Elevated exhaled nitric oxide is a clinical indicator of future uncontrolled asthma in asthmatic patients on inhaled corticosteroids

To the Editor:

Asthma is a chronic inflammatory process with airflow obstruction and hyperreactivity; however, diagnosis and monitoring rely on symptoms and lung function and do not routinely include inflammatory markers such as fractional exhaled nitric oxide (FENO). FENO levels >300% of predicted are associated with a high likelihood of a favorable response to inhaled corticosteroids (ICSs)[1] and also worsening asthma with ICS withdrawal.[2] We reported that highest versus lowest quartile FENO levels in asthmatic patients on ICSs were associated with excess short-acting β_2-agonist (SABA) use and exacerbations requiring oral corticosteroid (OCS) courses in a prior year, independent of an asthma control tool and spirometry.[3] We now test the hypothesis that FENO levels >300% predicted identify patients with future uncontrolled asthma, independent of an asthma control tool and spirometry.

We conducted a multicenter, prospective, noninterventional study among 304 patients aged 12 to 56 years with allergist-diagnosed persistent asthma from 4 Kaiser Permanente Southern California (KPSC) allergy departments. KPSC Institutional Review Board approved the study. Additional inclusions were (1) aero-allergen sensitization by using skin/RAST testing, (2) monotherapy or combination ICS for ≥1 month before enrollment, and (3) continuous KPSC membership with 1-year pharmacy benefit. Exclusions included (1) smokers; (2) OCS, theophylline, or anticholinergic use within 2 weeks of enrollment; (3) FEV_1 < 50% predicted; (4) chronic obstructive lung disease; (5) omalizumab use; or (6) participation in an asthma clinical trial.

During a scheduled allergist visit, enrolled patients completed questionnaires on demographics, asthma/allergy history, Asthma Control Test (ACT), medication use, and asthma utilization. KPSC pharmacy dispensings and utilization were captured in electronic medical records and research data warehouses.

The measurement of FENO levels was performed before or ≥20 minutes after spirometry by using the validated NIOX MINO hand-held device (Aerocrine AB, Solna, Sweden). FENO levels were masked by using an electronic chip downloaded at the data analysis site. Spirometry by American Thoracic Society standards was performed on a KOKO electronic pneumotach spirometer.

Impairment was defined as SABA dispensings both as a count variable (number dispensed) and as a dichotomous variable (≥7 canisters dispensed: yes/no) since patients with ≥7 SABA canisters dispensed in a future year is a validated administrative data surrogate for asthma impairment.[4] *Risk* was defined as OCS courses dispensed within 2 days of an asthma exacerbation–coded provider visit or an asthma-related emergency department visit or hospitalization (defined as a primary asthma diagnosis [493.xx] or secondary asthma diagnosis when the primary diagnosis was related to a respiratory disease). Expert Panel Report-3–recommended step-care level was calculated by using an algorithm and formula based on asthma medication and amount dispensed.[5]

Absolute FENO levels were transformed into percent predicted values by using reference equations for adolescents[6] and adults[7] to better generalize findings for clinical care as is done for spirometry. FENO was dichotomized by 300% predicted levels based on its clinical relevance[1,2] as described earlier to provide clinically actionable information.

Poisson regression models with a robust error variance were constructed to calculate the unadjusted and adjusted relative risk (RR) and 95% CI separately for patients with ≥7 SABA canisters dispensed and ≥2 exacerbations with OCS courses in the follow-up year. Negative binomial models using a robust error variance were used to calculate the unadjusted and adjusted incidence rate ratio (IRR) and 95% CI for number of SABA counts and number of exacerbations requiring OCS courses. Multivariate analyses were adjusted for ACT score and FEV_1 % predicted. Analyses were 2-tailed with significance at .05 and were performed using SAS software (version 9.2 for Windows, SAS Institute, Cary, NC).

FENO levels were elevated at 41.0 ± 36.2 ppb mean and 28 ppb median levels (range from 7 to 215 ppb) and 48% to 1855% predicted. Patients were predominately young adult, female, white, and highly atopic (Table I). Asthma burden was high in the follow-up year, with 20.4% dispensed ≥7 SABA canisters, 21.4% with an asthma exacerbation requiring OCS, and approximately 75% at a step-care level of 3 to 5.

Patients with FENO levels of >300% compared with those with ≤300% predicted were dispensed ≥7 SABA canisters more frequently (33% vs 13.6%) and also received more SABA canisters during the 1-year follow-up (both $P < .001$) (Table I). Moreover, both ≥2 and total number of asthma exacerbations requiring OCS occurred significantly more frequently in patients with FENO levels of >300% compared with ≤300% predicted (Table I). No association occurred between FENO levels and ACT score, and only a marginal one occurred with FEV_1 ≤ 80% predicted (P = .052) (Table I).

After adjusting for ACT score and FEV_1 % predicted control categories, FENO levels at >300% compared with ≤300% predicted were associated with an RR of 2.26 (95% CI, 1.46-3.50; $P < .001$) for ≥7 SABA canisters dispensed (Table II) and an IRR of 1.45 (95% CI, 1.12-1.89, $P = .005$) for the total number of SABA canisters dispensed in the follow-up year. After similar adjustments, >300% compared with ≤300% predicted FENO levels was associated with ≥2 (RR, 3.26; 95% CI, 1.17-9.10; $P = .024$) (Table II) and marginally with the total number (IRR, 1.61, 95% CI, 0.99-2.62; $P = .055$) of exacerbations with OCS in the follow-up year. Similar findings were observed for adjustments with continuous ACT score and FEV_1 % predicted levels or for adjustments with age, gender, and ethnicity (data not presented).

FENO is (1) an indicator of airway inflammation, with higher concentrations observed in ICS-naive patients, (2) sensitive to alterations in ICS treatment, (3) helpful in asthma diagnosis, and (4) predictive of loss of asthma control.[8] Our study extends these relationships to real-world clinical care. Specifically, in patients with persistent asthma on ICS, FENO levels >300% compared with ≤300% predicted were significantly associated during a follow-up year, independent of an asthma control tool and spirometry, with (1) a 2.3-fold higher RR for ≥7 SABA canisters dispensed and about a 1.5 times higher IRR for the total number of SABA canisters dispensed and (2) a modest increase in patients with ≥2 asthma exacerbations requiring OCS.

TABLE I. Demographics, atopic history, and asthma features at baseline and during 1-y follow-up of total study patients and patients grouped by FENO status at baseline (% predicted ≤300% vs >300%)

		FENO % predicted	
Demographics, atopy, asthma features	**Total cohort (N = 304)**	**≤300% (n =199)**	**>300% (n =105)**
Baseline			
FENO (ppb), median (range)	28 (7-215)	22 (7-47)	61 (32-215)
Age (y)	35.9 (14.9)	38.4 (14.3)	31.0 (14.8)*
Females	183 (60.2%)	121 (60.8%)	62 (59%)
Geocoded median household income ($)	71,991 (31,862)	72,870 (32,898)	70,297 (29,833)
Ethnicity			
Hispanic	80 (26.3%)	42 (21.1%)	38 (36.2%)*
White	169 (55.6%)	121 (60.8%)	48 (45.7%)*
Black	51 (16.8%)	31 (15.6%)	20 (19%)*
Asian/Pacific Islander	39 (12.8%)	20 (10.1%)	19 (18.1%)*
Other races and combinations	70 (23%)	44 (22.1%)	26 (24.8%)
Atopy			
Allergic rhinitis	177 (58.2%)	114 (57.3%)	63 (60%)
Atopic dermatitis	88 (28.9%)	56 (28.1%)	32 (30.5%)
Aero-allergen sensitivities	4.29 (2.30)	4.12 (2.38)	4.62 (2.11)*
ACT score	19.6 (4.4)	19.9 (4.4)	19.2 (4.5)
Spirometry			
FEV_1 % predicted	86.4 (14.9)	87.2 (14.5)	84.8 (15.4)
FEV_1 % predicted ≤80%	108 (35.5%)	63 (31.7%)	45 (42.9%)
1-y follow-up			
No. of SABA canisters dispensed	4.3 (5.1)	3.6 (4.1)	5.7 (6.3)†
7 or more	62 (20.4%)	27 (13.6%)	35 (33.3%)†
Asthma exacerbations			
No. of OCS courses	0.29 (0.66)	0.23 (0.50)	0.41 (0.87)*
≥1	65 (21.4%)	39 (19.6%)	26 (24.8%)
≥2	14 (4.6%)	5 (2.5%)	9 (8.6%)*
Step-care level based on NAEPP guidelines			
1	24 (7.9%)	14 (7%)	10 (9.5%)
2	53 (17.4%)	33 (16.6%)	20 (19%)
3	109 (35.9%)	74 (37.2%)	35 (33.3%)
4	80 (26.3%)	51 (25.6%)	29 (27.6%)
5	38 (12.5%)	27 (13.6%)	11 (10.5%)

Data presented as mean (SD) or frequency N (%).
NAEPP, National Asthma Education and Prevention Program.
**P* < .05 and †*P* ≤ .001 were calculated using χ^2 test or Fisher exact test for categorical variables and ANOVA or Kruskal-Wallis test for continuous variables and negative binomial model for count variables.

TABLE II. Unadjusted and adjusted* RR (95% CI) by Poisson regression with a robust error variance for the listed outcomes during the follow-up year

	FENO % predicted		
Outcomes during follow-up year	**≤300% (n = 199)**	**>300% (n = 105)**	***P* value**
Patients with ≥7 SABA canisters dispensed			
Unadjusted	1.00	**2.46 (1.58-3.83)**	**<.001**
Adjusted	1.00	**2.26 (1.46-3.50)**	**<.001**
Patients with ≥2 OCS courses with asthma exacerbations			
Unadjusted	1.00	**3.41 (1.17-9.92)**	**.024**
Adjusted	1.00	**3.26 (1.17-9.10)**	**.024**

Significant differences noted in bold.
*Variables adjusted in multivariate analyses were ACT scores, categorized by its 3 control categories: >19 (controlled), 16-19 (not well controlled), and <16 (very poorly controlled), and FEV_1 % predicted, categorized by >80% predicted (controlled) and ≤80% predicted (uncontrolled).

These findings support the addition of a measure of inflammation (FENO) to asthma control questionnaires and spirometry during routine asthma visits to identify patients at risk for future uncontrolled asthma. As such, FENO levels >300% of predicted identified patients, additional to those identified by ACT score and spirometry, who were dispensed excessive SABA or experienced ≥2 asthma exacerbations during a follow-up year. Studies conflict on the usefulness of FENO-based asthma management.[9] The present study does not deal with management directly, but does provide novel information concerning future uncontrolled asthma and its relationship with high FENO levels in a real-world setting. The current study is limited by its single visit and determination of FENO. However, the independent relationship found between FENO >300% of predicted at a single point in time to excessive future SABA canister dispensings identifies its potential importance in assessing patients.

In summary, our prospective findings highlight the independent relationship of FENO levels >300% of predicted to increased future 1-year asthma impairment and risk. As such, FENO determination appears clinically useful in identifying persistent atopic, nonsmoking asthmatic patients on ICS at risk for future uncontrolled asthma. Studies are needed to determine whether such FENO information will improve future asthma care and outcomes.

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Age- and atopy-dependent effects of vitamin D on wheeze and asthma

To the Editor:

The role of vitamin D in a myriad of physiologic processes has recently become a focus of controversy. Growing evidence suggests a role for vitamin D in the regulation of IgE and the development of allergic sensitization, as well as in lung development, incident asthma, and asthma exacerbation, although the studies are not all consistent.[1-3] Despite these data, the Institute of Medicine recently reviewed the literature about vitamin D and concluded that there were insufficient data to recommend supplementation with vitamin D for the prevention of non–bone-related diseases.[4] Here we use nationally representative data from the National Health and Nutrition Examination Survey (NHANES) to assess the relationship between vitamin D levels and respiratory outcomes.

Study participants included 6857 US subjects 6 years of age and older who participated in NHANES 2005-2006, as discussed in the Methods section and Table E1 of this article's Online Repository at www.jacionline.org. The relationships between serum vitamin D levels and wheeze, history of asthma, and asthma exacerbation were assessed by means of logistic regression in analyses that accounted for the complex survey methods and were adjusted for age, sex, race/ethnicity, household income, and body mass index (BMI) z score. Analyses were performed with STATA 11.0/SE (StataCorp, College Station, Tex) and R 2.12.2 (R Foundation, Vienna, Austria) software.

Serum vitamin D levels were inversely associated with both current wheeze and asthma in adjusted analyses (Table I and see Table E2 in this article's Online Repository at www.jacionline.org). Each 10 ng/mL decrease in vitamin D level was associated with a 26% greater odds (odds ratio [OR], 1.26 [95% CI, 1.09-1.46]) of current wheeze and an 8% greater odds of asthma (OR, 1.08 [95% CI, 1.01-1.16]). Among those with asthma, lower vitamin D levels were associated with increased odds of both emergency department visit and exacerbation in the past year (OR for each 10 ng/mL decrease in vitamin D level: 1.53 [95% CI, 1.01-2.32] and 1.38 [95% CI, 1.06-1.80], respectively; see Table E3 in this article's Online Repository at www.jacionline.org). Results relating to asthma are described in more detail in the Results section in this article's Online Repository at www.jacionline.org.

The association between a lower vitamin D level and wheeze was similar for asthmatic and nonasthmatic subjects ($P = .37$ for interaction term). The higher odds of current wheeze associated with lower vitamin D levels was driven by a strong inverse relationship between vitamin D level and current wheeze in older subjects ($P = .007$ for interaction term, Table I, Fig 1). This was not due to a stronger relationship between vitamin D level and wheeze in patients who reported chronic obstructive pulmonary disease (COPD; OR per 10 ng/mL vitamin D: 1.23 [95% CI, 1.02-1.55] for those with COPD and 1.32 [95% CI, 1.13-1.55] for those without COPD). Nor was the vitamin D effect among older subjects on current wheeze caused by smoking: the relationship between vitamin D level and wheeze was similar in current, former, and never smokers (ORs of 1.28 [95% CI, 1.04-1.57], 1.35 [95% CI, 1.03-1.81], and 1.24 [95% CI, 0.88-1.74], respectively, for every 10 ng/mL decrease in vitamin D level).

In addition to age, there was a suggestion that the relationship between vitamin D level and current wheeze was also modified by atopy and total IgE level, with a stronger relationship found in nonatopic subjects and among those with lower IgE levels ($P = .096$ and .08 for the interaction between vitamin D level and atopy and total IgE level, respectively; Table I). Moreover, the relationship between vitamin D level and wheeze was not mediated by either atopy or total IgE level (see Table E4 in this article's Online Repository at www.jacionline.org).

In this broadly representative sample of the US population, lower serum vitamin D levels were associated with increased risk of current wheeze, and this relationship varied by age, suggesting an age-dependent relationship between vitamin D level and wheeze that has not previously been reported. In addition, although vitamin D deficiency is known to be associated with higher total IgE levels in this population,[5] the vitamin D/wheeze