

Diagnostic Value of Lung Function Parameters and FeNO for Asthma in Schoolchildren in Large, Real-Life Population

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Summary. Background and Objective: To establish a diagnostic value of fractional exhaled nitric oxide (FeNO), interrupter resistance measurement (Rint), specific resistance of the airways (sRaw), spirometric parameters in asthma diagnosis in schoolchildren. Methods: It was a retrospective, cross-sectional study. We evaluated data from medical documentation of 6,439 children (aged 6–18) with symptoms suggestive of asthma, who attended our Pediatric Allergic Outpatient Clinic. Medical documentation of the patients was analyzed with special attention to the first ever obtained results (before the introduction of controller medication) of: FeNO, Rint, sRaw, spirometry, diagnoses of allergic diseases, and allergen sensitization (specific IgE results). Results: We included 3,612 children in the analysis. Older age, male gender, the presence of allergic rhinitis, sensitization to perennial and seasonal allergens, higher FeNO and Rint, and FEV₁/FVC <80% were significantly associated with asthma. We observed a significant association between FeNO and Rint in the prediction of asthma diagnosis. Optimal cutoff points to differentiate asthmatics from non-asthmatics were established. Thus, Rint >175.4% was defined as asthma-predicting Rint, and FeNO >15.8 ppb was defined as asthma-predicting FeNO. In all study subgroups, sensitivity for asthma-predicting Rint was significantly higher than for asthma-predicting FeNO with an inverse trend in specificity value. Conclusion: Our results suggest that asthma-predicting Rint and, to a lesser extent, asthma-predicting FeNO, defined in the present study, could serve as a reliable tool to exclude asthma in schoolchildren. However, our results also indicate a clinically important fact that all lung function parameters or FeNO should be interpreted in the context of age, gender, allergy profile, and the presence of co-morbidities in schoolchildren. **Pediatr Pulmonol.** © 2013 Wiley Periodicals, Inc.

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INTRODUCTION

Asthma is a clinical diagnosis and there is no single diagnostic test for the disease.¹ The background pathology of asthma is often, but not always, a result of eosinophilic airway inflammation.¹ The data on correlation between FeNO, atopic status and sRaw, Rint, FEV₁, FEV₁/FVC, MMEF in children with atopic asthma and healthy controls for all the above factors combined are scarce and thus no clear conclusion can be given.^{2,3} FeNO has been shown to predict the likelihood of steroid responsiveness more consistently than spirometry, bronchodilator response, peak flow variation, or airway hyperresponsiveness to methacholine in children with asthma.^{4–6} Some studies also conclude that FeNO does not contribute to the detection of asthma in the community, as results may be confounded by other atopic conditions.⁷ It needs to be noted that there are studies indicating a lack of correlation between FeNO and the measurements of pulmonary function values in children with asthma.^{6,8–9}

Our study was conducted to shed more light on the problem of the justification of use and surrogate predictive values of the combined measurements of FeNO, specific IgE, and mechanic lung function measurements in schoolchildren with newly diagnosed allergic diseases in a typical pediatric out-patient, clinical, allergology setting. We also aimed to distinguish whether, for asthmatic children, FeNO can be treated as a direct, specific inflammatory marker or to confirm that the presence of allergic comorbidities confounds this relationship.

The final objective of this study was to establish a diagnostic value of FeNO, important spirometric parameters, Rint, sRaw in asthma diagnosis in schoolchildren.

MATERIALS AND METHODS

Study Design

It was a retrospective, cross-sectional study. We evaluated data from the medical documentation of 6,439 children (aged 6–18) with symptoms suggestive of asthma who attended our Allergic Outpatient Clinic from January 2005 to December 2012. We included 3,612 subjects with minimum 2 years of clinical observation, whose asthma was either confirmed or excluded. We did

only include in the analyses subjects who had all the tests performed: FeNO, Rint, whole-body plethysmography, spirometry, and specific IgE results. The diagnosis of asthma, allergic rhinitis, atopic dermatitis were universally established by the allergy specialists according to the standard definitions of diseases in the latest guidelines^{10–12} or their respective previous versions (due to the fact that patients were admitted since January 2005). Diagnosis of asthma was made by allergy specialists based on the symptoms of asthma, the findings of the physical examination of the respiratory system, and an improvement in the pre-bronchodilator FEV₁ ≥12% after the administration of salbutamol (200 µg) in all the patients.¹⁰ All parents and patients were asked questions to consider in the diagnosis of asthma according to GINA standard.¹⁰ Medical documentation of the patients was analyzed by allergy specialists with particular attention to the initially obtained results (possibly before the introduction of controller medication) of: FeNO, Rint, whole-body plethysmography, spirometry, an asthma diagnosis, an allergic rhinitis diagnosis, and an atopic dermatitis diagnosis as well as allergen sensitization (specific IgE results). As a standard procedure in our allergic outpatient clinic the sequence of measurements is: FeNO, Rint, whole body plethysmography, and spirometry. All lung function testing was only conducted on clinically stable outpatients, who were able to perform reproducible measurements of: FeNO, Rint, whole-body plethysmography, and spirometry.

The study was approved by the Medical Ethics Committee of the Medical University of Lodz. All parents or guardians of the patients gave their oral and written consent for the evaluation of data from medical documentation of their children. The study was registered on: www.ClinicalTrials.gov, with ClinicalTrials.gov ID: NCT01805635.

Allergen Sensitization

Allergen sensitization was defined as specific IgE of ≥0.35 kU/L for at least one of the tested allergens (chemiluminescence method (CLIA), Immulite 2000, XPI, Siemens, Erlangen, Germany). For the purpose of the study we defined perennial allergy as a presence of serum IgE of ≥0.35 kU/L specific for perennial allergens, that is, dust mites, molds, cat, and dog dander. We also defined seasonal allergy as a presence of serum IgE of ≥0.35 kU/L specific for seasonal allergens, that is, grasses, wild grasses, and trees pollens.

Nitric Oxide Measurement

The NO measurements were performed according to the European Respiratory Society/American Thoracic Society (ERS/ATS) recommendations,^{13,14} with a chemiluminescence analyzer (model 280i nitric oxide analyzer;

ABBREVIATIONS:	
ATS/ERS	American Thoracic Society/European Respiratory Society
BHR	bronchial hyperresponsiveness
FeNO	fractional exhaled nitric oxide
FEV ₁	forced expiratory volume in one second
FEV ₁ /FVC	Tiffeneau index
MMEF [MEF25/75]	maximal midexpiratory flow
sRaw	specific resistance of the airways
Rint	interrupter resistance measurement

Sievers, Boulder, CO) and defined in parts per billion. The analyzer provides an on-line continuous measurement of NO in a single exhalation with a detection range of 0.1–500 ppb. Environmental NO was measured before and after each test and it never exceeded 5 ppb. All subjects were tested in a sitting position, without wearing a nose clip. The subjects exhaled at a constant flow rate (50 ml/sec) from total lung capacity to residual volume without breath holding. They maintained a constant mouth pressure (17 cm H₂O) by monitoring a visual display in order to eliminate contamination from nasal NO. Dead space and nasal NO (which are reflected by the NO concentration peak during exhalation) and NO from the lower respiratory tract (determined by the plateau value after the peak) were recorded automatically by using the manufacturer's software. Three FeNO measurements of the plateau phase were obtained, with <10% variation. The mean value of three successive, reproducible recordings was retained for statistical analysis.

Pulmonary Function Tests

Pulmonary function testing (Rint, whole body plethysmography, spirometry) was conducted with a Master Screen unit (Erich Jaeger GmbH-Hochberg, Hochberg, Germany). Flow and volume were measured with a pressure-screen-type pneumotachograph, calibrated daily. All measurements were performed by a trained investigator. The sequence of measurements was (after FeNO as a first) Rint, whole body plethysmography, and spirometry. Measurements were carried out in a familiar and quiet room. Standing height and weight were assessed: the subjects were measured without shoes, wearing light summer clothing. During measurements, the children were instructed to sit upright, and a nose clip and a non-compressible mouthpiece were used. When needed, an adult accompanied the subject during testing. Predicted values for all lung function variables were based on a previous study of healthy controls, provided by the lung function test equipment manufacturer. All pulmonary function tests were performed according to the American Thoracic Society/European Respiratory Society standards.^{14–18}

Rint

Measurements were carried out using the device including a shutter and pneumotachograph, connected to a computer with an online display showing mouth pressure, time of shutter closure and Rint values recorded during one session. Its software calculates Rint using the back extrapolation technique to $t = 15$ msec after shutter closure during 100 msec. Measurements were made during tidal breathing. The position of the pneumotachograph with Rint was adjusted on a support arm to facilitate unobstructed breathing. The functioning of the shutter was demonstrated once to make the children familiar with

the sound. A number of five correct tracings was then obtained for the expiratory maneuver. During this process the cheeks and chin were supported from behind by the observer, the head was positioned in a slight extension. Shutter closure was programmed at a maximal expiratory tidal flow. Thus, Rint values were obtained at or near midexpiration, minimizing the breath-to-breath variation in inflation level and hence on Raw. The timing of the shutter closure (at the peak of the flow) can be checked on the display. Tracings were inspected immediately after the measurement in the presence of the child. Rejection criteria were: tachypnea, the usage of the vocal cords, extreme neck flexion, or extension, the leakage of the mouthpiece. Tracings not showing the timing of the shutter closure were discarded; tracings with a horizontal or declining pressure signal after the shutter closure were considered artifacts owing to air leakage or altered ventilation pattern and were discarded as well.¹⁹ The mean value of at least five consecutive, acceptable measurements was used as the result.

sRaw

Measurements were made during tidal breathing. sRaw was measured in a constant-pressure, whole-body plethysmograph as the relationship between simultaneous variations in respiratory flow and maximum changes in plethysmographic pressure during inspiration and expiration. sRaw was calculated from the S-shaped resistance loops presented graphically by the computer connected with the plethysmograph. The relationship between flow and pressure was displayed on-line. The measurement was rejected if any alteration in the shape of the resistance loops was seen, since this could reflect face mask leakage, coughing, swallowing, or vocalization. Compensation for body temperature, barometric pressure, and water vapor saturated (BTPS) conditions was done electronically.²⁰

The respiratory rate was 30–45 breaths/min. The mean value of three sequential measurements of sRaw was used as the result.

Spirometry

The highest of three successful measurements was taken and analyzed. The results were expressed as the percentage of a predicted value.

Statistical Methods

Associations between asthma diagnosis, defined as a dependent variable, and all studied parameters as independent variables were assessed by a logistic regression analysis in a univariate and multivariate model, which allows to point out the best predictor of a dependent variable. To estimate the cutoff level of Rint and FeNO for the prediction of asthma diagnosis ROC curve analysis was implemented. For

all significant predictors of asthma sensitivity, specificity, positive and negative predictive values were estimated. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 11.5. $P < 0.05$ was used as a definition of statistical significance.

RESULTS

We included 3,612 children in the analysis (the absolute number of patients who had all the following tests performed: FeNO, Rint, whole-body plethysmography, spirometry, specific IgE results).

Clinical characteristics are given in Table 1.

Association Analysis

A univariate logistic regression analysis showed the following significant associations with asthma: older age, male gender, the presence of allergic rhinitis, sensitization to perennial and seasonal allergens, higher FeNO and Rint, and FEV₁/FVC <80%. All of these confounders increased the risk of asthma. Additionally, higher (specific IgE above 100 kU/L) sensitization increased the risk of asthma. We also observed a significant association between FeNO and Rint in the prediction of asthma diagnosis; odds ratio for FeNO/Rint was higher (OR = 1.83) than for both variables analyzed separately in logistic regression. All other variables (listed in Table 2) were not associated with asthma diagnosis.

ROC Curve Analysis

Since we showed a significant association of FeNO and Rint with asthma, we established an optimal cutoff point using ROC curve analysis to differentiate asthmatics from non-asthmatics. For both FeNO and Rint the area under the ROC curve was significantly higher than the reference 0.5 and was 0.533 and 0.565, respectively.

TABLE 1—Baseline Characteristics

	N	%
Age (mean ± SD)	10.4 ± 4.1	
Male gender	2,180	60.4
Asthma	2,178	60.3
Allergic rhinitis	1,805	50.0
Asthma with allergic rhinitis	1,267	35.1
Atopic dermatitis	417	11.54
Sensitization to perennial allergens	863	49.9
High ¹ sensitization to perennial allergens	139	8.3
Sensitization to seasonal allergens	802	56.4
High ¹ sensitization to perennial allergens	208	15.8
FEV ₁ /FVC <90%	1,263	51.1
FEV ₁ /FVC <80%	259	10.5

N = 3,612 (the absolute number of patients who had all the tests done: FeNO, Rint, whole-body plethysmography, spirometry, specific IgE results).

¹Specific IgE >100 kU/L.

TABLE 2—Associations Between Potential Confounders and Presence of Asthma in Logistic Regression Analysis

Confounders	OR ¹	−95% CI	+95% CI	P-value
Age (years) ²	1.02	1.00	1.03	0.0330
Male gender	1.60	1.48	1.73	<0.0001
Allergic rhinitis	2.39	2.20	2.59	<0.0001
Sensitization to perennial allergens	3.08	2.72	3.50	<0.0001
High ³ sensitization to perennial allergens	3.12	2.38	4.09	<0.0001
Sensitization to seasonal allergens	2.58	2.24	2.96	<0.0001
High ³ sensitization to perennial allergens	3.12	2.38	4.09	<0.0001
FeNO (ppb) ²	1.007	1.003	1.011	0.0008
sRaw (%pred.) ²	1.000	0.999	1.001	0.5391
Rint (%pred.) ²	1.002	1.001	1.004	0.0010
FEV ₁ (%pred.) ²	1.000	0.999	1.001	0.5781
FVC (%pred.) ²	1.001	0.996	1.006	0.7394
FEV ₁ /FVC (%pred.) ²	0.990	0.979	1.001	0.0693
PEF (%pred.) ²	1.000	0.999	1.001	0.8117
MEF75/25 (%pred.) ²	1.000	0.999	1.001	0.8913
FEV ₁ <90%	1.10	0.89	1.37	0.3836
FEV ₁ /FVC <90%	1.11	0.94	1.30	0.2101
FEV ₁ /FVC <80%	1.33	1.02	1.74	0.0366

Data are presented with odds ratios (OR) with 95% confidence intervals (95% CI).

¹Dependent variable: presence of asthma.

²Continuous variable.

³Specific IgE >100 kU/L.

The optimal cut off point for FeNO and Rint was 15.8 ppb and 175.4%, respectively. Both FeNO and Rint were included in the next step of the analysis as categorized variables: Rint >175.4% was defined as asthma-predicting Rint, FeNO >15.8 ppb was defined as asthma-predicting FeNO.

Subgroup Association Analysis

According to the results of a univariate logistic regression analysis we conducted the analysis of association in the following subgroups: (i) with and without allergic rhinitis (ii) with and without sensitization to perennial allergens, and (iii) with and without sensitization to seasonal allergens. We showed that asthma-predicting Rint increased the risk of asthma in patients with and without allergic rhinitis. FEV₁/FVC below 80% was associated with asthma only in patients with concomitant allergic rhinitis; in patients without rhinitis FEV₁/FVC below 80% was not related with asthma diagnosis (Table 3).

Asthma-predicting FeNO and Rint increased the risk of asthma in patients sensitized to perennial allergens only. Additionally, we observed a significant association between asthma-predicting Rint and asthma diagnosis in children without seasonal allergy (Table 3).

TABLE 3—Associations Between Potential Confounders and Presence of Asthma in Logistic Regression Analysis

	Allergic rhinitis (–)		Allergic rhinitis (+)		Allergic rhinitis (–)		Allergic rhinitis (+)	
	Asthma (–)	Asthma (+)	Asthma (–)	Asthma (+)	OR ¹	95% CI	OR ¹	95% CI
FeNO <15.8 ppb	240	201	104	234	Ref		Ref	
FeNO >15.8 ppb	217	227	164	397	1.2	0.96–1.6	1.1	0.80–1.4
Rint <175.4%	387	353	166	470	Ref		Ref	
Rint >175.4%	275	327	115	429	1.3	1.1–1.6	1.3	1.0–1.7
FEV ₁ /FVC >80%	586	547	341	738	Ref		Ref	
FEV ₁ /FVC <80%	65	77	26	91	1.3	0.89–1.8	1.6	1.0–2.5
	Sensitization to perennial allergens (–)		Sensitization to perennial allergens (+)		Sensitization to perennial allergens (–)		Sensitization to perennial allergens (+)	
	Asthma (–)	Asthma (+)	Asthma (–)	Asthma (+)	OR ¹	95% CI	OR ¹	95% CI
FeNO <15.8 ppb	162	99	78	93	Ref		Ref	
FeNO >15.8 ppb	109	60	116	217	0.90	0.60–1.3	1.6	1.1–2.3
Rint <175.4%	233	132	160	229	Ref		Ref	
Rint >175.4%	181	138	83	185	1.3	0.99–1.8	1.6	1.1–2.2
FEV ₁ /FVC >80%	365	233	189	313	Ref		Ref	
FEV ₁ /FVC <80%	34	19	28	37	0.88	0.49–1.6	0.80	0.47–1.3
	Sensitization to seasonal allergens (–)		Sensitization to seasonal allergens (+)		Sensitization to seasonal allergens (–)		Sensitization to seasonal allergens (+)	
	Asthma (–)	Asthma (+)	Asthma (–)	Asthma (+)	OR ¹	95% CI	OR ¹	95% CI
FeNO <15.8 ppb	117	63	66	90	Ref		Ref	
FeNO >15.8 ppb	89	54	99	193	1.1	0.71–1.8	1.4	0.96–2.1
Rint <175.4%	182	90	132	218	Ref		Ref	
Rint >175.4%	125	98	91	168	1.6	1.1–2.3	1.1	0.80–1.6
FEV ₁ /FVC >80%	259	169	202	283	Ref		Ref	
FEV ₁ /FVC <80%	30	15	23	30	0.77	0.40–1.5	0.93	0.53–1.7

Ref, reference category.

Analyses were performed in children with and without allergic rhinitis. Data are presented with odds ratios (OR) with 95% confidence intervals (95% CI). Odds ratios were adjusted for the effect of age and gender.

¹Dependent variable: presence of asthma.

Diagnostic Value

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of asthma-predicted FeNO, asthma-predicted Rint, and FEV₁/FVC <80% in all study subgroups are presented in Figure 1. In all study subgroups sensitivity for asthma-predicting Rint was significantly higher than for asthma-predicting FeNO. An inverse trend for those variables was observed in specificity value. In patients with concomitant allergic rhinitis, we showed significantly higher NPV for asthma-predicting Rint than for asthma-predicting FeNO in asthma diagnosis. We observed high sensitivity level (>90%) together with low specificity (<20%) for FEV₁/FVC <80% in all study subgroups (Figs. 2 and 3).

When assessed the co-incidence of asthma-predicting Rint and FeNO in all studied subgroups, we observed an increased negative predictive value (reaching from 74% to 82% depending on the subgroup) without a significant decrease of positive predictive value (from 31% to 46% depending on the subgroup).

DISCUSSION

We performed a retrospective, cross-sectional study to establish a diagnostic value of lung function parameters and FeNO in asthma diagnosis in children. We showed that among all studied lung function parameters, only Rint and FEV₁/FVC <80% were associated with asthma diagnosis. Additionally, we observed an increased risk of asthma diagnosis with a higher FeNO. We defined the optimal value of Rint and FeNO for the clinical diagnosis of asthma as follows: Rint >175% and FeNO >15 ppb. What is more, both parameters, categorized in the optimal cut off point, were associated in the prediction of asthma diagnosis. Here we showed a higher negative predictive value (NPV) for asthma-predicting Rint than for asthma-predicting FeNO in asthma diagnosis, especially in patients with concomitant allergic rhinitis. Moreover, when Rint <175% was observed together with FeNO <15 ppb, the probability of asthma exclusion increased. Therefore, we demonstrated the utility of Rint and FeNO measurements in excluding asthma. We found that Rint

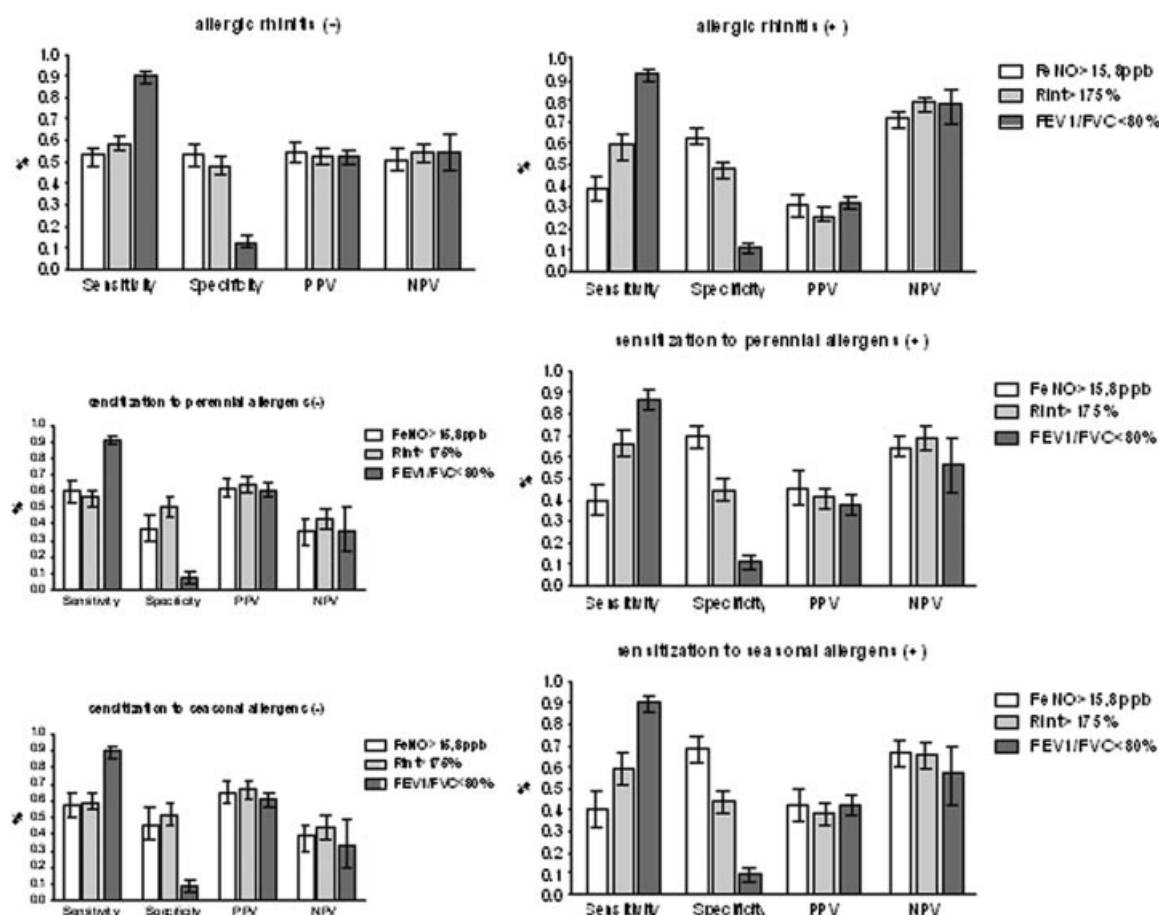


Fig. 1. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of asthma-predicting FeNO, asthma-predicting Rint, and FEV₁/FVC < 80% in all study subgroups.

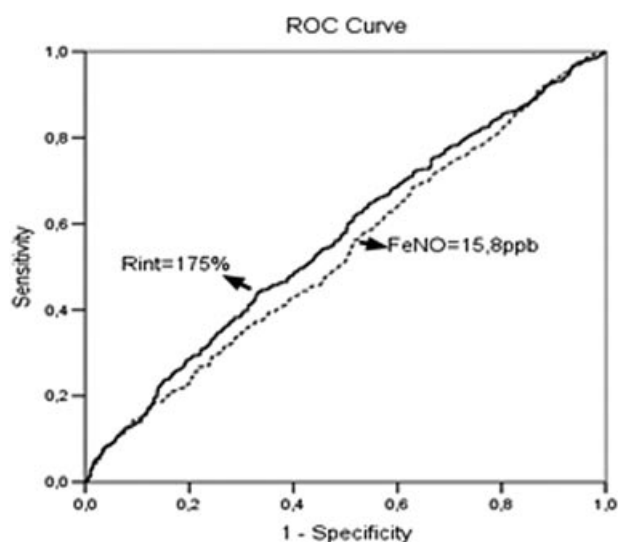


Fig. 2. ROC curves for Rint and FeNO in the prediction of asthma diagnosis. Optimal cut off points for both variables are given.

could be used as a fairly sensitive marker of asthma, in particular to exclude asthma.

To date, only Caudri et al.²¹ during a prospective, longitudinal study found that in preschool children with symptoms suggestive of asthma, both FeNO and sIgE measured at age 4, but not Rint, improved the prediction of asthma symptoms until the age of 8 independently of clinical history. In our schoolchildren, we showed a significant association between Rint measurement and asthma diagnosis; what is more, this association was still significant in each study subgroup. This discrepancy could be explained by an unspecific bias of Rint measurement in preschoolers such as cooperation, tonsils enlargement, and recurrent upper respiratory tract infections. We also decided to find initial Rint cut off value which might predict the exclusion of asthma diagnosis. Surprisingly, this cut off was much higher than a border reference range suggesting that asthma in schoolchildren significantly increases the occlusion

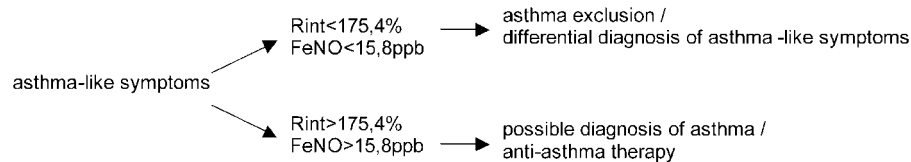


Fig. 3. The role of Rint and FeNO measurements in the initial management of asthma in schoolchildren according to the results of the current study.

resistance of the airways, and, consequently, this cut off should be used in clinical practice to make the exclusion of diagnosis of asthma easier. The main advantages of Rint, as described by Child F., are that it is an easy, cheap, non-invasive, effort-independent measurement, reproducible in children as young as 2–3 years old and helpful in assessing bronchodilator responsiveness.²² It also has its disadvantages. It was discovered that Rint was not useful in the long-term management of individual preschool children.^{21–24} van de Kant et al.²⁵ showed that there is no marked difference in Rint baseline and reversibility value between wheezing phenotypes in preschool children, between atopics and non-atopics, and that Rint is not significantly increased in 5-year old children with persistent wheeze and augmented airway inflammation. Rint had poor sensitivity to detect baseline obstruction, but fairly good sensitivity and specificity to detect reversibility in schoolchildren with asthma.²⁴ Both the within-subject and between-observer variability is high in children,^{22–23} and the individual changes of Rint show too large fluctuations and too low sensitivity and specificity to use it in order to diagnose BHR in individual pediatric patients.²⁶

American Thoracic Society (ATS) guidelines recommend that low FeNO, <20 ppb in children, should be used to indicate that eosinophilic inflammation and responsiveness to corticosteroids are less likely.¹ Furthermore, ATS recommends accounting for the age as a factor affecting FeNO in children younger than 12.¹ Taking these recommendations into account, we suspect that many of our asthmatics did not have eosinophilic inflammation in the airways; then it is possible that non-allergic asthma could affect the FeNO cut off level (15 ppb) in our study.¹ Also treatment with inhaled corticosteroids could affect FeNO levels in our study (in the patients who were on controller treatment when included). The most important consideration is whether or not the patient has current respiratory symptoms or a prior diagnosis of an airway disease; that is, the interpretation of FeNO levels should be determined in individual patients with reference to the context in which the measurement is obtained.¹ In our study, the association between FeNO and asthma diagnosis was significant only in children with perennial allergy, which confirms the above hypothesis and recommendations.¹ It is necessary to always keep in mind the fact that differential diagnoses

and/or co-morbidities of the lungs/airways other than asthma may affect the results of the lung function tests,²⁷ as well as FeNO.¹ However, we studied schoolchildren with allergic diseases (asthma, allergic rhinitis, atopic dermatitis) and no co-morbidities (other than allergic diseases).^{1,22} The role and considerable value of sIgE and FEV₁/FVC <80% as significant predictors of asthma in children are well known.¹⁰ We used those reliable parameters to compare them with the new proposed ones, namely Rint and FeNO, in our cohort. The lack of importance of sRaw in our study could possibly be explained by its too high variability in schoolchildren, or a weak relationship between baseline FEV₁ and sRaw, which was previously reported.^{23,28} The same could be true for other spirometry indices in our study.^{29–31}

The major strength of this study is a large sample size, which overcomes the problem of natural variability of lung function parameters and makes our results more reliable.

The main limitation of our study is the retrospective design. We gathered data from the patients' medical documentation, which could have partly influenced the accuracy of our results. The same could be true for a relatively wide range of the study subjects' age (from 6 to 18). We evaluated data from the medical documentation of the patients of an allergy clinic; thus, it is possible that our study population was skewed. However, all patients participating in this study remain under the regular care of allergy specialists from our clinic, including physical examination, lung function measurements, and other necessary tests, which exclude any doubts concerning the heterogeneity of diagnostic and therapeutic procedures. Therefore, all lung function tests were performed according to guidelines.^{13–18} Four hundred forty-two of the asthmatic patients were on current anti-asthma treatment with the controller medication for asthma at the time of the testing, but the results of these patients were within a single standard deviation for the whole group.

In general, although we defined statistically significant predictors of asthma diagnosis exclusion, all of them seem to have a relatively low diagnostic value. Keeping in mind the results of the negative predictive value, the measurements of FeNO and, even more of Rint, may help to differentiate asthmatics from non-asthmatics. Guidelines define asthma by the presence of a reversible airways

obstruction, which therefore requires the performance of spirometric tests and, if normal, bronchial provocation tests. However, in children with asthma-like symptoms, bronchial obstruction in diagnostic process is rarely and variably observed,²⁹ and physicians are reluctant to dispense with bronchial provocation tests.¹⁰ It would have been preferable—for the purpose of excluding asthma—if some additional test of bronchial hyperresponsiveness had been included in our study. Unfortunately, we were not able to find a significant number of initial data on BHR in our patients that we could include in the analyses.

Lately, there has been a trend towards asthma prediction at school age among preschool children.³² It is emphasized that further improvements in this prediction might be obtained by using more objective measures instead of symptom assessment, such as lung function in early infancy and FeNO measurement in 4-year-old children.³² In the context of our results, we should possibly screen all children with suspected asthma with Rint and FeNO, as opposed to just analyzing histories. Such an approach helps to decide on asthma exclusion in children with asthma-like symptoms. It is reasonable to treat symptomatic children with high FENO and Rint with obligatory assessment of efficacy.

Our results suggest that asthma-predicting Rint and asthma-predicting FeNO, defined in the present study, could serve as a reliable tool to exclude asthma in schoolchildren. However, we also indicate a clinically important issue that all lung function parameters or FeNO should be interpreted in the context of age, gender, allergy profile, and the presence of co-morbidities.

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