

Infants and toddlers without asthma with eczema have elevated exhaled nitric oxide levels

To the Editor:

Asthma, atopic dermatitis (eczema), and hay fever are allergic disorders that have increased in incidence in the last 3 decades. Approximately 40% of infants with atopic dermatitis develop asthma at the age of 3 to 4 years.¹ This association between atopic dermatitis and the subsequent development of asthma is often referred to as the *atopic march*. Development of strategies that aid in detection of asthma before the immunopathology of the disease is fully established, and hence potentially preventable, is the current focus of effective asthma management. Indeed, the presence of physician-diagnosed atopic dermatitis is considered a risk factor for the development of asthma by the National Asthma Education and Prevention Program Expert Panel, with the most recent update recommending long-term controller therapy for wheezing high-risk infants.

Fractional concentration of exhaled nitric oxide (FeNO) is a biomarker that is an accurate, reproducible, rapid, and noninvasive indicator of disease activity and response to anti-inflammatory therapy.^{2,3} As recently reviewed, a number of studies show normal FeNO levels to be 5 to 20 parts per billion (ppb), and FeNO values >15 ppb may serve as a cutoff for asthma with 90% specificity and 95% positive predictive value.³ FeNO can be elevated in subjects with "subclinical asthma" (normal lung function, negative bronchodilator tests, and elevated sputum eosinophilic cationic protein), and in atopic patients without asthma with bronchial hyperresponsiveness.^{4,5} Balboa et al⁶ noted in a recent study in children 6 to 14 years with and without wheeze that FeNO was higher in those with atopic dermatitis. In this preliminary study, we attempted to establish baseline FeNO levels in children 6 months to 3 years of age with eczema, before the development of recurrent wheezing episodes. We hypothesized that children without asthma with eczema had increased FeNO compared with children without eczema. Increases in FeNO may eventually serve as an early noninvasive predictor of the development of asthma in young children.

A convenience sample of 23 healthy control children 6 months to 3 years of age without atopic dermatitis (eczema), and 22 similarly aged children with eczema and active symptoms for at least 1 month were enrolled. We calculated that a sample size of 20 patients in each group would have a 90% power for detecting a 50% increase in patients with atopic dermatitis (assuming a 2-sided test at $\alpha = 0.05$), presuming that the SD of the log-transformed FeNO values was 0.38.⁷ Caretakers of study participants signed Institutional Review Board–approved informed consent before testing. Information was obtained on the following: history of atopy/asthma, medication use, diet in the past 24 hours, feeding history (breast/formula), and exposure to tobacco smoke. Exclusion criteria included more than 1 episode of non–respiratory

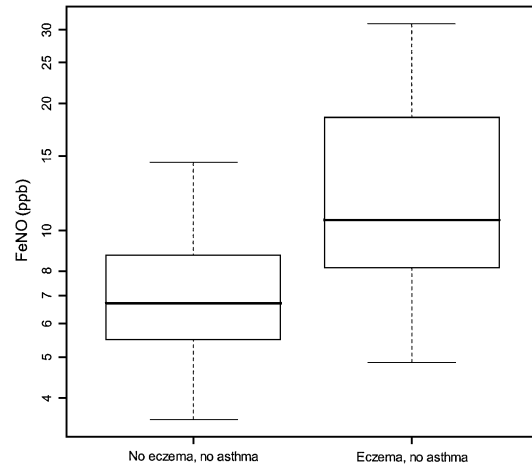


FIG 1. Distribution of exhaled NO levels in nonwheezing infants and toddlers with and without eczema. FeNO values plotted on a log scale in parts per billion (ppb). Groups differ significantly ($P = .02$).

syncytial virus–related wheezing, diagnosis of asthma, use of albuterol or inhaled steroid, concurrent or recent (2 weeks) upper respiratory tract infection, use of oral steroids within the past month, chronic pulmonary disease, and chronic skin disorders other than eczema. FeNO was measured by using tidal breathing offline collection following guidelines by the American Thoracic Society.⁸ Each study participant performed relaxed tidal breathing using a face mask with nasal occlusion connected to a 1-way valve and nitric oxide (NO) scrubber that allowed inspiration of NO-free air to avoid contamination by ambient NO. After establishment of a stable breathing pattern, expired tidal breath was collected for 15 to 45 seconds in a nonreactive sample bag fitted with a port providing resistance of 2 cm H₂O during expiration. The expired breath was analyzed in parts per billion within 1 hour of sample collection using a Sievers 280 Nitric Oxide Analyzer (Sievers Instruments Inc, Boulder, Colo). Two samples were taken from each study participant. Data on 2 children in the noneczematous group and 2 in the eczema group were discarded. One child had an undisclosed history of asthma. Two children in each group respectively had discrepancies (>5 ppb) in the 2 FeNO readings.

The demographic profile of the participants revealed similar baseline characteristics for age (mean age, 23–26 months), environmental tobacco exposure (30% to 35%), and sex (noneczema group: males 65%; eczema group: males 50%). A greater proportion of the children without eczema were bottle-fed (80%). Sixty percent of the children with eczema were clinically classified as mild, 30% as moderate, and 10% as severe. Forty percent of them had a personal history, and 25% had a family history, of atopy. Only 25% subjects in the eczema group had previous allergy testing performed. None of the children in either group had wheezed before entry into the study.

Data were analyzed by using a 2-sample *t* test on the measured values as well as log-transformed values. The

geometric mean and geometric SD of FeNO levels in the 20 healthy children was 7.0 ppb (SD, 1.52; Fig 1). The geometric mean FeNO level in the 20 children with eczema was 11.7 ppb (SD, 1.71). Statistical analysis using a 2-tailed *t* test comparing the 2 groups showed a statistically significant difference between the 2 groups ($P = .002$; 95% CI for ratio of geometric means, 0.44-0.81). There was no significant correlation between FeNO levels and severity of eczema ($P = .37$), topical steroid use ($P = .53$), and symptoms of allergic rhinoconjunctivitis/positive allergy tests ($P = .56$).

To our knowledge, this is the first study looking specifically at the levels of FeNO in infants and toddlers with eczema. Our study demonstrates that accurate offline sampling of exhaled NO in children as young as 6 months of age is feasible and valid, and serves to establish normative FeNO data on infants and toddlers. In our study, children younger than 3 years with eczema had FeNO levels that were significantly higher than those of healthy control children, before the onset of significant wheezing. Some of the children with eczema had FeNO levels similar to those of children without eczema, whereas a subset had elevated levels. However, unlike the cohort at risk for wheezing in the Prevention of Early Asthma in Kids study that had evidence of aeroallergen/food sensitization and atopy,⁹ we did not find a difference in parameters such as the severity of eczema or presence of allergy that might predict the elevated FeNO among that subset. Notably, the numbers of subjects in the subsets were small, and not all children with eczema underwent allergy testing.

Balboa et al⁶ performed a cross-sectional study of 105 healthy children age 6 to 14 years designed to evaluate FeNO in healthy children and children with asthma and to relate this variable to different treatment regimens. They observed that, depending on the severity of their disease, children with atopic dermatitis had higher FeNO concentrations (23.07 ppb) than those without atopic dermatitis (11.68 ppb; $P < .001$). Franklin et al¹⁰ investigated various methodological issues on tidal breathing FeNO in 88 infants with and without wheeze. They found no significant difference in mixed FeNO between healthy and wheezing children, but children with doctor-diagnosed eczema had significantly raised levels ($P = .014$).

In conclusion, our preliminary study shows that eczematous infants and toddlers <3 years with no previous history of wheezing had FeNO levels that were significantly higher than those of control healthy children. Serial FeNO measurements over time, along with symptom monitoring, may be of potential benefit in predicting the development of asthma in these high-risk children. Early detection of preclinical asthma could open the door to early intervention, such as the use of inhaled fluticasone in the Prevention of Early Asthma in Kids trial.⁹ Larger trials looking at other biomarkers and parameters of atopy may help answer some of these questions in a more definitive manner.

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Prostate-specific antigen as allergen in human seminal plasma allergy

To the Editor:

Human seminal plasma allergy is made up of a spectrum of clinical symptoms caused by local or systemic hypersensitivity reactions after contact with human ejaculate. Symptoms manifest during or soon after sexual intercourse and range from localized vulvovaginal pruritus to life-threatening anaphylaxis.¹

Reactions may have varying origin and are not always referable to true sensitization against allergens present in the seminal plasma. They may also be related to sensitizations against latex (condoms), spermicidal agents (vaginal contraceptives), local anesthetics (in some condoms), or components of lubricants. In addition, there have been