



Portable Exhaled Nitric Oxide as a Screening Tool for Asthma in Young Adults During Pollen Season*

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Background: The fraction of exhaled NO (FeNO) is valuable for the follow-up of asthmatic patients. However, its usefulness as a screening tool for asthma is not established.

Methods: We screened a population of 961 university students with a modified European Community Respiratory Health Survey questionnaire that has been previously used for the screening of respiratory symptoms related to asthma. All subjects with a positive answer to at least one question ($n = 149$) were submitted to FeNO measurement with a portable nitric oxide analyzer. Subsequently, they were submitted to spirometry and evaluated by a physician blinded to FeNO measurements. Seventy students with no respiratory symptoms served as control subjects.

Results: Asthma was diagnosed in 63 subjects, and allergic rhinitis was diagnosed in 57 subjects. Asthmatics presented higher FeNO values than control subjects (median, 20 parts per billion [ppb]; interquartile range, 14 to 31 ppb; vs median, 11 ppb; interquartile range, 7 to 13 ppb, respectively; $p < 0.0001$), whereas they did not differ from patients with allergic rhinitis (median, 17 ppb; interquartile range, 12 to 23 ppb; $p = 0.28$). FeNO values > 19 ppb presented 85.2% specificity and 52.4% sensitivity for the diagnosis of asthma (area under the curve [AUC], 0.723). The diagnostic performance of FeNO was better in nonsmokers (AUC, 0.805), yet FeNO values > 25 ppb were characterized by specificity $> 90\%$ for the diagnosis of asthma both in smokers and in nonsmokers. However, FeNO was not a good marker for the differentiation between asthma and allergic rhinitis.

Conclusions: FeNO measurement with a portable analyzer is useful for the screening for asthma in young adults. Significant confounding factors are allergic rhinitis and current smoking.

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Key words: allergic rhinitis; asthma; exhaled nitric oxide; screening; smoking

Abbreviations: AUC = area under the curve; CI = confidence intervals; FeNO = fraction of exhaled nitric oxide; ppb = parts per billion; ROC = receiver operating characteristic

Asthma is a common chronic inflammatory airway disorder that is underdiagnosed and undertreated.¹ The diagnosis of asthma is based on clinical history and

presentation, combined with evidence of reversibility after inhaled bronchodilators or a trial of corticosteroids. The presentation is not always straightforward, and clinicians may need to confirm the diagnosis with

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For editorial comment see page 837

objective measurements that present several limitations. Spirometry results are often normal in asymptomatic asthmatics, and bronchodilator reversibility testing may not constantly be evident, presenting low sensitivity and specificity,² whereas the recording of peak expiratory flow variability requires patient compliance.³ Bronchial challenge tests present higher sensitivity and

specificity² but require a dedicated laboratory and experienced technicians and are usually offered in tertiary centers.⁴

Biomarkers in exhaled air have been used for the assessment of airway inflammation.⁵ The fraction of exhaled nitric oxide (FeNO) is the most extensively studied biomarker and is increased in steroid-naïve patients with asthma.⁶ FeNO is related with airway hyperresponsiveness, sputum and blood eosinophilia, and total IgE in patients with asthma.^{7–9} FeNO is reduced after treatment with inhaled corticosteroids¹⁰ and has been used as a guide to determine appropriate asthma treatment.¹¹ Moreover, FeNO is elevated in patients with allergic rhinitis.¹² FeNO has been studied as a screening tool for asthma^{13,14} and as a predictor of exercise-induced bronchoconstriction in children.¹⁵ However, FeNO has not been evaluated as a screening tool for asthma in an adult population.

The aim of the present study was to evaluate the performance of FeNO measured with a portable nitric oxide analyzer as a screening tool for asthma in a population of young adults, including smokers, during pollen season. Possible confounding factors and the repeatability of FeNO measurements were additionally evaluated.

METHODS AND MATERIALS

Study Subjects

A screening questionnaire based on the European Community Respiratory Health Survey II short screening questionnaire¹⁶ was distributed to 1,053 students of the University of Thessaly and the Technological Education Institute of Larissa in the spring of 2006. This questionnaire has been previously used for the screening of respiratory symptoms related to asthma^{17,18} and is provided in the online depository. All students with at least one positive answer were considered eligible for the study. Subjects were excluded if they had any of the following: (1) previous diagnosis of asthma or rhinitis treated with antiinflammatory medication (inhaled or nasal corticosteroids, long-acting β_2 -agonists, leukotriene modifiers, antihistamines, or methylxanthines), (2) history of respiratory tract infection within the past 6 weeks, and (3) recent smoking cessation (< 2 months prior to the study). We excluded recent quitters on the basis that FeNO levels return to normal levels 4 to 8 weeks after smoking cessation,¹⁹ in order to stratify our subjects as either current smokers or nonsmokers. Seventy healthy subjects with no respiratory symptoms were randomly selected as control subjects. Study participants were initially submitted to FeNO measurement and were subsequently submitted to spirometry and evaluated by a respiratory physician who was blinded to FeNO measurements. The study protocol was approved by the local ethics committee, and participants provided informed consent.

Measurement of FeNO

FeNO was measured using a portable nitric oxide analyzer (NIOX MINO Airway Inflammation Monitor; Aerocrine; Solna,

Sweden) that provides FeNO measurements at 50 mL/s exhalation flow rate, expressed in parts per billion (ppb).²⁰ Measurements with this device are in clinically acceptable agreement to measurements provided by a stationary analyzer (NIOX; Aerocrine) according to American Thoracic Society guidelines.^{21–23} The accuracy range of the NIOX MINO device is ± 5 ppb for measured values of < 50 ppb and $\pm 10\%$ for values ≥ 50 ppb. All FeNO measurements were performed in the morning (between 10:00 and 12:00 AM) and subjects had not consumed food or beverages and had not smoked 2 h before, under supervision of one investigator. A single NIOX MINO analyzer was used throughout the study. Details on FeNO measurements with this analyzer have been provided in the online Supplement.

Diagnosis of Asthma and Allergic Rhinitis

Diagnosis of asthma and allergic rhinitis was established after FeNO measurements, based on evaluation by a respiratory physician blinded to FeNO measurements (K.K.) under pre-specified criteria.^{1,24} Asthma was defined based on a history of relevant lower respiratory tract symptoms, along with one of the following: significant bronchodilator reversibility, positive methacholine bronchial challenge test, or clinical and spirometric response to a 4-week trial of inhaled corticosteroids, prescribed after FeNO measurements. Allergic rhinitis was defined based on compatible symptoms (nasal obstruction, rhinorrhea, sneezing, itching of the nose and/or postnasal drainage, with or without ocular symptoms) in patients with atopy. In patients without previously confirmed atopy, positive skin-prick test results to 10 common aeroallergens (dermatophagoides mix, birch, parietaria, cypress, sycamore, olive, alternaria, cladosporium, cat epithelium, dog epithelium) confirmed the diagnosis. Patients with concomitant asthma and allergic rhinitis were considered asthmatics. Subjects with positive answers to the questionnaire not fulfilling criteria for diagnosis of asthma or rhinitis were classified in the “nonspecific” respiratory symptoms group.

Spirometry, Bronchodilator Reversibility, and Bronchial Challenge Tests

Spirometry was performed with a dry spirometer (KoKo Legend; Ferraris; Hertford, UK).²⁵ Bronchodilator reversibility was evaluated after inhalation of 400 μ g of salbutamol; an increase in FEV₁ $> 12\%$ and > 200 mL from baseline was considered significant.¹ Methacholine challenge testing was performed in a subgroup of patients with diagnostic uncertainty ($n = 47$) in order to confirm the diagnosis of asthma in this subgroup using a commercially available system (APS; Viasys; Hoechst, Germany) according to American Thoracic Society guidelines.⁴

Repeatability of FeNO Measurements

Repeatability of FeNO measurements was evaluated on 2 consecutive days in 30 study participants (10 patients with asthma, 10 patients with allergic rhinitis, and 10 control subjects) in the morning (between 10:00 and 12:00 AM), following the same protocol. Subjects for repeatability testing were selected randomly based on their availability for a second evaluation on the following morning, until the predefined number of 30 was reached. Repeatability on 2 consecutive days was chosen to evaluate short-term within-subject variability of FeNO measurements.

Statistical Analysis

Demographic data are presented as mean $\pm$ SD; FeNO data were skewed and are presented as median and interquartile

range. Comparisons of FeNO values were performed with Mann-Whitney *U* tests (between two groups) or with Kruskal-Wallis tests (among three or more groups). Repeatability of FeNO measurements in stable subjects on 2 consecutive days was evaluated with the Bland and Altman method.²⁶ A multiple linear regression model was created to define independent predictors of FeNO, using FeNO as dependent variable, and age, sex, height, FEV₁, FEV₁/FVC, current smoking, diagnosis of asthma, and diagnosis of rhinitis as independent variables. Diagnostic performance of FeNO was evaluated with receiver operating characteristic (ROC) curves created by plotting sensitivity against 1 – specificity, and the area under the curve (AUC) with 95% confidence intervals (CIs) was calculated. Additionally, sensitivities and specificities with 95% CIs were calculated for specific FeNO cut-off points.

RESULTS

Completed questionnaires were returned from 961 students, providing a response rate of 91.2%. From the 208 subjects with at least one positive answer, 59 subjects were excluded for reasons presented in Figure 1. From the remaining 149 subjects, asthma was diagnosed in 63 subjects and allergic rhinitis was diagnosed in 57 subjects, whereas 29 subjects presented nonspecific symptoms. Demographic characteristics and FeNO measurements are presented in Table 1.

FeNO Measurements

Patients with asthma presented higher FeNO values than control subjects and subjects with non-

specific symptoms ($p < 0.0001$, both comparisons). Similarly, patients with allergic rhinitis presented higher FeNO values than control subjects and subjects with nonspecific symptoms ($p < 0.0001$, both comparisons). FeNO levels between patients with asthma and allergic rhinitis did not differ ($p = 0.28$) [Fig 2, top, A].

Stratification of patients with asthma or allergic rhinitis according to smoking habit is presented in Figure 2, bottom, B. Asthmatic nonsmokers presented higher FeNO compared to smokers ($p = 0.005$). A trend toward higher FeNO in nonsmokers with allergic rhinitis compared to smokers was observed; however, it did not reach statistical significance ($p = 0.06$). In nonsmokers, asthmatics presented higher FeNO values than patients with rhinitis ($p = 0.03$); however, no such difference was observed in smokers ($p = 0.54$).

Predictors of FeNO

In the multiple linear regression model, independent predictors of FeNO ($R = 0.517$, $p < 0.0001$) were a diagnosis of asthma ($p = 0.002$), a diagnosis of allergic rhinitis ($p < 0.001$), and current smoking ($p = 0.003$).

Diagnostic Performance of FeNO

Data regarding the diagnostic performance of FeNO are presented in Table 2 and Figure 3. The

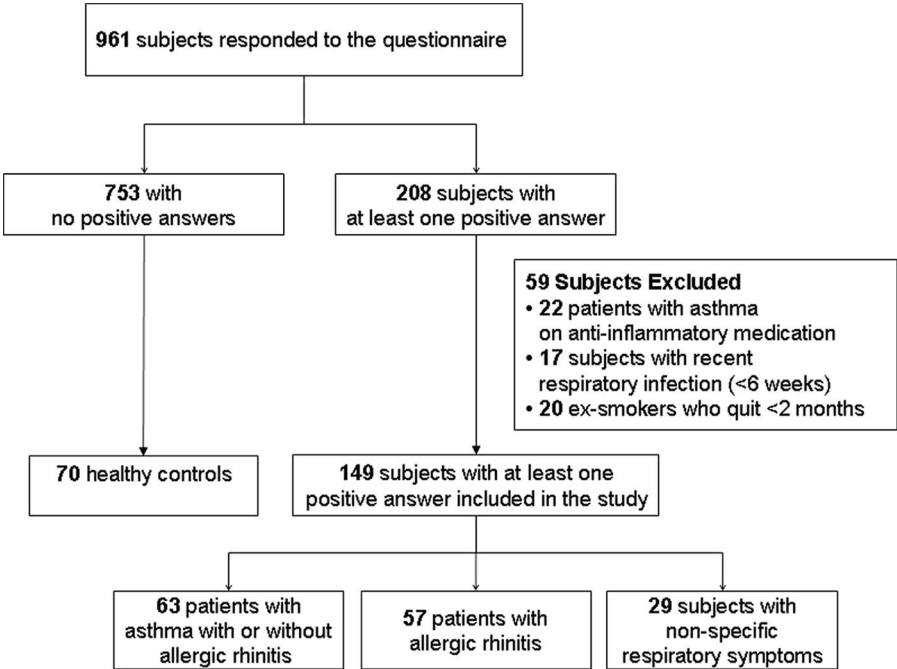


FIGURE 1. Flow diagram of study participants.

Table 1—Demographic Characteristics and FeNO Measurements of Study Participants*

Variables	Control Subjects (n = 70)	Asthma (n = 63)	Allergic Rhinitis (n = 57)	Nonspecific Symptoms (n = 29)
Age, yr	21.4 ± 2.3	21.6 ± 2.7	21.8 ± 3.0	22.1 ± 3.1
Male/female gender, No.	37/33	34/29	29/28	13/16
Smokers	23 (32.8)	23 (36.5)	19 (33.3)	11 (37.9)
FEV ₁ % predicted	108.7 ± 12.5	83.8 ± 12.2	106.9 ± 11.2	103.5 ± 11.7
FVC % predicted	107.0 ± 14.3	95.2 ± 12.3	105.5 ± 12.2	102.5 ± 16.4
FEV ₁ /FVC, %	91.3 ± 7.5	81.7 ± 8.9	89.3 ± 6.3	88.7 ± 11.2
FeNO, ppb				
All	10.5 (7.0–13.0)	20.0 (14.0–31.0)	17.0 (12.5–23.0)	11.0 (8.5–12.5)
Nonsmokers	11.0 (8.0–13.0)	24.0 (16.0–39.0)	17.5 (14.5–25.5)	11.0 (9.0–12.5)
Smokers	9.0 (7.0–13.0)	16.0 (9.0–20.5)	16.0 (9.0–20.5)	9.0 (7.5–14.0)

*Data are presented as mean ± SD, No. (%), or median (interquartile ranges) unless otherwise indicated.

optimal cut-off point that provided the best combination of specificity and sensitivity for the diagnosis of asthma in the entire study population was > 19 ppb, providing 85.3% specificity and 52.4% sensitivity, with an AUC of 0.723 (Table 2). The diagnostic performance of FeNO was superior for a combined diagnosis of asthma or allergic rhinitis (AUC, 0.823)

and for a diagnosis of asthma when patients with allergic rhinitis were excluded (AUC, 0.835). However, FeNO could not discriminate asthma and allergic rhinitis (AUC, 0.544; Fig 3, *top*, A).

FeNO was a better marker for the diagnosis of asthma in nonsmokers (AUC, 0.805), providing 84.9% specificity and 66.7% sensitivity for a cut-off point > 19 ppb. Again, FeNO was a better indicator of a combined diagnosis of asthma or allergic rhinitis (AUC, 0.873) and for a diagnosis of asthma when patients with allergic rhinitis were excluded from the analysis (AUC, 0.899); however, FeNO was not a good marker for the differentiation between asthma and allergic rhinitis (AUC, 0.640; Fig 3, *center*, B).

In contrast, FeNO was not a good marker for the diagnosis of asthma in smokers, with an AUC of 0.648; nevertheless, FeNO presented a specificity of 85.7% for a cut-off point > 19 ppb. FeNO could not differentiate between asthma and allergic rhinitis in smokers (AUC, 0.544; Fig 3, *bottom*, C).

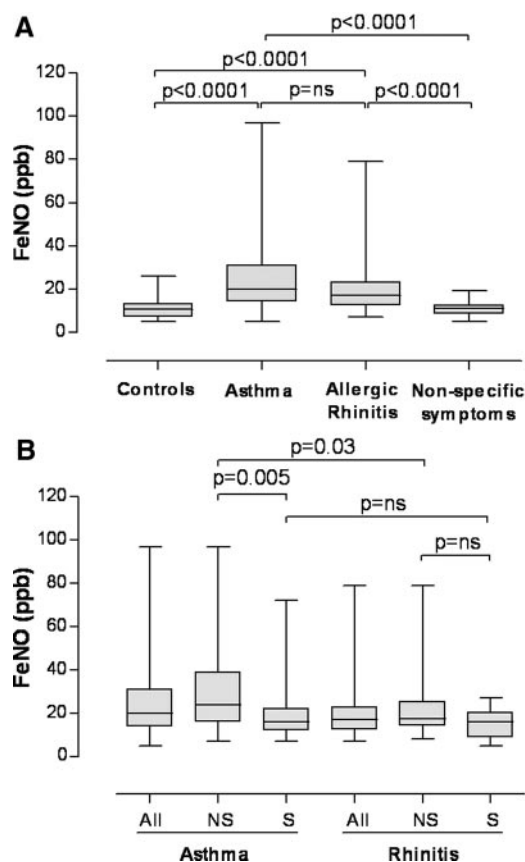


FIGURE 2. *Top*, A: Levels of FeNO in the study groups. *Bottom*, B: Levels of FeNO in smokers (S) and nonsmokers (NS) with asthma and rhinitis. Data are presented as box plots representing the median value with interquartile range. ns = not significant.

Selection of “Optimal” FeNO Cut-off Points

The diagnostic performance of FeNO in the study population using different cut-off points in the range of 10 to 30 ppb is presented in Table 3. Briefly, FeNO values > 25 ppb are characterized by specificity > 90% for the diagnosis of asthma in all study groups; specificity rises further to approximately > 95% for FeNO values > 30 ppb. In contrast, a cut-off point > 10 ppb presents sensitivity > 85% in the whole study group, rising to approximately 95% in nonsmokers.

Repeatability of FeNO Measurements

FeNO measurements on 2 consecutive days presented acceptable repeatability. Mean difference was – 1.47 ppb, and limits of agreement were – 10.98 to 8.05 ppb. All measurements were within the limits of

Table 2—Diagnostic Performance of ROC Analysis of FeNO*

Variables	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
All			
Asthma vs other all	52.4 (39.4–65.1)	85.3 (78.7–90.4)	0.723 (0.658–0.781)
Combined asthma or rhinitis vs other	45.0 (35.9–54.3)	98.0 (92.9–99.7)	0.823 (0.766–0.871)
Asthma vs other, excluding allergic rhinitis	52.4 (39.4–65.1)	98.0 (92.9–99.7)	0.835 (0.768–0.889)
Asthma vs allergic rhinitis	51.6 (38.7–64.2)	62.5 (48.5–75.1)	0.544 (0.450–0.635)
Nonsmokers			
Asthma vs other all	66.7 (49.8–80.9)	84.9 (76.6–91.1)	0.805 (0.731–0.866)
Combined asthma or rhinitis vs other	53.8 (42.2–65.2)	100.0 (94.6–100.0)	0.873 (0.807–0.923)
Asthma vs other, excluding allergic rhinitis	66.7 (49.8–80.9)	100.0 (94.6–100.0)	0.899 (0.825–0.949)
Asthma vs allergic rhinitis	66.7 (49.8–80.9)	57.9 (40.8–73.7)	0.640 (0.522–0.746)
Smokers			
Asthma vs other all	29.2 (12.7–51.1)	86.0 (73.3–94.2)	0.648 (0.527–0.756)
Combined asthma or rhinitis vs other	28.6 (15.7–44.6)	93.7 (79.2–99.1)	0.741 (0.626–0.836)
Asthma vs other, excluding allergic rhinitis	29.2 (12.7–51.1)	93.7 (79.2–99.1)	0.699 (0.562–0.814)
Asthma vs allergic rhinitis	27.8 (9.8–53.5)	72.0 (50.6–87.9)	0.586 (0.425–0.733)

*Values of sensitivity and specificity refer to a cut-off point of 19 ppb, which provides the best combination of sensitivity and specificity for the diagnosis of asthma in the whole population.

agreement, excluding a few measurements corresponding to mean FeNO values > 50 ppb (Fig 4).

DISCUSSION

This is the first study to our knowledge that has evaluated FeNO measured with a portable nitric oxide analyzer as a screening tool for asthma in a population of young adults including smokers. FeNO values were increased both in patients with asthma and with allergic rhinitis, not differing between the two. FeNO presented a moderate diagnostic performance for the diagnosis of asthma in the whole study population, yet its performance was better in non-smokers. Asthma, allergic rhinitis, and smoking were independent predictors of FeNO values. Finally, FeNO measurements presented acceptable repeatability on 2 consecutive days.

Our results are comparable with previous studies^{27,28} evaluating FeNO as a diagnostic tool for asthma. The overall diagnostic performance of FeNO in our population provided an AUC of 0.723, which is lower than those reported by Deykin et al.²⁸ However, we have evaluated a general population screened for respiratory symptoms with a questionnaire that allowed us to identify several subjects with allergic rhinitis, and this may have influenced our results. Another unique characteristic of our study is the inclusion of smokers and nonsmokers. Indeed, the performance of FeNO for the diagnosis of asthma was better in nonsmokers, providing an AUC of 0.805, which is comparable to those reported by Deykin et al.²⁸ However, our data still present inferior diagnostic performance for FeNO compared to other authors, as the studies

undertaken by Smith et al¹¹ (AUC, 0.864) and Berkman et al²⁹ (AUC, 0.896); in contrast, in a recent study by Menzies et al²³ using the same portable analyzer with our study, FeNO presented an AUC of 0.619. Differences in selection of study populations are likely to account for these discrepancies. Subjects included in the studies by Berkman et al²⁹ and Smith et al¹¹ had been referred to tertiary centers by primary care practitioners, whereas the study by Menzies et al²³ included a large number of steroid-treated asthmatics. The design of our study was entirely different, and FeNO was evaluated as a screening tool in a population of steroid-naïve young adults, including smokers, in the majority of whom the diagnosis of asthma was established for the first time, providing useful implications for primary care practice.

In the interpretation of FeNO values, allergic rhinitis and current smoking were identified as major confounding factors for the diagnosis of asthma. Atopy is a major determinant of FeNO in a population-based study,³⁰ and patients with allergic rhinitis have higher values than control subjects.¹² In contrast, asthmatic smokers present lower FeNO than nonsmokers.³¹ Our study confirmed previous findings, nevertheless with important differences. FeNO values of patients with asthma and allergic rhinitis did not differ significantly in the whole study population, whereas a difference was found in nonsmokers. Thus, FeNO may discriminate between asthma and allergic rhinitis only in nonsmokers, yet with a relatively poor performance (AUC, 0.640), and only FeNO values > 62 ppb provided > 95% specificity. Heffler et al³² proposed FeNO as a marker for the identification of

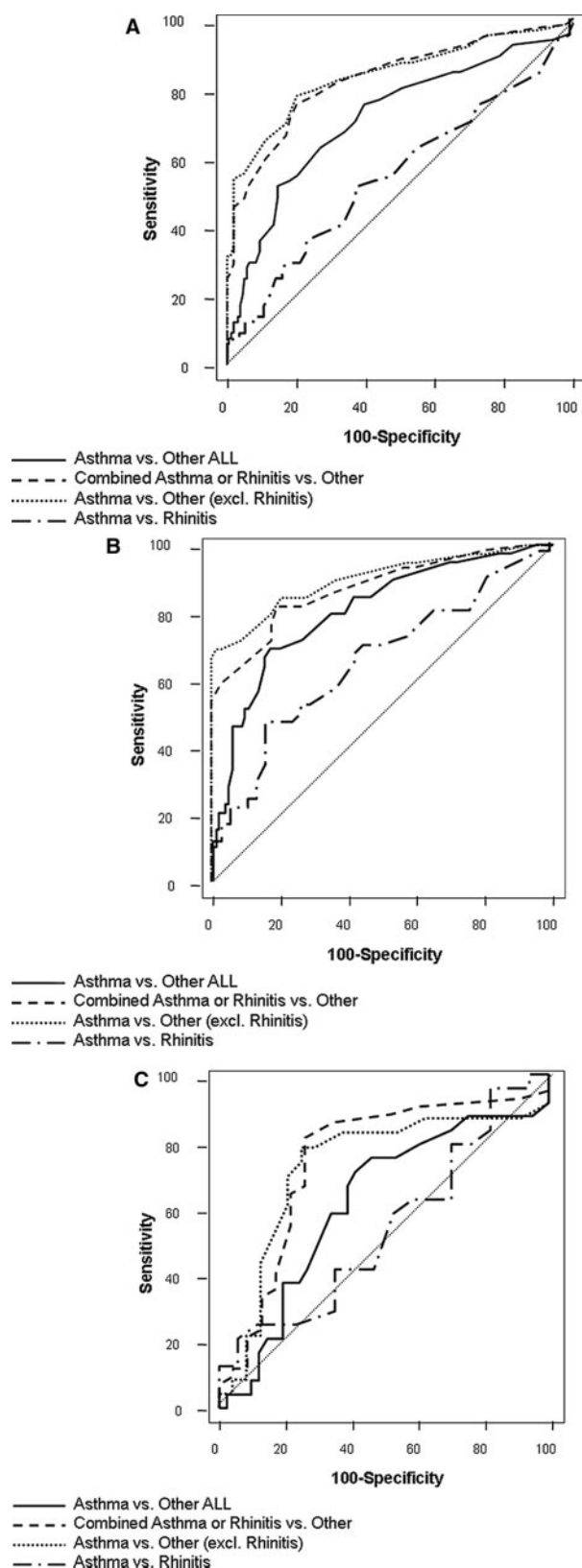


FIGURE 3. ROC curves for the evaluation of the diagnostic performance of FeNO. *Top*, A: Whole study population; *center*, B: nonsmokers; *bottom*, C: smokers. The ROC curves represent the diagnostic performance of FeNO for the differentiation of patients with asthma from the rest of the population, for the

patients with rhinitis with concomitant asthma. Despite significant differences in design (only patients with rhinitis were included) and the smaller study population in that study, a FeNO cut-off level > 65 ppb provided 86.7% specificity, 70.8% accuracy, with an AUC of 0.780 for a diagnosis of asthma, in accordance with our findings.

In further support of the above, we have shown that FeNO represents a good marker for the diagnosis of combined asthma and allergic rhinitis, especially in the entire population and in nonsmokers. Furthermore, its diagnostic performance for asthma improved when patients with allergic rhinitis were excluded from the analysis. Our data suggest that FeNO represents a robust screening tool for pan-airway eosinophilic inflammation, further supporting the concept of “one airway one disease.”^{33,34} A study¹³ in children suggested that FeNO is not a useful screening tool for asthma because it could not discriminate between asthmatic and atopic symptoms. We have shown, using ROC analysis, that this is not exactly the case in young adults. Allergic rhinitis is a significant confounding factor, yet FeNO presented acceptable diagnostic performance for asthma, especially in nonsmokers.

Besides the interpretation of possible confounding factors, we attempted to obtain FeNO cut-off points that may be useful for clinical practice. We have shown that there is no single “optimal” cut-off point, presenting a combination of high sensitivity and specificity. However, values > 25 ppb are highly suggestive of asthma with > 90% specificity, both in smokers and nonsmokers, resulting in < 10% false-positive findings. Additionally, a cut-off point of 10 ppb provides > 85% sensitivity in the whole population, rising to 95% in nonsmokers (5% false-negative results in that subgroup). For FeNO values between 10 ppb and 25 ppb, clinical judgment and additional diagnostic tests are warranted. This “dual” strategy for FeNO interpretation has been previously proposed by Dupont and coworkers²⁷; that study, however, was performed in a tertiary referral center and, as most FeNO studies, did not include smokers, in contrast to our study. We believe that in clinical practice high FeNO values are more important because they may reflect eosinophilic (plausibly steroid-responsive) airway inflammation,³⁵ and we have shown that this is the case both in smokers and nonsmokers.

differentiation of combined patients with asthma and allergic rhinitis from the rest of the population, for the differentiation of patients with asthma from the rest of the population when patients with allergic rhinitis were excluded, and for the differentiation between patients with asthma and patients with allergic rhinitis; excl = excluding.

Table 3—Diagnostic Performance of FeNO in the Entire Study Population in Nonsmokers and in Smokers, Using Different Cut-off Points

Cut-off Points	All		Nonsmokers		Smokers	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
> 30 ppb	25.4 (15.3–37.9)	94.9 (90.1–97.8)	41.0 (25.6–57.9)	94.3 (88.1–97.9)	4.8 (1.6–14.4)	96.0 (86.3–99.4)
> 25 ppb	30.2 (19.2–43.0)	91.7 (86.2–95.5)	46.2 (30.1–62.8)	91.5 (84.5–96.0)	6.2 (3.7–21.2)	92.0 (80.7–97.7)
> 20 ppb	49.2 (36.4–62.1)	85.3 (78.7–90.4)	64.1 (47.2–78.8)	84.9 (76.6–91.1)	25.0 (9.8–46.7)	86.0 (73.3–94.2)
> 15 ppb	68.3 (55.3–79.4)	66.0 (58.0–73.4)	79.5 (63.5–90.7)	65.1 (55.2–74.1)	50.0 (29.1–70.9)	68.0 (53.3–80.5)
> 10 ppb	85.7 (74.6–93.2)	34.6 (27.2–42.6)	94.9 (82.6–99.2)	30.2 (21.7–39.9)	70.8 (48.9–87.3)	44.0 (30.0–58.7)

Given the relatively low cost of FeNO measurements with the MINO analyzer, significant reductions in the cost of diagnosis of asthma sparing more complicated and expensive procedures may be achieved.

FeNO measurements in our study presented acceptable repeatability on 2 consecutive days, with the exception of a few measurements corresponding to mean FeNO values > 50 ppb. This is in agreement with analyzer specifications that report greater accuracy for FeNO measurements < 50 ppb and with previous findings.²² However, this variability is probably of small clinical significance, especially in the diagnostic setting that we have evaluated in the present study, because values > 50 ppb are highly indicative of eosinophilic airway inflammation.

A limitation of this study and of previous studies is that FeNO represents a marker of eosinophilic airway inflammation; thus, it is not elevated in patients with noneosinophilic asthma. However, a great proportion of asthma is characterized by airway eosinophilia, and this represents a marker of response to inhaled corticosteroids³⁵; thus, FeNO may be useful

for the diagnosis of treatment-responsive asthma. A second possible limitation is that the “gold standard” was physician-diagnosed asthma. However, in all cases with diagnostic uncertainty, bronchodilation reversibility and methacholine challenge were performed, and this strategy was undertaken in order to simulate clinical practice. Another limitation is that we have studied a population of young adults. However, this is an important target group of asthmatic patients who do not easily accept a diagnosis of asthma.³⁶ Finally, the majority of our patients had mild-to-moderate asthma because they did not receive antiinflammatory medication. This may account for the lower FeNO values in our asthmatics compared to studies including patients with severe asthma³⁷; however, FeNO values in our asthmatic patients were comparable to those reported in a population-based study.³⁰ Additionally, screening is useful in a minimally symptomatic population because patients with more severe forms of asthma usually seek medical care early in the course of the disease.

In conclusion, we report that FeNO measured by a portable analyzer may be used as a screening tool for asthma in a steroid-naïve population of young adults during pollen season. Significant confounding factors are allergic rhinitis and current smoking. In the era of wider availability and lowering cost of FeNO analyzers, further studies in other age groups are warranted for its validation as a screening tool for asthma in the general population.

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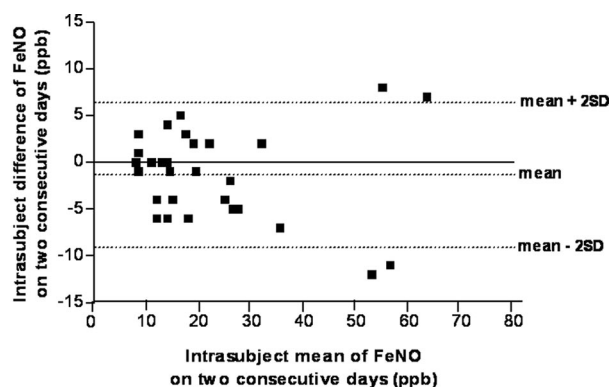


FIGURE 4. Bland and Altman plot for the evaluation of repeatability of FeNO measurements in 30 study participants (10 control subjects, 10 patients with asthma, and 10 patients with allergic rhinitis) on 2 consecutive days. Horizontal dotted lines represent the mean difference with limits of agreement (± 2 SD of the difference) between the 2 days.

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Online Supplement

**PORTABLE EXHALED NITRIC OXIDE AS A SCREENING TOOL FOR
ASTHMA IN YOUNG ADULTS DURING POLLEN SEASON**

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Study Questionnaire

The screening questionnaire was based on the European Community Respiratory Health Survey (ECRHS) II short screening questionnaire.^{1,2} The questions included in the questionnaire were the following:

- Did you have any of the following complaints during the last 12 months:
 - wheezing or whistling in your chest?
 - cough lasting for at least 2 weeks?
 - breathing difficulties or cough during mild exercise?
- Have you woken up with chest tightness or with shortness of breath or by an attack of coughing in the last 12 months?
- Have you had an attack of asthma in the last 12 months?
- Have you ever had to visit your doctor for wheezing or long-lasting cough?
- Are you currently taking any medicine (including inhalers, aerosols or tablets) for asthma?
- Do you have allergic rhinitis or hay fever?

All subjects with at least one positive answer were considered eligible for inclusion in the study.

Measurement of FeNO

FeNO was measured using a portable NO analyzer (NIOX MINO[®] Airway Inflammation Monitor, Aerocrine, Solna, Sweden). MINO measurements are in clinically acceptable agreement to measurements provided by a stationary analyzer (NIOX, Aerocrine, Solna, Sweden) according to the ATS guidelines.³⁻⁵

The subjects are instructed to exhale and take a deep breath of NO-scrubbed air from the device until total lung capacity. Then they are instructed to perform a 10-seconds slow steady exhalation that is assisted by audio and visual feedback provided from the device. Exhalation is kept at an exhalation pressure of 10-20 cmH₂O with calibrated dynamic flow resistors, in order to maintain a fixed flow rate of 50±5 ml/sec. The software within the device automatically checks that the expiratory maneuver is according to the ATS guidelines,³ and it regularly controls that the sensor baseline level, stability and noise levels are within preset limits to secure accurate measurements.⁶ FeNO measurements are performed by a specially designed electrochemical sensor, from the last 3-sec portion of the exhaled air corresponding to the exhaled NO plateau and are expressed in parts per billion (ppb). The measurement range is 5-300 ppb and analysis takes place in 100 sec. The accuracy range of NIOX MINO is ±5 ppb for measured values of less than 50 ppb and ±10% for FENO of 50 ppb or greater. NIOX MINO is CE marked according to Medical Device Directive MDD 93/42/EEC and is approved for clinical use in European Union countries. Further information is available at www.aerocrine.com.

All FeNO measurements were performed in the morning (between 10:00 and 12:00 a.m.) and subjects had not consumed food or beverages and had not smoked two hours before, under supervision of one investigator. A single NIOX MINO analyzer was used throughout the study.

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