

Is Home Spirometry Useful in Diagnosing Asthma in Children With Nonspecific Respiratory Symptoms?

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Summary. Background: Variation of lung function is considered to be a hallmark of asthma. Although guidelines recommend measuring it as a diagnostic tool for asthma, the usefulness of this approach has not been studied in children. Aim: To assess the usefulness of home spirometry in children with nonspecific lower respiratory tract symptoms, to diagnose or exclude asthma. Methods: In school-aged children, referred by their general practitioner because of chronic respiratory symptoms of unknown origin, the diagnosis of asthma was made or excluded by a pediatric pulmonologist (gold standard), based on international guidelines and a standardized protocol. Additionally, children measured peak expiratory flow (PEF) and forced expiratory flow in 1 sec (FEV₁) twice daily for 2 weeks on a home spirometer, from which diurnal variation was calculated. These results (index test) were not revealed to the pediatric pulmonologist. The value of home spirometry to diagnose asthma was calculated. Results: Sixty-one children (27 boys) were included (mean age: 10.4 years; range: 6–16 years). Between asthma and no asthma, the mean difference in PEF variation was 4.4% (95% CI: 0.9–7.9; $P=0.016$) and in FEV₁ variation 4.5% (95% CI: 1.6–7.4; $P=0.003$). Sensitivity and specificity, based on the 95th-centile of the reference values for PEF and FEV₁ variation (12.3% and 11.8%, respectively) were 50% and 72% for PEF variation and 45% and 92% for FEV₁ variation. The likelihood ratio was 1.8 for PEF and 5.6 for FEV₁. Conclusions: The contribution of home spirometry in the diagnostic process for asthma in schoolchildren with nonspecific respiratory symptoms is limited. **Pediatr Pulmonol.** © 2010 Wiley-Liss, Inc.

Key words: peak expiratory flow; diagnostic test; childhood asthma.

INTRODUCTION

Asthma in children is a clinical diagnosis, and international guidelines recommend to use reversibility of bronchial obstruction measured by flow-volume curves to establish the diagnosis.^{1,2} Spirometry is particularly indicated if symptoms are nonspecific and the diagnosis remains uncertain.^{1,2} However, because variation of airway obstruction is a hallmark of asthma, most children with asthma will not exhibit reversibility at each assessment.³ Therefore, the snap-shot lung function test lacks sensitivity.² Increased diurnal variation of lung function over a period of 1–2 weeks has been proposed as a diagnostic tool for asthma.⁴ However, population studies using portable mechanical peak expiratory flow (PEF) meters, showed considerable overlap in PEF variation between healthy and asthmatic children.⁵ As a consequence, the role of measuring diurnal PEF variation as a diagnostic tool for asthma in children has diminished.⁶ Guidelines have been adapted accordingly,¹ although the GINA guideline still considers diurnal PEF variation of additional value for the diagnosis and classification of asthma.²

All original studies on the diagnostic usefulness of PEF variation used mechanical PEF meters and written diaries,

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Competing interests: All authors have no conflicts of interest to declare.

Grant sponsor: AstraZeneca, NL.

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Received 3 August 2009; Revised 13 November 2009; Accepted 13 November 2009.

DOI 10.1002/ppul.21183

Published online in Wiley InterScience
(www.interscience.wiley.com).

which have proven to be unreliable.⁷ Recently, we published reference values of PEF and forced expiratory flow in 1 sec (FEV₁) variation using electronic home spirometry, showing limited overlap between healthy and treated, well-controlled asthmatic children on inhaled corticosteroids (ICS).⁸ From earlier studies, we know that PEF variation decreases significantly during the first 2 months of treatment with ICS.⁹ This suggests that the difference in diurnal PEF and FEV₁ variation between not yet diagnosed—untreated—children with asthma and nonasthmatic children may be larger than previously thought, and that home spirometry could be a diagnostic tool for asthma when symptoms are nonspecific. To test this hypothesis, we studied the usefulness of home spirometry in diagnosing asthma in school-aged children referred for evaluation of nonspecific lower respiratory tract symptoms.

PATIENTS AND METHODS

This study was set up to evaluate the diagnostic value of home spirometry in children with nonspecific respiratory symptoms, such as cough and breathlessness, in whom the general practitioner was uncertain about the diagnosis of asthma. Consecutive children, 6–16 years of age, referred to our hospital-based pediatric asthma clinic because of chronic respiratory symptoms of unknown origin were asked to participate in this study. The following children were excluded: children with a straightforward diagnosis of asthma based on classical respiratory symptoms, children referred because of poorly controlled asthma and children with reported use of systemic corticosteroids or long-acting beta-2-agonists within 4 weeks prior to the referral date. This study was approved by the hospital ethics review board, a certified subsidiary of the Dutch central committee on research involving human subjects.

Based on earlier studies, a period of 2 weeks of home spirometry measurements was chosen because this is sufficient to show increased lung function variation in children with untreated asthma,⁴ and adherence to home spirometry is high.^{10,11} A sample size calculation was

performed as follows: for PEF and FEV₁ variation, we anticipated a standard deviation of 3.5%, equal for both groups.¹¹ In order to be able to detect a minimal difference of 4% in PEF and FEV₁ variation between an asthma and a no asthma group—with an α of 0.05 and a power of 90%—, 18 data pairs were needed. We estimated that in approximately 60% of the referred patients the diagnosis of asthma would be made; therefore, including 45 patients would suffice. In order to allow noncompliance or data errors, we aimed to include 60 patients.

After obtaining written informed consent from patients and parents, children were included and if applicable, ICS were withdrawn. Fourteen days later, at a first visit to our asthma clinic, a semi-structured medical history was taken and physical examination was performed by a pediatric pulmonologist. The fraction of exhaled nitric oxide (FeNO) was measured using a portable NO-meter NIOX MINO, Aerocrine, Solna, Sweden)¹² according to international recommendations,¹³ and expressed in parts per billion (ppb). Subsequently, patients performed flow-volume loops before and 20 min after inhalation of 800 µg salbutamol. All lung function measurements were performed on a Jaeger Masterlab pneumotachograph (Erich Jaeger, Würzburg, Germany), following ATS/ERS guidelines,¹⁴ and short-acting bronchodilators were withdrawn for 8 hr prior to each lung function session. At the second study visit 2 weeks later, history, physical examination, and FeNO measurements were repeated, and bronchial responsiveness was assessed by methacholine provocation using the dosimeter method.^{15,16} Results were expressed as the provocative dose of methacholine causing a 20% fall in FEV₁ (PD₂₀). During the 2-week study period, only short acting bronchodilators when needed were allowed, and children were instructed to return to our clinic immediately if symptoms remained uncontrolled.

During the 2-week study period between the two study visits, children measured PEF and FEV₁ twice daily on a home spirometer (index test). These results were not revealed to the pediatric pulmonologist at any time during the study. During the first visit, patients were instructed carefully how to use the electronic portable spirometer (Koko Peak Pro, Ferraris, Louisville, CO).^{14,17}

This home spirometer has been validated both in vitro by using a precision waveform generator (Pulmonary Waveform System; MH Custom Design and Mfg, Midval, UT) demonstrating its agreement with performance standards as recommended by international guidelines,¹⁴ and in vivo in schoolchildren with asthma.¹⁸ Patients were instructed to perform three forced expiratory flow manoeuvres twice daily between 6 and 10 a.m. and between 6 and 10 p.m. throughout the whole study period of 2 weeks. The device automatically stored the highest of the three correctly performed PEFs on a microchip, along with the accompanying FEV₁. All instructions were given

ABBREVIATIONS

PEF	Peak expiratory flow
FEV ₁	Forced expiratory flow in 1 sec
FeNO	Fraction of exhaled nitric oxide
ATS/ERS	American Thoracic Society/European Respiratory Society
ICS	Inhaled corticosteroids
PD ₂₀ -methacholine	The provocative dose of methacholine causing a 20% fall in FEV ₁
ROC	Receiver operating characteristic
AUC	Area under the curve
FVC	Forced vital capacity
MEF ₅₀	Maximal expiratory flow at 50% of expired volume
SABA	Short-acting beta-2-agonists

by the same experienced technician, encouraging the children to obtain optimal lung function values. At least one parent attended the instruction session. Patients were instructed to achieve PEF as rapidly as possible and to continue the forced expiratory manoeuvre for at least 2 sec. An integrated quality check warned the user by an exclamation mark when a cough was detected, the blow was not long enough, or there was a slow start. After careful inspection following a predefined algorithm,¹⁹ recordings due to technical errors and unexplained outliers were excluded. During analyses, measurements were only accepted if forced vital capacity exceeded FEV₁ and recordings were performed within the given time frame.

Adherence to home spirometry was calculated by comparing the number of recordings expected over 2 weeks with the number of recordings actually obtained. The PEF was expressed as percentage of the personal best value (%PB) and the FEV₁ as percentage of the predicted value (%pred).²⁰ Variation of PEF (and of FEV₁) was expressed as the amplitude (maximum–minimum) as a percentage of the day's mean (ampl%mean).²¹

After reviewing history, physical examination, and lung function data, but without the home spirometry results (index test), a single experienced pediatric pulmonologist made or excluded the diagnosis of asthma in each patient at the second visit (gold standard). When asthma was diagnosed, ICS treatment was initiated. When asthma was excluded, the differential diagnosis was evaluated and further appropriate testing was performed—if necessary—until the diagnosis was reached.

The gold standard (asthma diagnosis by the pediatric pulmonologist) and the index test (PEF or FEV₁ variation by home spirometry) were compared, and test characteristics were calculated by using the 95th-centile for PEF and FEV₁ variation in healthy schoolchildren, 12.3% and 11.8%, respectively, as the cut-off between normal and increased PEF or FEV₁ variation.⁸ Receiver operating characteristic (ROC) curves for PEF and FEV₁ variation were produced to assess the diagnostic performance of the index test. Data were analyzed using PRISM™ (GraphPad Software, San Diego, CA) for Windows™ version 3.00.

RESULTS

Sixty-one children (27 boys) were included in this study, with a mean age of 10.4 years (range: 6–16 years). At inclusion, children had experienced nonspecific symptoms of recurrent wheeze or cough and breathlessness for at least 3 months, reported as partly relieved by bronchodilators. All children were able to perform pulmonary function measurements reproducibly. All children completed the study. In 21 children (34%) asthma was diagnosed (asthma group). The remaining 40 children

(64%) comprised the no asthma group and were diagnosed as follows: 13 children (33%) (allergic) rhinitis, treated successfully with nasal corticosteroids, 13 (33%) dysfunctional breathing, defined as chronic or recurrent changes in breathing pattern, causing respiratory and nonrespiratory complaints,²² which was confirmed and treated successfully by a physiotherapist, eight (20%) recurrent upper respiratory tract infections, two (5%) serologically proven pertussis, and three (7%) chronic persistent cough. In addition, there was one patient (3%), who, after further diagnostic work-up including body plethysmography and diffusion capacity measurements, appeared to have a restrictive lung function deficit, for which the underlying cause could not be determined. Asthma was excluded in this patient by the absence of wheeze, even while symptomatic, absence of bronchodilator and methacholine responsiveness, and normal FeNO values. Patient characteristics in the two groups are shown in Table 1, and lung function results in Table 2.

Home spirometry data from two patients (one with asthma and one with no asthma) were lost due to battery failure of the device. There were no other technical errors. For the remaining 59 patients, mean adherence to home spirometry during the 2-week study period was 93% (SD 8.8%), and this was comparable in the asthma and no asthma group (mean difference 0.1%, 95% CI –4.9%–4.7%; $P = 0.98$). Figure 1 shows the distributions of PEF and FEV₁ variation in the asthma and the no asthma groups. The mean differences in PEF variation and FEV₁ variation between the two groups were 4.4% (95% CI 0.9–7.9; $P = 0.016$) and 4.5% (95% CI 1.6–7.4; $P = 0.003$), respectively. Test characteristics of increased PEF and FEV₁ variation for the diagnosis of asthma, using the 95th-centile of the reference values for PEF and FEV₁ variation (12.3% and 11.8%, respectively) as cut-off,⁸ are shown in Table 3. ROC curves for PEF and FEV₁ variation are shown in Figure 2A,B, respectively. The area under the curve (AUC) is 0.69 for PEF variation and 0.77 for FEV₁ variation.

DISCUSSION

This study shows that the diagnostic value of home spirometry in making or excluding the diagnosis of asthma in schoolchildren with nonspecific respiratory symptoms, such as cough and breathlessness, is limited. Although mean variation of PEF and FEV₁ using home spirometry were significantly lower in the no asthma group than in the asthma group, the difference was small, and the distributions of PEF and FEV₁ variation showed complete overlap between the two groups (Fig. 1). Home spirometry contributed marginally to the likelihood of asthma, with likelihood ratios of 1.77 and 5.85 for PEF and FEV₁ variation, respectively. The ROC curves (Fig. 2) illustrate the poor diagnostic performance of PEF and FEV₁

TABLE 1—Distribution of Patient Characteristics Between the Asthma and no Asthma Group

Diagnosis	No asthma (n = 40)	Asthma (n = 21)	P-value
Mean age (years)	10.5 ± 2.5	10.2 ± 2.7	0.690
Sex: (%male)	17 (43%)	10 (48%)	0.702
Family history of asthma (1st degree)	23 (58%)	16 (76%)	0.149
Symptoms			
Wheeze	11 (28%)	18 (86%)	<0.0001
Cough	22 (55%)	15 (71%)	0.212
Breathlessness	40 (100%)	21 (100%)	1.000
Smoking			
Parent(s)	12 (30%)	5 (24%)	0.608
Patient	0 (0%)	1 (5%)	0.164
Sensitization			
No sensitization	22 (55%)	1 (5%)	<0.0001
Only aero allergens	15 (37%)	17 (80%)	0.001
Only food allergens	1 (3%)	1 (5%)	0.637
Both	2 (5%)	2 (10%)	0.498
Medication			
No inhaled medication	7 (17%)	0 (0%)	0.042
SABA ¹ only	12 (30%)	6 (29%)	0.907
ICS ²	21 (53%)	15 (72%)	0.213
Other asthma drugs	—	—	—

¹Short-acting beta-2-agonists.²Inhaled corticosteroids.

variation using home spirometry in schoolchildren with chronic nonspecific respiratory symptoms.

A well-recognized difficulty in the diagnosis of asthma in children is the lack of one reliable diagnostic test, in particular when symptoms are nonspecific. Asthma is a clinical diagnosis based on multiple key indicators increasing the probability of the presence of the disease.^{1,2} Wheezing is considered a key symptom in asthma, but because patients and parents vary considerably in their

interpretation of “wheeze” (which may include any kind of noisy or difficult breathing),^{23,24} the presence of expiratory wheeze, as a sign for the presence of airflow obstruction, should be confirmed by a health care professional, either by physical examination or by lung function testing.^{2,24,25} This is corroborated by the results of our study, in which a history of wheezing, although more common in the asthma group, was also present in a quarter of the patients in the no asthma group (Table 1).

TABLE 2—Lung Function Characteristics of the 61 Participating Children Showing Statistically Significant Differences

Diagnosis	No asthma (n = 40)	Asthma (n = 21)	95% CI; P-value
1st visit FEV ₁ (% pred) ¹	101.1 ± 11.3	86.4 ± 15.2	7.8–21.8; <0.0001
Increase in FEV ₁ (% pred) after 800 µg salbutamol	3.5 ± 4.1	11.7 ± 6.0	5.5–10.9; <0.0001
1st visit FVC (% pred) ²	100.1 ± 11.5	91.8 ± 13.8	1.7–15.1; 0.0153
1st visit FEV ₁ /FVC (%pred)	101.3 ± 6.5	94.0 ± 11.1	2.4–11.5; 0.0035
1st visit MEF ₅₀ (% pred) ³	83.2 ± 16.5	62.3 ± 20.4	11.1–30.7; <0.0001
1st visit FeNO (ppb) ⁴	28.5 ± 26.6	72.8 ± 39.1	26.6–62.0; <0.0001
2nd visit FEV ₁ (% pred)	101.0 ± 11.5	85.4 ± 19.5	4.2–15.6; 0.0005
2nd visit FeNO (ppb)	32.2 ± 27.9	67.1 ± 41.5	15.5–54.2; 0.0007
logPD ₂₀ -methacholine (µg) ⁵	3.15 [2.71–3.15]	1.83 [1.61–2.31]	0.8–1.3; <0.0001
Home spirometry (2 weeks)			
PEF (%PB) ⁶	84.0 ± 8.3	76.9 ± 13.9	1.1–13.0; 0.0203
FEV ₁ (%pred)	89.3 ± 13.5	75.5 ± 18.5	5.1–22.5; 0.0024

Values are presented as mean ± SD, or as median and inter-quartile range for PD₂₀.

¹Forced expiratory volume in 1 sec expressed as percentage of predicted value.

²Forced vital capacity.

³Maximal expiratory flow at 50% of expired volume.

⁴Fraction of exhaled nitric oxide expressed in parts per billion.

⁵Provocative dose of methacholine causing a 20% fall in FEV₁.

⁶Peak expiratory flow expressed as percentage of the personal best value.

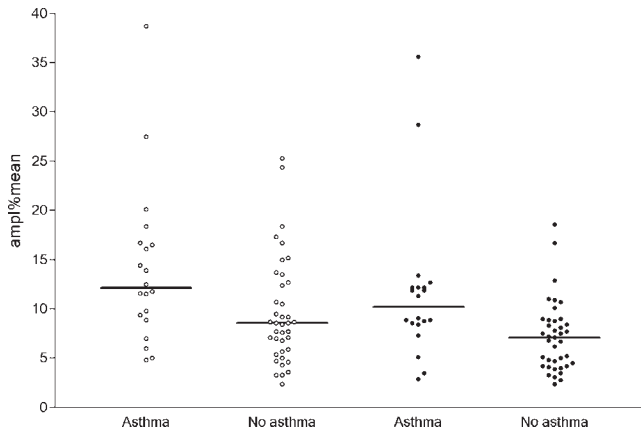


Fig. 1. Distributions of PEF and FEV₁ variation in the asthma and the no asthma group showing complete overlap for both home spirometry indices between the two groups. Open circles represent PEF variation. Solid circles represent FEV₁ variation. Lines represent median values.

Because we aimed to assess the diagnostic value of home spirometry in children with nonspecific respiratory symptoms specifically, we excluded children with a straightforward diagnosis of asthma based on classical respiratory symptoms. The main reason for this approach was that home spirometry would not have to be used in such patients to confirm the diagnosis of asthma. In clinical practice, an assessment of lung function variation is primarily used to help making or rejecting the diagnosis of asthma in patients in whom history and physical examination alone are insufficient to make or reject the diagnosis. This study was designed to test the usefulness of home spirometry in exactly that clinical population. Children referred because of poorly controlled asthma were excluded because of the increased exacerbation risk after the withdrawal of ICS.

Guidelines recommend additional lung function tests to establish the diagnosis,¹ or increase its likelihood.² In this study, we used FeNO, lung function, bronchodilator response, and bronchial hyperresponsiveness to help making or rejecting the diagnosis of asthma in school-children experiencing nonspecific respiratory symptoms. By combining the results of these tests and the suspected

presence of asthma based on the semi-structured medical history and the physical examination, we assured that the diagnosis of asthma was made reliably and according to international guidelines.^{1,2} As a result of this study design, the diagnostic properties of each of the separate tests which were used to make the diagnosis cannot be reported. Home spirometry did not emerge as a reliable diagnostic test for asthma in children with nonspecific respiratory symptoms.

The likelihood ratio of a test represents the change in disease probability after performing the test.²⁶ With a pre-test probability of asthma of 34% in our study population, the likelihood ratio of 1.77 for PEF variation leads to a post-test disease probability of approximately 44%. Such a small increase in disease likelihood underscores the poor diagnostic value of PEF variation in the diagnosis of asthma.^{26,27} The likelihood ratio of 5.85 for FEV₁ variation increases the post-test disease probability considerably to approximately 73%, mainly because the specificity of increased FEV₁ variation is larger than that of PEF variation (Table 3). However, the sensitivity of increased FEV₁ variation was poor, identifying less than half of the asthmatics in the present study (Table 3, Fig. 1). The ROC curve of FEV₁ variation (Fig. 2B) shows that the false positive rate rises quickly when lower cut-off values of FEV₁ variation are used to increase sensitivity. In addition, the large degree of overlap in FEV₁ variation between the asthma and no asthma group (Fig. 1) limits its usefulness in individual patient care. Therefore, despite the reasonable likelihood ratio, the applicability of FEV₁ variation as a diagnostic test for asthma in children with nonspecific respiratory symptoms is limited.

Some limitations of the present study need to be discussed. Firstly, the quality of data obtained by home spirometry must be considered. Previous studies have consistently shown that home spirometry provides reproducible and technically reliable results,^{27–29} although they are slightly lower than those obtained by hospital spirometry.¹⁸

Secondly, like earlier diagnostic studies in childhood asthma,^{4,30} this study was powered to detect a minimal difference between two groups, but not to establish agreement between two tests (gold standard and index

TABLE 3— Test Characteristics Calculated When the 95th-centile of the Reference Values for PEF and FEV₁ are Used

	PEF ¹ variation $\geq 12.3\%$	FEV ₁ ² variation $\leq 11.8\%$
Sensitivity (95% CI)	0.50 (0.30–0.70)	0.45 (0.25–0.67)
Specificity (95% CI)	0.72 (0.56–0.84)	0.92 (0.80–0.97)
Positive predictive value (95% CI)	0.48 (0.28–0.68)	0.75 (0.47–0.91)
Negative predictive value (95% CI)	0.74 (0.58–0.85)	0.77 (0.63–0.86)
Likelihood ratio (95% CI)	1.77 (0.91–3.45)	5.85 (1.78–19.24)

¹Peak expiratory flow.

²Forced expiratory volume in 1 sec.

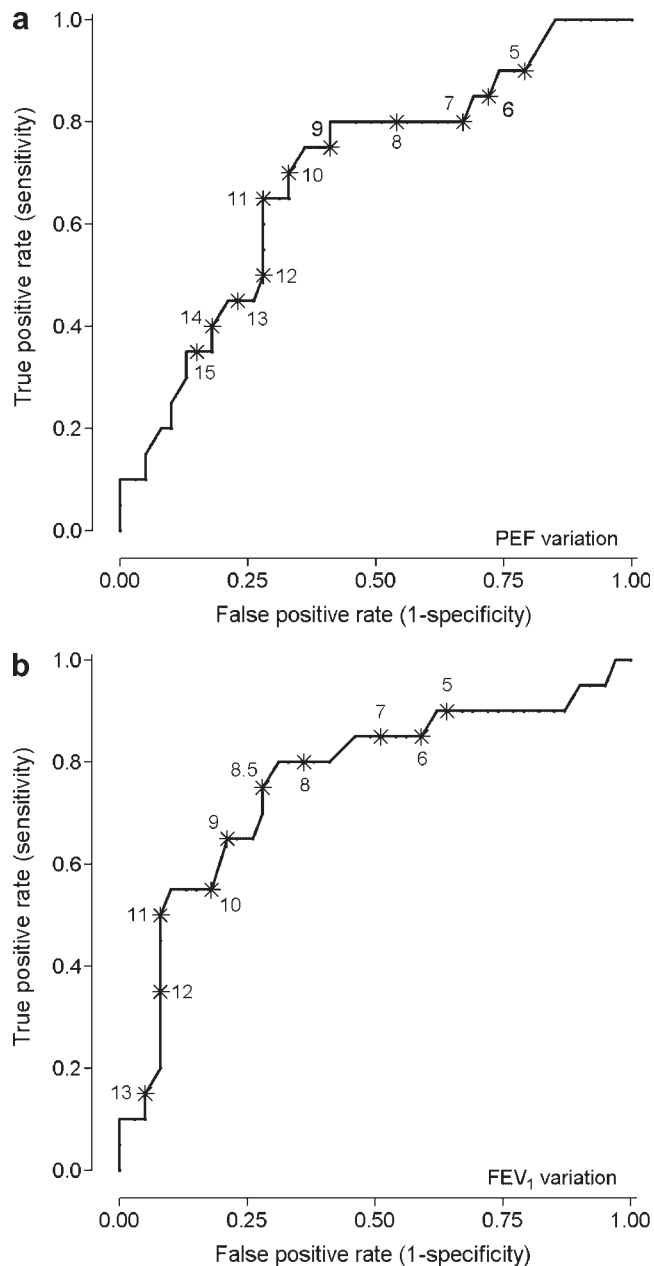


Fig. 2. Receiver operating characteristics curves for (a) PEF variation and (b) FEV₁ variation showing the poor diagnostic performance of both home spirometry indices. Area under the curve (AUC) for PEF variation: 0.69; AUC for FEV₁ variation: 0.77. Numbers in the graphs represent the associated cut-off values for PEF and FEV₁ variation, respectively (ampl%mean).

test). Although adequately sized groups were formed and the expected minimal difference of 4% was found, establishing agreement between two clinical tests would have taken at least 50 data pairs.³¹ With only 34% of the referred children receiving a diagnosis of asthma, a total of 150 inclusions would have been necessary. Nevertheless, the complete overlap in distributions of PEF and FEV₁ variation between the asthma and no asthma group (Fig. 1)

makes it unlikely that increasing the sample size of our study would have changed its results in a clinically relevant way.

In conclusion, this study shows that the usefulness of home spirometry in the diagnostic process of asthma in children with nonspecific respiratory symptoms is limited. Even if obtained by electronic home spirometry, PEF and FEV₁ variation should not be used as a diagnostic tool for asthma in children with nonspecific chronic respiratory symptoms.

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