 90 mm cellulose extraction thimbles. All layers of the bedding were vacuumed for a total of 10 min. Allergen concentrations (μg/g dust) for Der f 1, Der p 1, Fel d 1, and Bla g 2 were quantified by ELISA. Consistent with previous analyses in our cohort, concentrations of dust mite allergen were grouped in categories potentially relevant to respiratory disease outcomes. [16] For dust mite, we used the highest concentration of Der f 1 or Der p 1 in the child's bed to categorize allergen levels as ≥ 10 μg/g or below. For cat allergen, levels were categorized as ≥ 8 μg/g or below. Cockroach allergen in bed dust was defined as above or below detectable levels. In addition to the current allergen exposure measurements listed above (average age 11.8 years), prior allergen exposures (Der f 1, Der p 1, Fel d 1,and Bla g 2) were also assessed at a mean age of 7 years, using the same methodology and exposure cut-points.

Assessment of Allergic Sensitization

At a mean age of 12 years (range, 11.2 to 13.5 years), IgEs specific to common allergens were measured in 189 children, and allergy skin testing was performed in an additional 19 children with FENO measurement. Serum samples were assayed for IgE to common indoor (cat dander, dog dander, cockroach [Blatella germanica], dust mite [Dermatophagoides pteronyssinus and Dermatophagoides farinae], and mouse epithelial extract) and outdoor (ragweed, mixed trees, Aspergillus, Alternaria, mixed grasses, Cladosporium, and Penicillium) allergens using the UniCAP 250 system. IgE to specific allergens were considered positive at a level of ≥ 0.35 IU/mL. Allergy skin testing was performed on the volar aspect of the lower arms for the allergens listed above. A subset of children (n=36/244 or 15%) were missing allergic sensitization assessment at age 12, even though data on allergen exposures, respiratory symptoms and exhaled NO levels were complete. For these individuals, allergic sensitization data from an earlier time point (mean age 7.4), was used in the analysis. In children with data at both time points, sensitization at age 7.4 was associated with sensitization at age 12 (χ^2=39.7, p<0.0001). Seventy four percent had the same sensitization status at both time points. Of the children who were unsensitized at age 7.4, thirteen percent later tested positive for allergic sensitization at age 12.

Assessment of TV Watching/Video Game Playing

Data on hours of watching TV or playing video games was gathered every 6 months by telephone questionnaire. We used data from the questionnaire closest in time to FENO measurement to assess hours of weekday and weekend time spent watching TV or playing video games. Respondents classified TV watching/video game playing by choosing a category that best represented their child's exposure (None, 1-5 hours, 6-10 hours, 11-15 hours, or 16-20 hours). Total hours of exposure during the week (weekday) and the total exposure over the weekend were assessed separately. Data on physical activity was also gathered for comparison with time spent TV watching/video game playing. Children were asked “How many of the past 7 days did you participate in physical activity for at least 20

minutes that made you sweat/breathe hard?" The response to this question was used to characterize the number of "physically active" days per week for each subject.

Definition of Respiratory Symptom Outcomes

Health outcome data were gathered every 6 months by telephone questionnaire. The disease and symptom data closest to the time of FENO measurement was used in the cross-sectional analysis. Outcomes included (1) current asthma, defined as a doctor's diagnosis of asthma with any wheeze in the past twelve months, including wheeze after exposure to cold air or exercise (current asthma); (2) any wheeze (≥ 1 wheezing event in the last year); (3) dry cough at night without cold or flu; (4) current rhinitis, defined as a doctor's diagnosis of hayfever with runny nose apart from cold in the past twelve months.

Spirometry

Standard spirometry was performed in accordance with ATS criteria[19]. To determine bronchodilator response (BDR), albuterol was administered (180 μg; 2 puffs with spacer). The subjects were asked to wait 10 minutes. Spirometry was then repeated. A positive BDR response was defined as ≥ 12% increase in predicted FEV_1 following the administration of albuterol. Children were asked to refrain from both long acting bronchodilator use 12 hours before assessment, and short acting bronchodilator use 4 hours before assessment.

Measurement of FENO

FENO levels were evaluated using a portable electrochemical device (NIOX MINO; Aerocrine AB), which is in agreement with published procedures for FENO measurement.[20]This method has been validated by chemiluminescence technology, with an accuracy of ± 5 parts per billion (ppb) (NIOX MINO; Aerocrine AB). Prior to FENO measurement, subjects breathed in through an NO scrubbing filter and exhaled out into the room air twice, before inhaling a third time through the filter and exhaling into the FENO analyzer. Exhaled FENO measurements were conducted without a nose clip, at a flow rate of 50ml/sec. (The last 3 seconds of the exhalation was utilized for FENO measurement, to ensure quantification of lower, rather than upper airway FENO.) In accordance with ATS guidelines we did not use nose clips, because blocking the nasal passages can cause FENO to accumulate in the nose, and potentially leak into exhaled air stream via the posterior nasopharynx[20]. This procedure was performed three times, so that each subject had a total of 3 FENO measurements. The median of these three measurements was used in data analysis.

Data Analysis

In children followed up to age 12, Chi square analyses were used to determine if demographic characteristics were different in those with vs. without FENO measurements. FENO levels were log transformed (ln) to approximate normality. To investigate the association of specific allergic sensitization with FENO, a multiple regression model containing dichotomous variables for individual indoor and outdoor allergies was constructed. Allergic sensitization variables that were significant in univariate analyses were included in the multiple regression model. (Variance inflation factors were examined to ensure that multicollinearity was not an issue when adding multiple allergic sensitization variables to the same model). Mean levels of FENO (Least square (LS) means) in those with adverse respiratory health outcomes (current asthma, any wheeze, dry cough at night, current rhinitis) were examined in models controlling for sex and maternal asthma. Inhaled corticosteroid (ICS) use was examined as apotential confounder of the association between asthma symptoms and FENO. For the entire group with allergy testing as well as for the subgroup with diagnosed asthma or hay fever, we also compared LS means for FENO in

those sensitized vs. not-sensitized. To determine if the relationship between allergic sensitization and FENO was modified by allergen exposure, we entered an interaction term, as well as main effects of specific allergy and allergen exposure level into models for FENO. Sex, race, season and age at FENO measurement were considered as potential confounders. A p value of ≤ 0.05 was considered to be significant, whereas p values of ≤ 0.10 were taken to indicate borderline significance.

The statistical software package, SAS 9.1.3 (Cary, NC) was used to perform the statistical analyses.

Results

FENO Measurement

The median level of FENO was 16.0 ppb (range 2.0 ppb to 169 ppb) in all subjects with FENO measurement (Table 1). On average, children were 11.7 years of age at the time of FENO quantification (age range, 11-13.9 years). Of the 430 children followed to age 12 years by questionnaire, 277 (64%) had FENO measurements. Children with FENO measurements were more likely to be white, and less likely to be Hispanic. Distribution of sex and prevalence of maternal asthma were similar for those with vs. without FENO at age 12 (Table 1).

Symptoms and FENO

Of the children with FENO measurement and health data by questionnaire at age 12 (n=277), 16% had current asthma (n=44), 22% wheezed in the past year (n=60), and 14% had dry cough at night, without cold. Eighty one percent of the current asthmatics had allergic sensitization. Current asthma was associated with a two-fold increase in FENO levels ($p < 0.0001$), from 16.5 ppb (non-asthmatics) to 32.2 ppb (current asthmatics) (Table 2). Children with any wheeze in the past year also had elevated FENO (16.4 ppb in no wheeze vs. 27.0 for any wheeze). Current rhinitis was associated with a similar increase in FENO ($p < 0.01$). Dry cough at night was not associated with FENO. Eight percent of the subjects with FENO measurement reported use of ICS. Use of ICS did not confound the relationship between asthma symptoms and FENO. (see supplemental table 1). Sensitized children also produced higher FENO levels (24.5 ppb) compared to children who were unsensitized (12.6 ppb, $p<0.001$). The association of FENO with any allergic sensitization remained significant even after children with rhinitis (N=48) or prior diagnoses of asthma (N=84) were removed from the analysis (Table 2). Children with a prior asthma diagnosis who tested positive for allergic sensitization (67%) had higher FENO levels (26.1ppb) than unsensitized children diagnosed with asthma (14.2ppb, $p<0.0001$). Sensitized children with current asthma also produced higher levels of FENO than current asthmatics who were unsensitized (table 2).

Allergic Sensitization and FENO

The most prevalent indoor allergies were to dust mite (40%) and cat (28%). Allergic sensitization to other indoor allergens was much less common, with prevalence ranging from 5% (dog and cockroach allergy) to 2.4% (mouse allergy). The most prevalent outdoor allergy was to tree pollen (29%). Few subjects were allergic to fungi (4.4 to 11%). In univariate models, both indoor and outdoor allergies were significant predictors of increased FENO levels (Table 3). Allergies to mites, pets (dog and cat), pests (mouse and cockroach), pollen (tree and ragweed) and fungi (alternaria) were all associated ($p<0.05$) with FENO measurements at least double the levels in unsensitized individuals. However, in the multiple regression model, only the indoor allergies to dust mite, cat and dog remained significant (Table 3). In addition to considering specific allergic sensitization, we modeled

the association between the total number of positive sensitization tests and FENO. FENO was shown to increase with each additional positive skin test (0.13 log increase in FENO per positive allergic sensitization test). (Supplemental table 2) An increased percentage of circulating eosinophils was also associated with higher FENO levels (supplemental table 3).

Effect of Allergic Sensitization Modified by Allergen Exposure

The effect of allergic sensitization on FENO levels was modified by current allergen exposure (Table 4). Thirty two percent of the children fell into the category of high dust mite exposure (≥ 10 ug/g in bed dust) whereas 27% were observed to have increased cat allergen exposure. Detectable cockroach allergen was found in 6% of children's bed dust samples.

Current dust mite exposure did not increase FENO levels in children without dust mite allergy (p=0.2). However, amongst dust mite allergic children, higher exposure levels were associated with a significant elevation in FENO levels (p=0.003). This interaction remained even after children with a prior diagnosis of asthma were removed from the analysis (Supplemental Table 4). Unsensitized children produced the lowest levels of FENO. Sensitized but low exposed subjects produced levels twice as high (24.7ppb) as in unsensitized children (12.4 to 14.8 ppb) while the sensitized and exposed subjects produced three times the level of FENO (38.3 ppb) compared to unsensitized subjects. Similar interactions were observed for cat allergen exposure. Increased current cat allergen exposure was associated with higher FENO levels only in sensitized individuals. (However, this association was not observed in the subset without asthma or rhinitis). Exposure to cockroach allergen did not increase FENO levels in those with cockroach allergy. Similarly, an interaction between dog allergen exposure and sensitization to dog was not observed for FENO. Season did not confound the main effects or interaction terms in these models.

Prior allergen exposure (mean age 7) was also predictive of increased FENO at age 12 in allergic individuals. Prior allergen exposure levels tended to overlap with current allergen exposure. (Bed dust mite levels (≥ or < 10 μg/g) were consistent over time for 72% of subjects). For dust mite, the interaction observed for prior allergen exposure in bed dust was similar to the interaction observed for current allergen exposure. Prior allergen exposure (dust mite, cat or cockroach) as measured by assay of bed dust at age 7 showed a similar interaction of sensitization and exposure with the highest FENO levels in those both sensitized and exposed to elevated levels of the specific allergen. (Supplemental table 5)

Bronchodilator Response and FENO

Response to albuterol (12% increase in predicted FEV1) was associated with higher FENO levels (28.0 ppb vs. 17.9 for non-responders; p = 0.02). (Table 5) Of those who responded to albuterol, 56% (9/16) had a prior asthma diagnosis, 37% (6/16) had wheezed in the past year, and 31% (5/16) had current, active asthma. Of sensitized children with a past diagnosis of asthma, 9.8% (5/51) responded to albuterol, while 3.7% (1/27) of unsensitized asthmatic children were responders. Of sensitized children with prior asthma diagnosis and current symptoms, 11.1% (3/27) responded to albuterol, while none of the non-sensitized current asthmatics (0/7) were responders. Neither sensitization, nor allergen exposure (or their interaction) was predictive of bronchodilator response. (data not shown)

TV watching/Video Game Playing and FENO

Total hours of weekday TV watching or video game playing was associated with increased FENO levels as compared to the reference group (zero hours of TV watching/video game playing), even after controlling for allergen exposure, allergic sensitization and BMI. (Table 6) Ten percent of children did not watch television or play videogames during the week, 47% were in the 1- to 5-hour exposure category, 32% were in the 6- to 10-hour exposure

category, and the remaining 11% were in the greater than 10-hour exposure category. The 1-5 hours and 6-10 hours exposure categories showed similar effects when compared to the reference, and were therefore collapsed into a single 1-10 hour exposure category. In those with 1-10 hours of weekday exposure, FENO levels were associated with a 0.43 log increase in FENO(p=0.02). Greater than 10 hours of weekday exposure was associated with a slightly larger increase (0.64 log increase in FENO vs. reference category, p = 0.005). For weekend TV watching/video game playing the reference category (zero hours) had too few children (n=3) to make a valid comparison with higher exposure levels. Children's physical activity levels were inversely associated with TV watching/video game playing. Of children who did not watch TV during the week, 87% reported at least 5 “physically active” days per week, compared to 58% in the 1-10 hour category, and 42% in the > 10 hour TV/video game category. (p value for Chi square= 0.03).

Discussion

The importance of ascertainment of specific allergic sensitization when evaluating the clinical significance of allergen exposure on asthma morbidity was highlighted, first in the observational National Inner City Asthma Study[21, 22] and then in the subsequent intervention study that was targeted at allergen exposures to which asthmatic children were sensitized.[23] Our study highlights the importance of allergic sensitization when evaluating the effects of allergen exposures on subclinical pulmonary inflammatory outcomes that may ultimately have clinical import, even in asymptomatic children. Most prior research on allergen exposure and FENO has been focused on asthmatic populations. To the best of our knowledge, this is the first study to investigate the independent impact of home exposures (allergens) and sedentary home behaviors (TV viewing/video game playing) on FENO in a birth cohort at high risk for allergies and asthma.

Respiratory Symptoms, Bronchodilator Response, Allergic Sensitization and FENO

We reproduced several documented associations between clinical outcomes and FENO in our cohort. As in a number of other studies[1, 2, 9, 11], subjects with current asthma or wheeze had increased levels of FENO. Similar to prior reports[24, 25], bronchodilator response was associated with increased FENO levels. Rhinitis was an important contributor to FENO levels in our study and others [9, 26], suggesting that rhinitis may be linked to lower, as well as upper airway inflammation. The association we observed between increased FENO in sensitized individuals without allergic disease reflects similar reports of sensitization as a predictor of airway inflammation in healthy asymptomatic children.[1, 26, 27] The relationship between increased circulating eosinophils (%) and higher FENO demonstrated in this report provides further supportive evidence that allergic sensitization is a key factor in FENO production. Contrary to these results, other investigators have found elevated levels of FENO only in atopic individuals with concomitant asthma or rhinitis.[9, 28] In these studies[9, 28], offline FENO analysis (by collecting exhaled air into mylar bags prior to chemiluminescent detection) may have added noise to the measurement, potentially preventing discrimination between healthy atopic and non-atopic subjects.

In our analysis of specific allergic sensitization and FENO levels, indoor allergies to dust mites and pets (cats, dogs) explained approximately one third of the variability in FENO levels and were the only significant predictors remaining after adjustment for sensitization to other allergens, including plants (trees, ragweed) and fungi (Alternaria). This result is in agreement with a cross-sectional study of Dutch school children, which demonstrated that sensitization to indoor, rather than outdoor allergens, were the main determinants of increased FENO. [29]

Effect Modification of Allergic Sensitization by Allergen Exposure

This is the first study to investigate effect modification of specific allergic sensitization by home allergen exposure in a cohort of children at high risk for allergies and asthma. Of the few existing experimental and epidemiological studies on this type of interaction, all of have been conducted in individuals with symptomatic allergic disease. In one report, repeated low dose inhalant allergen challenges over the course of 6 days were shown to double FENO production in sensitized adult asthmatic, with a simultaneous increase in bronchial hyper-responsiveness to histamine over the study period.[13] Bronchial challenge with dust mite allergen in mite allergic adults with asthma or rhinitis has been shown to significantly increase FENO levels 24 hours post-challenge.[10] Dust mite allergic, asthmatic children living in a mite free environment for 3 months showed a significant increase in FENO levels only 4 days after returning to an area with natural mite exposure.[30] One epidemiologic survey demonstrated increased FENO levels among sensitized asthmatic subjects exposed to indoor allergens, although the authors lacked the power to analyze specific types of allergen exposure by means of sensitization interactions (subjects exposed and sensitized to any allergen were lumped together in one group).[12] Another study in asthmatic children did not detect any interaction between sensitization and home allergen exposure. [31]

In our study, the association between FENO levels and allergen exposure in dust mite sensitized individuals remained even after removing those with a prior asthma diagnosis from the analysis. This interaction was also observed after removing subjects with rhinitis from the analysis, although the p value for the interaction was borderline significant (p=0.09). Since allergen exposures tended to remain constant over time in our cohort, it is possible that current allergen levels reflect persistent exposure from age 7 to 12. Therefore, persistent, rather than transient, exposure to perennial allergens may be responsible for driving increased FENO levels in sensitized individuals. While some allergen exposures (dust mite and cat) were associated with substantial increases in FENO, exposures to cockroach and dog allergen did not appear to modify FENO levels. Lack of significant findings for these perennial allergens may simply be due to reduced power to detect effect modification in the relatively small groups of cockroach and dog sensitized individuals. Although our primary focus was on home exposures to perennial allergens, we also investigated the impact of the spring season (when tree pollen allergens are increased) on FENO levels in individuals sensitized to tree allergens (data not shown). We did not detect any significant interaction or trend, suggesting that perennial allergens may play a larger role than seasonal allergens in predicting elevated FENO in sensitized subjects.

Our findings have important implications for clinical practice. With the exception of the National Inner City Asthma trials, most asthma clinical trials are not focused on environmental intervention. Our study highlights the importance of considering modification of the home environment when planning a comprehensive intervention aimed at reducing airway inflammation in asthmatic or symptomatic allergic children. It is also possible that there are long-term clinical implications of our findings of elevated FENO in asymptomatic children who are sensitized and exposed to high allergen levels. Our geometric means levels of FENO in non-asthmatic children who were sensitized and exposed to dust mite (33.7 ppb) were similar to levels measured in uncontrolled asthmatics.[32] Persistent airway inflammation may lead to symptomatic disease and even to airway remodeling.[33, 34]

TV viewing/Video Game Playing and FENO Levels

Even taking into account allergic sensitization, allergen exposures and BMI, we demonstrated a positive association between hours of TV viewing or video game playing and FENO levels in children at age twelve. Although TV viewing has been associated with increased risk of wheeze and current asthma in school aged children[14, 15], ours is the first

report on the relationship between this sedentary behavior and a quantifiable biomarker of airway inflammation (FENO). Children who watch more TV engage in less physical activity[35], consume higher-calorie diets with lower amounts of fruits and vegetables[36, 37], and have increased body fat[38]. TV viewing/video game playing may represent a surrogate for one or a combination of these factors related to diet or physical activity. It has been hypothesized, and there is some evidence to suggest that decreased physical activity can alter physiologic or immune response (with potential implications for airway inflammation and asthma), while dietary factors (such as reduced antioxidant intake) may also play a role in asthma. Watching television has also been associated with decreased sigh rates, which could contribute to non-specific bronchial hyper-reactivity through airway smooth muscle "latching". [39]

Limitations

Although FENO data gathered at a single time point allowed us to examine multiple associations, measurement at additional points in time would have enabled us to study changes in FENO with alterations in clinical symptom status or environmental exposures. Previous studies have shown higher levels of FENO in atopic asthmatics vs. non-atopic asthmatics[28]. However, we were limited in our ability to assess the impact of atopy within our relatively small subgroup of current asthmatics. Since allergen levels tended to persist over time, we were unable compare the impact of continual vs. transient elevations in exposure on FENO levels.

Conclusion

This study demonstrates the importance of environmental contributions, in the form of biological exposures (allergens) and behaviors (TV viewing/video game playing), as potential determinants of FENO levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations Used

FENO	Fraction exhaled nitric oxide
BDR	Bronchodilator response

LS Mean Least Square Mean

TABLE 1
Characteristics of subjects tested for FENO

	Number (percent)	
Characteristic	**Children followed up to age 12 with FENO measurement**	**Children followed up to age 12 without FENO measurement**
Sex		
Male	160 (58)	76 (48)
Female	117 (42)	81 (52)
Race		
White	233 (84)	116 (74)*
Black	23 (8)	14 (9)
Hispanic	6 (3)	12 (7)*
Asian Other	15 (5)	15 (10)
Maternal Asthma	79 (29)	48 (31)
Age at FENO measurement (years)	Mean = 11.7, Range = 11 to 13.9	NA
FENO (ppb)	Median= 16, IQR = 11.0 to 32.0	NA

* $p<0.05$ for comparison with children followed to age 12 with FENO measurement

TABLE 2
Current Asthma, Rhinitis, Respiratory Symptoms, and Atopy and FENO*

	N	Disease Status	FE_{NO}, ppb (LS Mean)	P value
Current Asthma (all)	233	No	16.5	<0.0001
	44	Yes	32.2	
Current Asthma (non-atopic)	7	Yes	15.0	0.01**
Current Asthma (atopic)	29	Yes	36.7	
Any Wheeze	217	No	16.4	0.0008
	60	Yes	27.0	
Dry Cough at night	235	No	18.0	0.34
	40	Yes	20.4	
Current Rhinitis (all)	185	No	16.6	0.005
	56	Yes	23.2	
Current Rhinitis (non-atopic)	9	Yes	13.3	0.02**
Current Rhinitis (atopic)	39	Yes	26.5	
Allergic sensitization***	116	No	12.6	<0.0001
	130	Yes	24.5	
Allergic sensitization (in those without Dx of asthma or rhinitis)****	73	No	11.9	<0.0001
	43	Yes	22.4	

* Models controlled for sex and maternal history of asthma

** For comparison of atopic vs. non-atopic individuals with disease diagnosis

*** Sensitization to indoor allergens (cat, dog, dustmite, cockroach, mouse), outdoor allergens (pollen, ragweed, grass) or mold

**** All children ever diagnosed with rhinitis or asthma have been removed from this comparison

TABLE 3

Allergic Sensitization and FENO levels

		Univariate Models		Multiple Regression Model*			
Allergic Sensitization	**(N)**	**FENO, ppb (LS Mean)**	**P Value**	**FENO, ppb (LS Mean)**	**P value**	**Partial R^2**	**Model R^2**
Dust Mite	Neg (151)	13.5	<0.0001	22.8	<0.0001	19.1%	31.9%
	Pos (99)	27.0		36.6			
Cat	Neg (180)	14.3	<0.0001	22.6	<0.0001	8.7%	
	Pos (70)	31.4		37.0			
Dog	Neg (237)	16.9	<0.0001	22.3	0.01	2.1%	
	Pos (13)	43.9		37.5			
Cockroach	Neg (237)	17.3	0.014	27.9	0.7	0.05%	
	Pos (13)	29.6		30.0			
Mouse	Neg (241)	17.4	0.02	29.0	0.98	0.06%	
	Pos (6)	37.6		28.8			
Tree Mix	Neg (174)	16.6	0.03	31.1	0.2	0.5%	
	Pos (73)	20.9		26.9			
Ragweed	Neg (220)	17.1	0.02	28.3	0.77	0.06%	
	Pos (30)	24.0		29.6			
Alternaria	Neg (219)	17.1	0.03	27.8	0.43	0.8%	
	Pos (28)	23.9		31.0			
Penicillium	Neg (236)	17.7	0.60	--	--	--	
	Pos (11)	20.1					
Grass	Neg (206)	17.4	0.30	--	--	--	
	Pos (41)	20.0					

*Adjusted for sex and maternal history of asthma

TABLE 4

Effect of Current Allergen Exposure on FENO, as modified by Allergic Sensitization*

	Allergic Sensitization	Exposure Category**	N	FENO, ppb (LS Mean)	P value
Dust Mite (Der f 1, Der p 1)	−	< 10 μg/g	103	14.8	0.2
		≥ 10 μg/g	44	12.4	
	+	< 10 μg/g	64	24.7	0.003
		≥ 10 μg/g	33	38.3	
Cat (Fel d 1)	−	< 8 μg/g	123	14.9	0.9
		≥ 8 μg/g	51	14.6	
	+	< 8 μg/g	53	30.7	0.06
		≥ 8 μg/g	15	44.7	
Dog (Can f 1)	−	< 20 μg/g	158	18.5	0.2
		≥ 20 μg/g	62	16.2	
	+	< 20 μg/g	8	29.5	0.5
		≥ 20 μg/g	4	33.7	
Cockroach (Bla g 2)	−	Non-detectable	217	17.9	0.7
		Detectable	13	19.7	
	+	Non-detectable	11	33.6	0.3
		Detectable	2	18.2	

* Models controlled for sex and maternal history of asthma

** Allergens measured in bed dust samples at mean age of 12

TABLE 5
Bronchodilator Response and FENO levels*

Bronchodilator Response	Level	N	LS Mean	P value for Difference
12% increase in FEV_1 after albuterol	N	218	17.9	0.02
	Y	16	28.0	

*Model adjusted for sex and maternal history of asthma

TABLE 6

TV Watching/Video Game Playing and FENO levels (Multiple regression model)*

Weekday TV/Video Game Playing	N	Parameter Estimate Δ log FENO vs. reference	P value
None	27		
1-10 hours	220	0.43	0.02
>10 hours	30	0.64	0.005

* Model controlled for dust mite allergen (>10 μg/g), Fel d 1 (> 8 μg/g), endotoxin (> median) all measured in living room dust, BMI, sex, current asthma and allergic sensitization