Diagnosis of asthma in children: the contribution of a detailed history and test results

Carmen C.M. de Jong [1], Eva S.L. Pedersen[1], Rebeca Mozun [1], Myrofora Goutaki [1,2], Daniel Trachsel[3], Juerg Barben[4,5] and Claudia E. Kuehni [1,2,5]

Affiliations: [1]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. [2]Paediatric Respiratory Medicine, Children's University Hospital of Bern, University of Bern, Bern, Switzerland. [3]Paediatric Respiratory Medicine, Children's University Hospital of Basel, Basel, Switzerland. [4]Paediatric Respiratory Medicine, Children's Hospital of Eastern Switzerland, St Gallen, Switzerland. [5]These authors contributed equally.

Correspondence: Claudia E. Kuehni, University of Bern, Institute of Social and Preventive Medicine, Mittelstrasse 43, CH-3012 Bern, Switzerland. E-mail: claudia.kuehni@ispm.unibe.ch

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Diagnosing asthma in children is most accurately done by using information on triggers and severity of wheeze and by F_{eNO} measurement, methacholine and exercise challenge tests. http://bit.ly/2kDWaRr

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ABSTRACT

Introduction: There are few data on the usefulness of different tests to diagnose asthma in children.

Aim: We assessed the contribution of a detailed history and a variety of diagnostic tests for diagnosing asthma in children.

Methods: We studied children aged 6–16 years referred consecutively for evaluation of suspected asthma to two pulmonary outpatient clinics. Symptoms were assessed by parental questionnaire. The clinical evaluation included skin-prick tests, measurement of exhaled nitric oxide fraction (F_{eNO}), spirometry, bronchodilator reversibility and bronchial provocation tests (BPT) by exercise, methacholine and mannitol. Asthma was diagnosed by the physicians at the end of the visit. We assessed diagnostic accuracy of symptoms and tests by calculating sensitivity, specificity, positive and negative predictive values and area under the curve (AUC).

Results: Of the 111 participants, 80 (72%) were diagnosed with asthma. The combined sensitivity and specificity was highest for reported frequent wheeze (more than three attacks per year) (sensitivity 0.44, specificity 0.90), awakening due to wheeze (0.41, 0.90) and wheeze triggered by pollen (0.46, 0.83) or by pets (0.29, 0.99). Of the diagnostic tests, the AUC was highest for F_{eNO} measurement (0.80) and BPT by methacholine (0.81) or exercise (0.74), and lowest for forced expiratory volume in 1 s (FEV_1) (0.62) and FEV_1/forced vital capacity ratio (0.66), assessed by spirometry.

Conclusion: This study suggests that specific questions about triggers and severity of wheeze, measurement of F_{eNO} and BPT by methacholine or exercise contribute more to the diagnosis of asthma in school-aged children than spirometry, bronchodilator reversibility and skin-prick tests.

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Introduction

Diagnosing asthma in children is not straightforward, because we lack a stand-alone diagnostic test. Symptoms (cough, wheeze, breathlessness) are not specific for asthma and interpretation of commonly used diagnostic tests is complicated by the temporal variability and phenotypic heterogeneity of asthma. Thus, diagnostic guidelines suggest diagnosing asthma based on a characteristic pattern of respiratory symptoms, clinical examination, demonstration of reversible airway obstruction assessed by spirometry and airway inflammation measured by exhaled nitric oxide fraction (F_{eNO}) [1–4]. Allergy tests and measurement of bronchial hyperresponsiveness by direct and indirect challenge tests are used as further aids for diagnosis.

However, the diagnostic algorithm proposed by recent guidelines has been questioned for children and there are surprisingly few data available to assess the usefulness of the different tests in the diagnosis of asthma in school-aged children [5]. Systematic literature reviews done for recent guidelines and for the ongoing taskforce of the European Respiratory Society identified only a handful of publications assessing the accuracy of the different tests for children with suspected asthma [2, 3]. Most publications identified by the searches had a case–control design, comparing children with asthma to healthy controls instead of consecutive referrals of children suspected of having asthma. Available studies had included only few diagnostic tests and no detailed history, and asthma diagnosis used as reference standard was often poorly defined or too narrow, for instance including only allergic asthma. Additionally, papers used different cut-offs for positive tests (*e.g.* for F_{eNO} or forced expiratory volume in 1 s (FEV_1)), and it remains unclear which cut-offs are best for children [1–4]. In this study, we assessed the diagnostic accuracy of reported respiratory symptoms and different objective tests to diagnose asthma in consecutive referrals of school-aged children presenting symptoms suggestive of asthma.

Methods

Study population and study design

For this study, we re-analysed data from a clinical study performed in 2007–2008 in Switzerland. It included consecutive first-time referrals to the respiratory outpatient clinics of two paediatric hospitals (St Gallen and Basel) of 6–16-year-old children for evaluation of a possible asthma diagnosis with a history of wheezing, dyspnoea or cough. Children were excluded from the study if they had a known chronic respiratory disease such as cystic fibrosis, or a respiratory tract infection during the 4 weeks prior to the visit. The aim of the initial study had been to compare the results of mannitol challenge tests to exercise challenge tests [6].

Study procedures

All children referred for the first time by general practitioners or primary care paediatricians for evaluation of possible asthma were invited to participate in the study, which included two visits to the hospital within a week (figure 1). At the first visit, all children underwent clinical evaluation, skin-prick testing (unless printed results of a skin-prick test done during the past 2 years were available), measurement of F_{eNO}, spirometry, exercise bronchial provocation tests (BPT), methacholine BPT and bronchodilator reversibility test, in that order. Children who reacted to the exercise challenge and received salbutamol returned for an extra visit within the following few days to perform the methacholine challenge test. Within a week all children repeated the F_{eNO} measurement and performed a mannitol BPT. Between visits, the family completed a questionnaire. Ethical approval was obtained from the local ethics committee and all parents gave informed consent at baseline (EKSG 07/001).

Clinical asthma diagnosis (reference standard)

The study physicians, experienced paediatric pulmonologists, completed a physician's report form that included the clinical diagnosis (definite asthma, probable asthma or other disease), at two time points. At the first visit, physicians considered only medical history, clinical examination, allergy tests, F_{eNO} measurement and spirometry. At the second visit, the same physician reported the clinical diagnosis (as definite asthma, probable asthma or other disease) in the second physicians' report form, taking into account all the information available, *i.e.* medical history, clinical examination, allergy tests, F_{eNO} measurement, spirometry and results of the BPT and bronchodilator reversibility test. For our main analysis, we defined asthma (reference standard) as an affirmative answer to either definite or probable asthma in the second physician's report form. In a sensitivity analysis, we used the first physicians' report form (based on all the information except the BPTs) to define asthma (reference standard).

Assessment of respiratory symptoms and diagnostic testing

The parental questionnaire included the International Study of Asthma and Allergies in Childhood (ISAAC) key questions for lower respiratory symptoms and more detailed questions on wheeze and cough

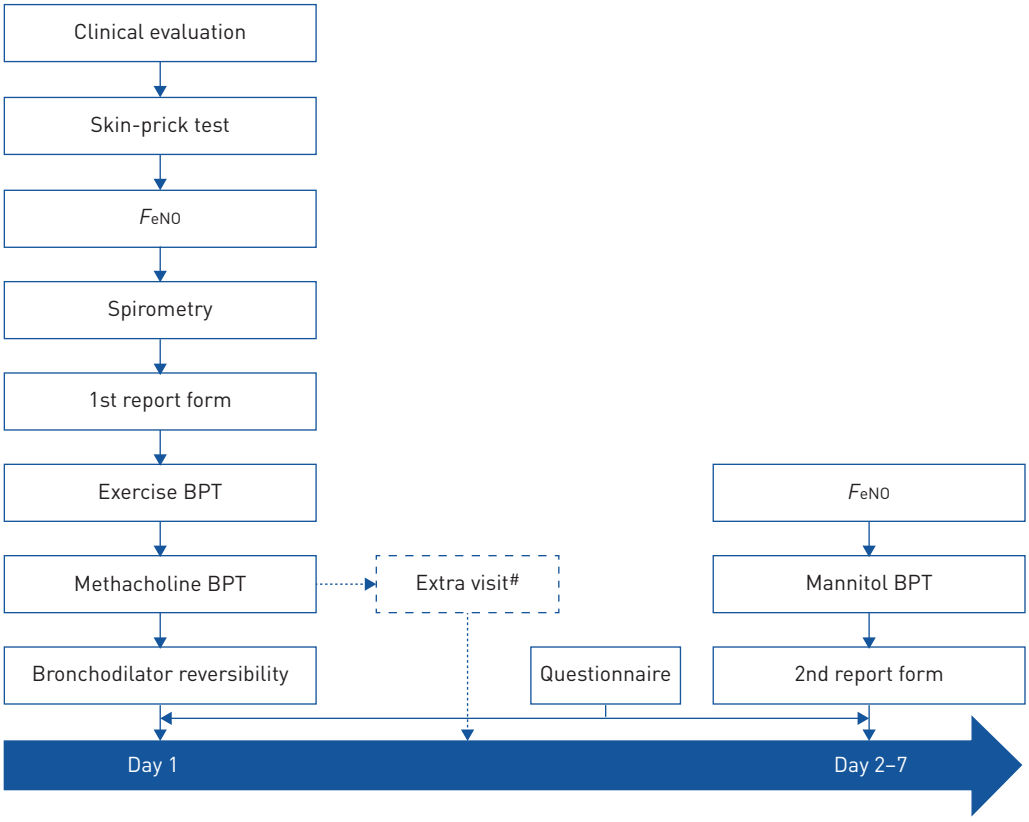

FIGURE 1 Study procedures. The report form is a standardised form for physicians to note down the clinical diagnosis. BPT: bronchial provocation test; F_{eNO}: fractional exhaled nitric oxide. #: children who received salbutamol after the exercise BPT conducted the methacholine BPT at an additional visit.

derived from the questionnaires used in the Leicester respiratory cohort studies (supplementary material) [7, 8]. All diagnostic tests were performed according to published guidelines [9–13]. Short-acting β_2-agonists were withheld for 8 h, inhaled corticosteroids, leukotriene antagonists and long-acting β_2-agonists for 24 h and antihistamines and sodium cromoglicate for >72 h.

Skin-prick test

We performed skin-prick tests using birch, grass, mugwort, alternaria, cat, house dust mites (*Dermatophagoides pteronyssinus*), histamine and saline. The skin-prick test was considered positive if the allergen wheal size was ⩾3 mm, the positive control (histamine) wheal size was ⩾3 mm and the negative control (saline) wheal size was <3 mm. These allergens cover 95% of allergies to inhaled allergens in Switzerland [14].

F_{eNO}

F_{eNO} was measured in doublets before spirometry, using the portable multi-gas analyser (NIOX MINO, Aerocrine, Sollentuna, Sweden), in accordance with published guidelines [10] and previous studies using this device [15, 16]. The portable analyser ensures a constant expiratory flow of 50±5 mL·s^{-1}, has an accuracy of ±10% with a minimum ±5 ppb and the quality was controlled by the lung function technician according to the manufacturer's guidelines.

Spirometry

Spirometry was performed using American Thoracic Society (ATS) criteria for paediatric lung function testing and a Jaeger Masterscope (Erich Jaeger, Würzburg, Germany), using JLAB software (version 4.34). Spirometry was performed in triplicate by experienced lung function technicians, who performed quality control during the measurement and recorded the best measurement. The flow–volume curve was then checked by the responsible paediatric pulmonologist. Results are expressed as proportion (FEV_1/forced vital capacity (FVC)) and as z-scores based on Global Lung Initiative 2012 reference standards [17].

Bronchial provocation tests

For all BPTs, baseline FEV_1 was measured in triplicate using ATS criteria for paediatric lung function testing [9] and the best measurement was recorded. We reported the results of the exercise BPT as the maximum fall of FEV_1 compared to baseline, the methacholine BPT as provocation dose causing a 20% decrease of FEV_1 from baseline (PD_{20}) and the mannitol BPT as provocation dose causing a 15% decrease of FEV_1 from baseline (PD_{15}). After the methacholine BPT, all children were given four puffs of salbutamol 100 µg to test for bronchodilator reversibility. In addition, children received salbutamol if FEV_1 had not returned to within 5% of baseline 15 min after the exercise or mannitol BPT, or in cases of dyspnoea. More details on the BPTs have been published before and can be found in the supplementary material [6].

Statistical analysis

For the reported respiratory symptoms and the different tests, we calculated sensitivity, specificity, positive predictive value and negative predictive value, Youden's index (sensitivity+specificity−1), area under the curve (AUC) and their 95% confidence intervals to diagnose asthma, using the final (post-BPT) physicians' diagnosis as reference standard. We did a sensitivity analysis using the first (pre-BPT) physicians' diagnosis. We displayed the cut-off values with the highest Youden's index in our study and those used in the literature. We used STATA software (version 15; College Station, TX, USA) for statistical analysis.

Results

Characteristics of the study population

Of the 124 children invited, 111 (90%) were recruited, 84 from St Gallen and 27 from Basel. The median (range) age was 12 (6–16) years and 62% were male. Most children were referred with wheeze and cough (47%) or wheeze without cough (23%). Inhaled medication had been used by 64% prior to referral, including 19% who had used inhaled corticosteroids (table 1). Of the 111 participants, 80 (72%) were diagnosed with asthma after all BPTs were done compared to 94 (85%) before the BPTs. The remaining children were diagnosed with cough unrelated to asthma (8% before BPTs and 13% after BPTs) and with inducible laryngeal obstruction and dysfunctional breathing (6% before BPTs and 7% after BPTs) (supplementary table S1). None of the children were diagnosed with a severe lung disease such as cystic fibrosis [18].

TABLE 1 Characteristics of the study participants

Age years	11 (6–16)
Male	69 (62)
Respiratory symptoms in the past 12 months	
Any wheeze	80 (72)
>3 attacks of wheeze	38 (34)
Wheeze with colds	43 (39)
Wheeze apart from colds	67 (60)
Exercise-induced wheeze	70 (63)
Wheeze triggered by pollen	36 (32)
Wheeze triggered by house dust	21 (19)
Wheeze triggered by pets	20 (18)
Awakening due to wheeze	36 (32)
Cough lasting >4 weeks	21 (19)
Night cough	48 (43)
Cough more than others	37 (33)
Dyspnoea	25 (23)
Hay fever[#]	49 (44)
Eczema[#]	26 (23)
Inhaled medication	
Any	71 (64)
Short-acting β_2-agonist, alone	49 (44)
ICS + short-acting β_2-agonist	6 (5)
ICS + long-acting β_2-agonist	16 (14)

Data are presented as median (range) or n (%). n=111. ICS: inhaled corticosteroids. [#]: ever in the past.

Diagnostic accuracy of respiratory symptoms to diagnose asthma

Reported wheeze in the past 12 months had the highest sensitivity (80%) for physician-diagnosed asthma (table 2). Specificity was highest for frequent wheeze (more than three attacks per year) (90%), awakening due to wheeze (90%) and wheeze triggered by pollen (83%), house dust (93%) or pets (99%). Combined sensitivity and specificity was highest for frequent wheeze in the past 12 months (Youden's index 0.34), awakening due to wheeze (0.31) and wheeze triggered by pollen (0.29) or pets (0.28) (table 2).

Diagnostic accuracy of tests to diagnose asthma

All 111 children completed skin-prick testing, F_{eNO}, spirometry and BPT by mannitol. BPT by exercise could not be completed in 12 children because of exhaustion (n=7), inspiratory stridor (induced laryngeal obstruction) (n=2), no cooperation (n=2) or technical difficulties (n=1) [6, 19]. Seven patients could not complete BPT by methacholine due to exhaustion and 36 children performed the test during an extra visit a few days later. In four patients the skin-prick test result was not considered valid because the histamine control was not positive. Test results in patients with and without asthma diagnosis are displayed in supplementary table S2.

The cut-off values with the best diagnostic accuracy were <80% for FEV_1/FVC, ⩽−0.8 z-score for FEV_1, ⩾10% increase of FEV_1 for bronchodilator reversibility test, ⩾8% decrease of FEV_1 for BPT by exercise, PD_{20} <0.7 mg for BPT by methacholine, PD_{15} <635 mg for BPT by mannitol, ⩾2 for the number of positive skin-prick tests, ⩾8 mm for the cumulative wheal size of skin-prick tests and ⩾21 ppb for F_{eNO} (table 3).

Accuracy overall was best for F_{eNO}, BPT by methacholine and BPT by exercise (AUC 0.80, 0.81 and 0.74, respectively). Accuracy was lower for BPT by mannitol and skin-prick test (AUC ∼0.70), and lowest for spirometry (AUC 0.62 and 0.66 for FEV_1 and FEV_1/FVC ratio, respectively) (figure 2).

Sensitivity analysis

In the sensitivity analysis with asthma diagnosis based on the pre-BPT report form, frequent wheeze and wheeze triggered by pollen or by pets in the past 12 months had the highest Youden's index, which was in line with the main analysis. In addition, night cough and hay fever had a high Youden's index for the asthma diagnosis pre-BPT (supplementary table S3), but not for the asthma diagnosis post-BPTs (table 2).

For the diagnostic tests, the Youden's index was highest at the same cut-offs for most tests (supplementary table S4 and supplementary figure S1). Cut-offs were higher for F_{eNO} (25 *versus* 21) and lower for BPT by exercise (6 *versus* 8), FEV_1 (−0.6 *versus* −0.8) and bronchodilator reversibility (2 *versus* 10).

The accuracy was higher pre-BPT than post-BPT for spirometry (AUC 0.71 for FEV_1/FVC and 0.65 for FEV_1 *versus* 0.66 and 0.62, respectively) and bronchodilator reversibility (AUC 0.72 *versus* 0.58) and lower for the BPTs (AUC 0.70 for exercise, 0.68 for methacholine and 0.60 for mannitol *versus* 0.74, 0.81 and 0.68, respectively). Accuracy was best for F_{eNO} measurement, bronchodilator reversibility, FEV_1/FVC ratio and BPT by methacholine and by exercise (AUC 0.78, 0.72, 0.71, 0.70 and 0.70, respectively).

TABLE 2 Diagnostic accuracy of respiratory symptoms in the past 12 months to diagnose asthma

	A^+S^+	A^-S^+	A^+S^-	A^-S^-	Sensitivity	Specificity	PPV	NPV	Youden's index[#]
Any wheeze	64	16	16	15	80 (70–88)	48 (30–67)	80 (70–88)	48 (30–67)	0.28
>3 attacks of wheeze	35	3	45	28	44 (33–55)	90 (74–98)	92 (79–98)	38 (27–50)	0.34
Wheeze with colds	32	11	48	20	40 (29–52)	65 (45–81)	74 (59–86)	29 (19–42)	0.05
Wheeze apart from colds	54	13	26	18	68 (56–78)	58 (39–75)	81 (69–89)	41 (26–57)	0.26
Exercise-induced wheeze	54	16	26	15	68 (56–78)	48 (30–67)	77 (66–86)	37 (22–53)	0.16
Wheeze triggered by:									
Pollen	31	5	37	24	46 (33–58)	83 (64–94)	86 (71–95)	39 (27–53)	0.29
House dust	19	2	46	26	29 (19–42)	93 (76–99)	90 (70–99)	36 (25–48)	0.22
Pets	20	0	50	17	29 (18–41)	99 (80–99)	99 (83–99)	25 (16–37)	0.28
Awakening due to wheeze	33	3	47	28	41 (30–53)	90 (74–98)	86 (71–95)	37 (26–49)	0.31
Cough lasting >4 weeks	11	10	68	21	14 (7–24)	68 (49–83)	52 (30–74)	24 (15–34)	−0.18
Night cough	38	10	42	20	48 (36–59)	67 (47–83)	79 (65–90)	32 (21–45)	0.15
Cough more than others	28	9	52	21	35 (25–46)	70 (51–85)	76 (59–88)	29 (19–41)	0.05
Dyspnoea	21	4	58	26	27 (17–38)	87 (69–96)	84 (64–95)	31 (21–42)	0.14
Hay fever[¶]	40	9	38	22	51 (40–63)	71 (52–86)	82 (68–91)	37 (25–50)	0.22
Eczema[¶]	21	5	58	25	27 (17–38)	83 (65–94)	81 (61–93)	30 (21–41)	0.10

Data are presented as n or % (95% CI), unless otherwise stated. n=111. A^+S^+: children with asthma diagnosis and reported symptom; A^-S^+: children without asthma diagnosis but with symptom; A^+S^-: children with asthma diagnosis but without symptom; A^-S^-: children without asthma and without symptom; PPV: positive predictive value; NPV: negative predictive value. [#]: sensitivity+specificity−1; [¶]: ever in the past.

TABLE 3 Diagnostic accuracy of clinical tests to diagnose asthma

	A^+T^+	A^-T^+	A^+T^-	A^-T^-	Sensitivity	Specificity	PPV	NPV	Youden's index[#]	AUC
Clinical tests										
Skin-prick test[¶]										0.70
⩾1 positive test	69	18	8	12	90 (81–95)	40 (23–59)	79 (69–87)	60 (32–81)	0.30	
⩾2 positive tests[+]	61	14	16	16	79 (68–88)	53 (34–72)	81 (71–89)	50 (32–68)	0.32	
Skin-prick test[§]										0.72
⩾4 mm	63	16	12	14	84 (74–91)	47 (28–66)	80 (69–88)	54 (33–73)	0.31	
⩾8 mm[+]	46	7	29	23	61 (49–72)	77 (58–90)	87 (75–95)	44 (30–59)	0.38	
F_{eNO}										0.80
⩾21 ppb[+]	47	4	33	27	59 (47–70)	87 (70–96)	92 (81–98)	45 (32–58)	0.46	
⩾22 ppb	44	4	36	27	55 (43–66)	87 (70–96)	92 (80–98)	43 (30–56)	0.42	
⩾25 ppb	40	2	40	29	50 (39–61)	94 (79–99)	95 (84–99)	42 (30–55)	0.44	
⩾35 ppb	31	2	49	29	39 (28–50)	94 (79–99)	94 (80–99)	37 (26–49)	0.33	
Spirometry										
FEV_1/FVC										0.66
<70%	6	0	74	30	8 (3–16)	99 (88–99)	99 (54–99)	29 (20–39)	0.08	
<80%[+]	37	2	43	28	46 (35–58)	93 (78–99)	95 (83–99)	39 (28–52)	0.40	
<90%	66	22	14	8	83 (72–90)	27 (12–46)	75 (65–84)	36 (17–59)	0.09	
FEV_1										0.62
⩽−0.8[+]	35	7	45	24	44 (33–56)	77 (59–90)	83 (69–93)	35 (24–47)	0.21	
⩽−1.0	28	5	52	26	35 (25–47)	84 (66–95)	85 (68–95)	33 (23–45)	0.19	
Bronchodilator reversibility										0.58
⩾10% increase FEV_1[+]	20	3	54	26	27 (17–39)	90 (73–98)	87 (66–97)	33 (22–44)	0.17	
⩾12% increase FEV_1	16	3	58	26	22 (13–33)	90 (73–98)	84 (60–97)	31 (21–42)	0.11	
BPT										
Exercise										0.74
⩾8% decrease FEV_1[+]	47	5	28	19	63 (51–74)	79 (58–93)	90 (79–97)	40 (26–56)	0.42	
⩾10% decrease FEV_1	39	4	36	20	52 (40–64)	83 (63–95)	91 (78–97)	36 (23–50)	0.35	
⩾12% decrease FEV_1	33	2	42	22	44 (33–56)	92 (73–99)	94 (81–99)	34 (23–47)	0.36	
Methacholine										0.81
PD_{20} <0.7 mg[+]	62	8	13	21	83 (72–90)	72 (53–87)	89 (79–95)	62 (44–78)	0.55	
PD_{20} <1 mg	64	9	11	20	85 (75–92)	69 (49–85)	88 (78–94)	65 (45–81)	0.54	
Mannitol										0.68
PD_{15} <635 mg[+]	31	1	49	30	39 (28–50)	97 (83–99)	97 (84–99)	38 (27–50)	0.36	

Data are presented as n or % (95% CI), unless otherwise stated. n=111. Cut-offs chosen based on proposed cut-offs from previous publications. A^+T^+: children with asthma diagnosis and positive test result; A^-T^+: children without asthma diagnosis but positive test result; A^+T^-: children with asthma diagnosis but negative test result; A^-T^-: children without asthma and negative test result; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve; F_{eNO}: exhaled nitric oxide fraction; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BPT: bronchial provocation test; PD_{20}: provocation dose causing a 20% decrease of FEV_1 from baseline; PD_{15}: provocation dose causing a 15% decrease of FEV_1 from baseline. [#]: sensitivity+specificity−1; [¶]: number of allergens for which the skin-prick test is positive: wheal size ⩾3 mm; [+]: cut-off with maximum combined sensitivity and specificity (highest Youden's index); [§]: cumulative wheal size.

Discussion

This is the first study to systematically assess the diagnostic accuracy of reported symptoms and a range of tests in asthma diagnosis in children compared to a defined reference standard (doctor-diagnosed asthma based on all available measurements and information). The main analysis and sensitivity analysis showed broadly comparable results, suggesting that a history of frequent wheeze, awakening due to wheeze and wheeze triggered by pollen or pets, F_{eNO} measurement, BPT by methacholine and BPT by exercise have the best ability to distinguish asthma from no asthma. FEV_1, FEV_1/FVC ratio and bronchodilator reversibility had low accuracy.

Only three other studies have assessed the accuracy of symptoms to diagnose asthma in school-aged children consecutively referred to paediatric hospitals [20–22]. They all found that reported wheeze was sensitive (range 0.75–0.86), but not specific (0.64–0.73) and that frequent wheeze and awakening due to dyspnoea were specific (0.84–0.90), but not sensitive (0.33–0.54), which is in line with our findings. Symptom definitions differed between studies, especially those for cough, which results in a wide range of sensitivities and specificities that cannot be compared [20–22]. Five other studies assessed the accuracy of diagnostic tests in school-aged children. Woo *et al.* [23] found that positive skin-prick tests were sensitive, but not specific (sensitivity and specificity 0.68 and 0.32, respectively) and that F_{eNO} had the best cut-off at 22 ppb (0.57 and 0.87, respectively), which was comparable with our study (21 ppb, 0.59 and 0.87,

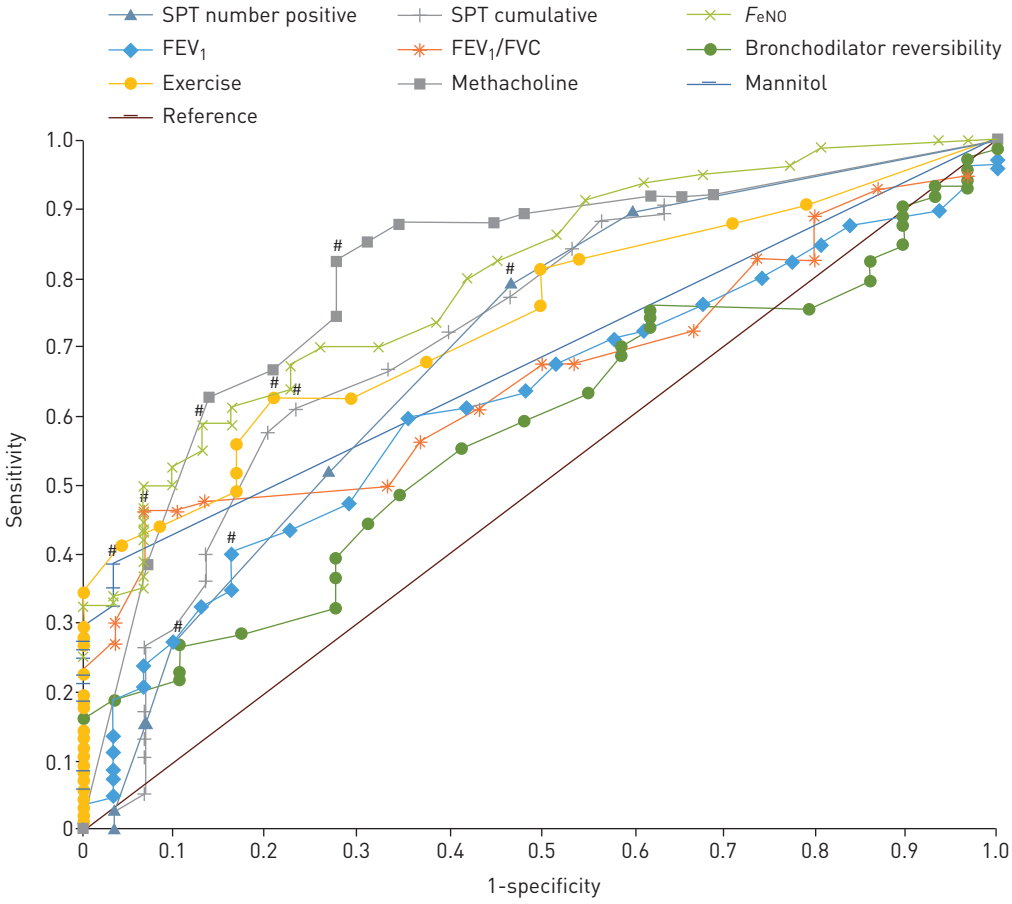

FIGURE 2 Receiver operating characteristic (ROC) curve of clinical tests to diagnose asthma. Test (unit): skin-prick test (SPT) number positive (decrease of 1 positive SPT); SPT cumulative wheal size (decrease of 1 mm cumulative wheal size); exhaled nitric oxide fraction (F_{eNO}) (decrease of 1 ppb); forced expiratory volume in 1 s (FEV_1) (increase of 0.1 z-score); FEV_1/forced vital capacity (FVC) (increase of 1%); bronchodilator reversibility (increase of 1% in FEV_1); exercise (decrease of 1% in FEV_1); methacholine (increase of 0.1 mg methacholine); mannitol (increase of 5 mg mannitol). #: cut-off with maximum combined sensitivity and specificity.

respectively). Grzelewski *et al.* [24] found that a FEV_1/FVC ratio of <80% was specific (0.91), but not sensitive (0.12) for asthma, which is in line with our findings (<79%; 0.90 and 0.46, respectively). For the bronchodilator reversibility test, Galant *et al.* [25] and Dundas *et al.* [26] found a 9% increase in FEV_1 to be the best cut-off to diagnose asthma, which is in line with our findings (10%); however, they compared children with asthma to healthy children. For BPT by exercise, Avital *et al.* [27] found an 8% decrease in FEV_1 to be the best cut-off for asthma diagnosis, which is the same as we found. For BPT by methacholine, Zaczeniuk *et al.* [28] reported a best cut-off of <0.7 mg, which was in line with our study. Anderson *et al.* [29] found a sensitivity of 0.63 and specificity of 0.81 for the widely used best cut-off of <635 mg for BPT by mannitol, while we found a lower sensitivity and higher specificity (0.43 and 0.93, respectively).

The recent National Institute for Health and Care Excellence (NICE) asthma diagnostic algorithm has been questioned in children. Murray *et al.* [5] tested the algorithm in the Manchester Asthma and Allergy Study, a population-based cohort of 1184 children aged 13–16 years, of whom 89 were symptomatic, but not regularly inhaling corticosteroids. However, the Manchester study relied on parent-reported data to define asthma (reported wheeze and asthma treatment in the past 12 months plus a doctor diagnosis of asthma ever in life) and compared children with asthma to healthy children, leaving out from the analysis all those with possible asthma. In clinical practice we want to distinguish children with asthma from children with respiratory symptoms due to other causes, not from healthy children. If we had applied the NICE algorithm to our clinical population, only four out of the 111 children would have been diagnosed with asthma at the initial visit (FEV_1/FVC ratio <70% and bronchodilator reversibility of ⩾12%). 106 would have needed 2 weeks peak expiratory flow monitoring followed by a second visit. In addition, we

found that less stringent cut-off values had higher sensitivity and specificity than those recommended by the NICE algorithm (FEV_1/FVC ratio <80% *versus* <70%, bronchodilator reversibility ⩾10% *versus* ⩾12% and F_{eNO} ⩾26 ppb *versus* ⩾35 ppb, respectively). This highlights the need to base diagnostic algorithms for children on clinical studies done in children, rather than in adults.

A main strength of our study is that it represents a real-life situation in everyday paediatric practice. With the clinical design, it reflects the typical mix of patients in a paediatric outpatient clinic. All children were first-time referrals for evaluation of possible asthma, which is the patient group the diagnostic tests are intended for. Therefore, the study population is representative of daily clinical practice, in contrast to many published studies that selectively include well-defined moderate-to-severe asthmatics comparing them to healthy controls and excluding patients with unclear degrees of airway reactivity. In addition, our patients had an extensive array of examinations for lung function, BPT and allergy, which allowed us to assess the accuracy of different symptoms and diagnostic tests simultaneously.

An important limitation of this study was that the reference standard for asthma diagnosis (the final diagnosis by the physician) took into account the results of the patient history and diagnostic tests for which the accuracy was assessed. However, as there is no single objective test to diagnose asthma and be used as a comparator, the clinician's judgement, taking into account the full history, examination and test results, is the best we can do. The sensitivity analysis using the physicians' diagnosis before BPTs were performed, showed comparable results. However, the small differences highlight the dependence of the physician's diagnosis on the array of tests performed. The reference diagnosis of asthma was made by experienced paediatric pulmonologists (three in Basel and two in St Gallen), trained in Switzerland, who met several times prior to and during the study to standardise their procedures and minimise centre-specific effects. In this study we restricted analysis to basic clinical tests. The advantage of this approach is that most of these tests are available in clinical routine. However, future studies should also evaluate the diagnostic accuracy of newer techniques such as component-resolved IgE diagnostic, multiple-breath or single-breath washout techniques.

Our findings, which need to be replicated in other populations of patients, will help to propose a more evidence-based paediatric diagnostic algorithm, which incorporates both information on symptoms and objective measures. This might be helpful in reducing the need for trials of asthma treatment, which can be costly, time consuming and can lead to misdiagnosis and overtreatment. Our study is therefore an important contribution to the small body of evidence about the value of different tests for the diagnosis of paediatric asthma on which guidelines should be based. Mild paediatric asthma is a disease with highly variable activity and paroxysmal clinical manifestation. It seems unlikely that any test performed at a specific time point will be accurate enough to either prove or exclude reactive airway disease. Future studies should ideally be larger, to allow analysing the value of combination of several tests, and focus on children newly referred for evaluation of possible asthma, and be referenced to a clearly defined and robust reference diagnosis.

Our results suggest that, until more evidence is available, diagnosis of asthma in school-aged children should rely primarily on reported triggers and severity of wheeze and results of F_{eNO}, and, if available, methacholine and exercise challenge testing which were most accurate in our study.

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