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Early View

Original article

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

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**Take Home Message (177/256 characters):** Diagnosing asthma in children is most accurately done by using information on triggers and severity of wheeze and by FeNO measurement, methacholine and exercise challenge tests.

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**Author Contributions:** Claudia Kuehni and Juerg Barben conceptualised and designed the study. Daniel Trachsel and Juerg Barben supervised data collection. Carmen de Jong analysed the data and drafted the manuscript. Eva Pedersen and Myrofora Goutaki supported the statistical analysis and gave input for interpretation of the data. All authors critically revised the manuscript and approved the final manuscript as submitted.

**Keywords**: asthma, wheeze, diagnostic testing, cohort, children, Switzerland

**Abstract (236/250)**

**Introduction**: There are little 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 fractional exhaled nitric oxide (FeNO), 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 (>3 attacks/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 FeNO measurement (0.80) and BPT by methacholine (0.81) or exercise (0.74), and lowest for FEV1 (0.62) and FEV1/FVC (0.66), assessed by spirometry.

**Conclusion**: This study suggests that specific questions about triggers and severity of wheeze, measurement of FeNO 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.

**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. Diagnostic guidelines thus 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 FeNO [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 little 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. Also, papers used different cut-offs for positive tests (e.g. for FeNO or FEV1), 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 done 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 four 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 FeNO, spirometry, exercise 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 next few days to perform the methacholine challenge test. Within a week all children repeated the FeNO 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, FeNO

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, FeNO measurement, spirometry and also results of the bronchial provocation tests 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 ISAAC key questions for lower respiratory symptoms and more detailed questions on wheeze and cough derived from the questionnaires used in the Leicester respiratory cohort studies (see supplementary material) [7, 8]. All diagnostic tests were performed according to published guidelines [9-13]. Children withheld short acting $beta_2$-agonists for 8 hours, inhaled corticosteroids, leukotriene antagonists, and long acting $beta_2$-agonists for 24 hours, and antihistamines and sodium cromoglycate for >72 hours.

Skin prick test

We performed skin prick tests using birch, grass, mugwort, alternaria, cat, house dust mites (*D. pteronyssinus*), histamine and saline. A wheal size of ≥3 mm was considered positive in case the positive control (histamine) had a wheal size of ≥3 mm and the negative control (saline) had a wheal size of <3mm. These allergens cover 95% of allergies to inhaled allergens in Switzerland [14].

Fractional exhaled nitric oxide

Fractional exhaled nitric oxide (FeNO) was measured in doublets before spirometry, using the portable multi-gas analyser (NIOX MINO®, Aerocrine, 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, has an accuracy of ±10% with a minimum of ±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 GmbH, Würzburg, Germany), using JLAB software (version 4.34). Spirometry was done 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 also checked by the responsible paediatric pulmonologist. Results are expressed as proportion ($FEV_1$/FVC) and as z-scores based on GLI-2012 reference standards [17].

Bronchial provocation tests

For all bronchial provocation tests, 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 (PD20) and the mannitol BPT as provocation dose causing a 15% decrease of $FEV_1$ from baseline (PD15). After the methacholine BPT, all children were given 4 puffs of salbutamol 100 μg to test for bronchodilator reversibility. Children also received salbutamol if 15 minutes after the exercise or mannitol BPT, $FEV_1$ had not returned within 5% of baseline or in case of dyspnoea. More details on the bronchial provocation tests 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 (CI) 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, Texas) 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 age was 12 years (range 6-16) 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 were done. 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) (table S1). None of the children was diagnosed with a severe lung disease such as Cystic Fibrosis [18].

**Table 1.** Characteristics of the study participants (N=111)

| | Total n% | |
|---|---|---|
| Age, median (range) | 11 | (6-16) |
| Sex, male | 69 | (62) |
| **Respiratory symptoms in the last 12 months** | | |
| Any wheeze | 80 | (72) |
| More than 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 longer than 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 B2-agonist, alone | 49 | (44) |
| ICS + short-acting B2-agonist | 6 | (5) |
| ICS + long-acting B2-agonist | 16 | (14) |

*Ever in the past, ICS = inhaled corticosteroids

**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 (>3 attacks/year) wheeze (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).

**Table 2.** Diagnostic accuracy of respiratory symptoms to diagnose asthma N=111

| | A+S+ n | A-S+ n | A+S- n | A-S- n | Sens % (95%CI) | Spec % (95%CI) | PPV % (95%CI) | NPV % (95%CI) | YI |
|---|---|---|---|---|---|---|---|---|---|
| **Respiratory symptoms in the past 12 months** | | | | | | | | | |
| 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 > 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 |

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, Sens = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value YI = Youden's-Index = Sensitivity + Specificity -1, *Ever in the past

**Diagnostic accuracy of tests to diagnose asthma**

All 111 children completed SPT, FeNO, 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 table S2.

The cut-off values with the best diagnostic accuracy were <80% for FEV1/FVC, ≤-0.8 z-score for FEV1, ≥8% decrease of FEV1 for BPT by exercise, PD-20 <0.7mg for BPT by methacholine, PD-15 <635mg for

BPT by mannitol, ≥2 for the number of positive skin prick tests, ≥8mm for the cumulative wheel size of skin prick tests, and ≥21ppb for FeNO (table 3).

Accuracy overall was best for FeNO, BPT by methacholine and BPT by exercise (AUC 0.80, 0.81, 0.74 respectively). Accuracy was lower for BPT by mannitol, and skin prick test (AUC around 0.70), and lowest for spirometry (AUC 0.66 and 0.62 for FEV1 and FEV1/FVC respectively) (figure 2).

**Table 3.** Diagnostic accuracy of clinical tests to diagnose asthma N=111

| | A+T+ n | A-T+ n | A+T- n | A-T- n | Sens % (95%CI) | Spec % (95%CI) | PPV % (95%CI) | NPV % (95%CI) | YI | AUC |
|---|---|---|---|---|---|---|---|---|---|---|
| **Clinical tests** | | | | | | | | | | |
| Skin prick test[1] | | | | | | | | | | 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[2] | | | | | | | | | | 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 | |
| FeNO | | | | | | | | | | 0.80 |
| ≥21ppb* | 47 | 4 | 33 | 27 | 59 (47-70) | 87 (70-96) | 92 (81-98) | 45 (32-58) | 0.46 | |
| ≥22ppb | 44 | 4 | 36 | 27 | 55 (43-66) | 87 (70-96) | 92 (80-98) | 43 (30-56) | 0.42 | |
| ≥25ppb | 40 | 2 | 40 | 29 | 50 (39-61) | 94 (79-99) | 95 (84-99) | 42 (30-55) | 0.44 | |
| ≥35ppb | 31 | 2 | 49 | 29 | 39 (28-50) | 94 (79-99) | 94 (80-99) | 37 (26-49) | 0.33 | |
| Spirometry | | | | | | | | | | |
| FEV1/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 | |
| FEV1 | | | | | | | | | | 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 rev. | | | | | | | | | | 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 <0.7mg* | 62 | 8 | 13 | 21 | 83 (72-90) | 72 (53-87) | 89 (79-95) | 62 (44-78) | 0.55 | |
| PD-20 <1mg | 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 | |

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, Sens = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value, YI = Youden's-Index = Sensitivity + Specificity -1, AUC = area under the curve, FeNO = fractional exhaled nitric oxide, ppb = parts per billion, $FEV_1$ = forced expiratory volume in 1 second, FVC = forced vital capacity, Bronchodilator rev. = bronchodilator reversibility, BPT = bronchial provocation test

Cut-offs chosen based on proposed cut-offs from previous publications

*Cut-off with maximum combined sensitivity and specificity (highest Youden's-Index)

[1] Number allergens for which the skin prick test is positive: wheel size ≥3

[2] Cumulative wheel size

**Sensitivity analysis**

In the sensitivity analysis with asthma diagnosis based on the pre BPTs 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. Night cough and hay fever also had a high Youden's index for the asthma diagnosis pre BPTs (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 (table S4 and Figure S1). Cut-offs were higher for FeNO (25 vs. 21) and lower for BPT by exercise (6 vs. 8), FEV1 (-0.6 vs. -0.8) and bronchodilator reversibility (2 vs. 10).

The accuracy was higher for spirometry (AUC 0.71 and 0.65 versus 0.66 and 0.62 post BPT) and bronchodilator reversibility (AUC 0.72 versus 0.58 post BPT) and lower for the BPTs (AUC 0.70, 0.68 and 0.60 versus 0.74, 0.81 and 0.68 post BPT). Accuracy was best for FeNO measurement, bronchodilator reversibility, FEV1/FVC and BPT by methacholine and by exercise (AUC 0.78, 0.72, 0.71, 0.70, 0.70).

**Discussion**

This is the first study that systematically assessed 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, FeNO measurement, BPT by methacholine and BPT by exercise have the best ability to distinguish asthma from no asthma. FEV1, FEV1/FVC and bronchodilator reversibility had a low accuracy.

Only three other studies 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 (ranging 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. found that a positive skin prick tests were sensitive but not specific (sensitivity/specificity 0.68/0.32) and that FeNO had the best cut-off at 22 ppb (0.57/0.87), which was comparable with our study (21ppb, 0.59/0.87)) [23]. Grzelewski et al. found that a FEV1/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, 0.46) [24]. For the bronchodilator reversibility test, Galant et al. and Dundas et al. found a 9% increase in FEV1 to be the best cut-off to diagnose asthma, which is in line with our finding (10%), however they compared children with asthma to healthy children [25, 26]. For BPT by exercise, Avital et al. found an 8% decrease in FEV1 to be the best cut-off for asthma diagnosis, which is the same as we found [27]. For BPT by methacholine, Zaczeniuk et al. reported a cut off of <0.7 mg as best, which was in line with our study [28]. Anderson et al 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) [29].

The recent NICE asthma diagnostic algorithm has been questioned in children. Murray et al. tested the algorithm in the Manchester Asthma and Allergy Study, a population-based cohort of 1184 children aged 13-16 years of which 89 were symptomatic but not regularly inhaling corticosteroids [5]. 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 would have applied the NICE algorithm to our clinical population, only 4 of the 111 children would have been diagnosed with asthma at the initial visit (FEV1/FVC <70% and bronchodilator responsibility of ≥12%). 106 would have needed 2 weeks peak expiratory flow monitoring followed by a second visit. We also found that less stringent cut off values

had higher sensitivity and specificity than those recommended by the NICE algorithm (FEV1/FVC <80% vs. <70%, bronchodilator reversibility ≥10% vs. ≥12% and FeNO ≥26ppb vs. ≥35ppb, 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 this 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 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. The small differences, however, highlight the dependence of the physician's diagnosis on the array of tests done. The reference diagnosis of asthma was made by experienced paediatric pulmonologists (3 in Basel and 2 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 FeNO, and if available methacholine and exercise challenge testing which were most accurate in our study.

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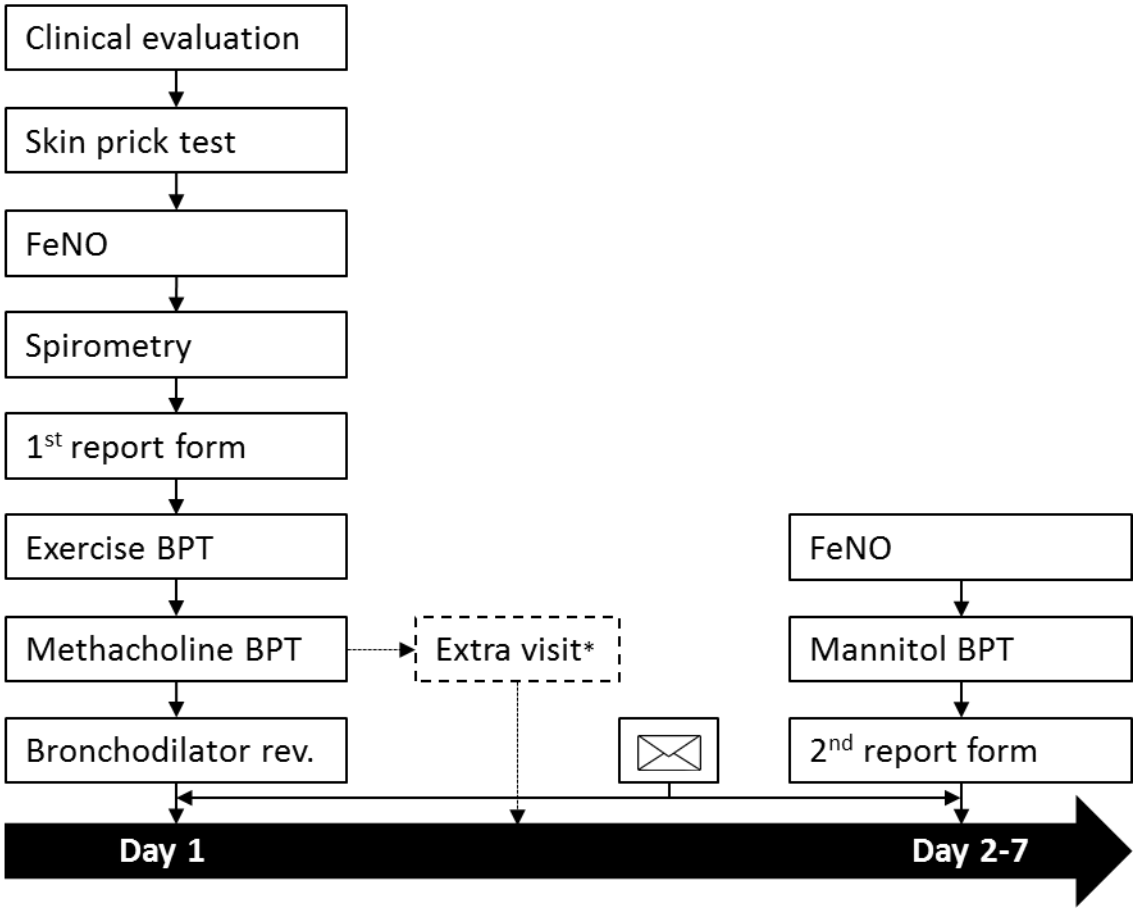


**Figure 1**. Study procedures. The report form is a standardised form for physicians to note down the clinical diagnosis. BPT: bronchial provocation test. Bronchodilator rev.: Bronchodilator reversibility. *Children who received salbutamol after the exercise BPT conducted the methacholine BPT at an extra visit. ✉ Between visits the family completed a questionnaire.

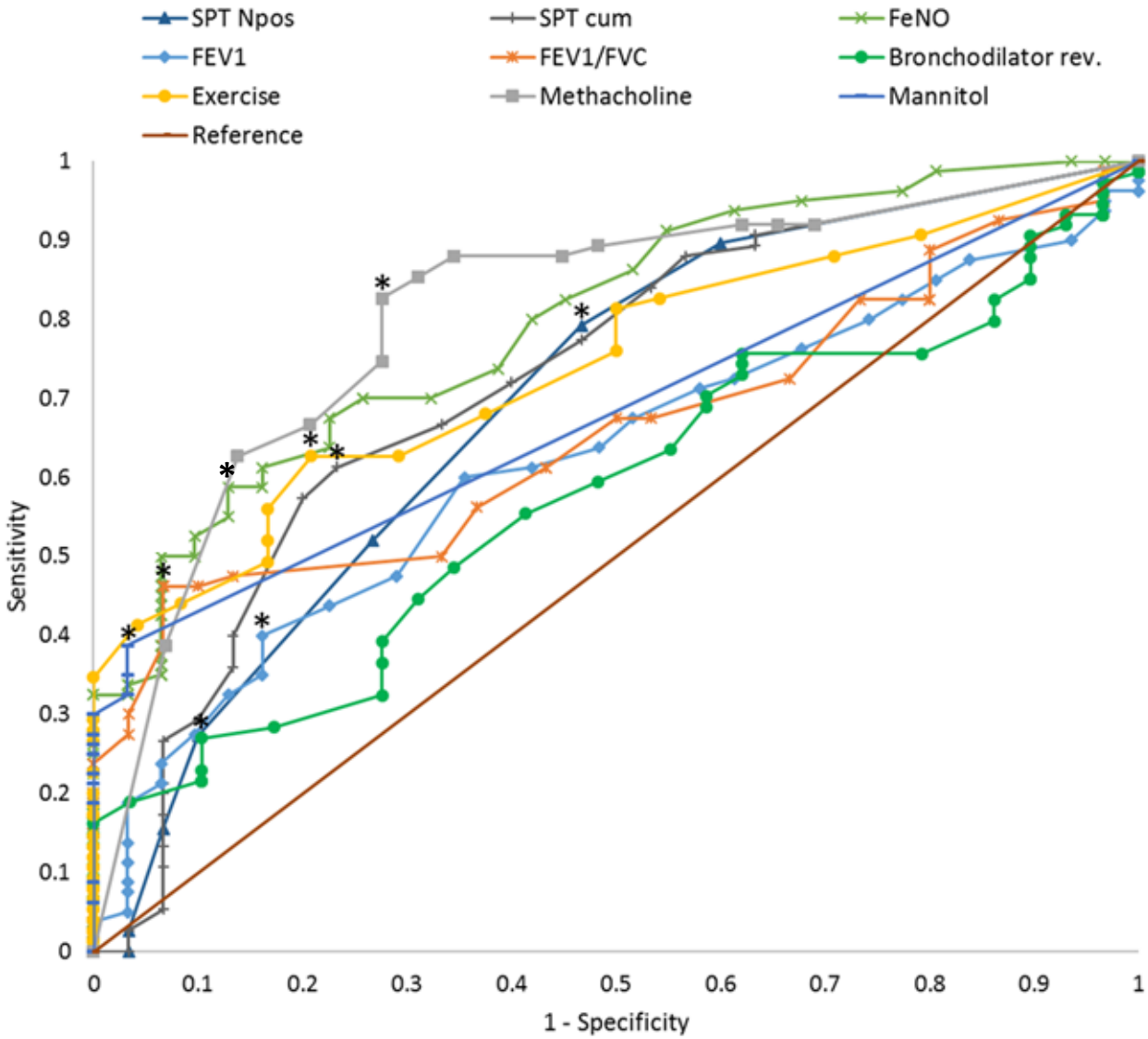


**Figure 2** Receiver operating characteristics (ROC) curve of clinical tests to diagnose asthma.
* Cut-off with maximum combined sensitivity and specificity

| **Test** | **Unit** |
|---|---|
| SPT number positive | decrease of 1 positive skin prick test |
| SPT cumulative wheel size | decrease of 1 mm cumulative wheel size |
| FeNO | decrease of 1 parts per billion (ppb) |
| FEV1 | increase of 0.1 z-score |
| FEV1/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 |

**Supplementary text:**

**Methods of bronchial provocation tests**

For all bronchial provocation tests, baseline $FEV_1$ was measured in triplicate using ATS criteria for paediatric lung function testing [1] and the best measurement was recorded. Children were excluded from the challenge if their baseline $FEV_1$ was ≤65% of predicted or if they were unwilling to cooperate. If 15 minutes after the bronchial provocation test, FEV1 had not returned within 5% of baseline or in case of dyspnoea, salbutamol 100 μg (2-4 puffs Ventolin® pMDI via spacer) was given to reverse the bronchoconstriction.

Exercise provocation test

The children performed the exercise challenge using a treadmill (T-2100, GE Healthcare, Freiburg, Germany) or a bicycle ergometer (ER Ergoselect 200, Ergoline GmbH, Bitz, Germany) for 8 min, inspiring room air according to published ATS and ERS guidelines [2, 3]. At one site, children chose between treadmill and bicycle, at the other only a treadmill was available. We performed exercise testing under controlled conditions (maintaining inspired air temperature at 20–25°C and humidity of <10 mg water/L) [4] and measured heart rate and oxygen saturation by pulse oximeter with a forehead sensor (Nellcor N595 OxiMax, Tyco Healthcare, Neustadt/Donau, Germany). After baseline spirometry we started exercise testing at 60% target workload (defined as Watt = measured $FEV_1$ x 53.76-11.07), rapidly increasing workload aiming at 75% of the target in the second minute, 90% in the third minute, and 100% in the fourth minute, sustaining the latter for ≥4 min. We increased workloads more rapidly if the heart rate was not expected to reach at least 85% of the predicted maximum (220-age in years).[2] Spirometry was performed 1, 3, 5, 7, 10, and 15 min after exercise, in duplicate [5].

We reported the results as the maximum fall of $FEV_1$ during the exercise provocation test.

Methacholine provocation test

The children performed the methacholine provocation test based on the Five-Breath Dosimeter Protocol [2, 4]. They first inhaled NaCL 0.9% to measure baseline values, then they inhaled stepwise 0.05mg, 0.05mg, 0.2mg, 0.3mg, 0.6mg and 1.2mg of methacholine (cumulative dose of 2.4 mg in children <14 years old) via a nebulizer. Children older than 14 years old had an additional inhalation step with a cumulative dose of 3.2mg methacholine. At end exhalation during tidal breathing, the children inhaled slowly and deeply from the nebulizer. The dosimeter was triggered after the inhalation begins, and the subject was encouraged to continue inhaling slowly and to hold the breath for another 5 seconds. This step was repeated for a total of five inspiratory capacity inhalations which should not take more than 2 minutes. The challenge was terminated when $FEV_1$ fell by 20% or more, or the highest dose was given. Lung function was measured in 5-min intervals until it had returned to within 5% of the baseline value. We reported the results of the methacholine provocation test as provocation dose causing a 20% decrease of $FEV_1$ from baseline (PD-20).

Mannitol dry powder provocation test

The mannitol provocation test was performed according to the protocol recommended by Anderson et al. [6], with slight modifications [7, 8]. Baseline $FEV_1$ was measured in triplicate and the highest of these measures was recorded. The mannitol dry powder (MDP) provocation test (AridolTM, Pharmaxis, French Forests, New South Wales, Australia) was conducted as described in our previous study [8]. The children were asked to inhale the

contents of an MDP capsule through the delivery device (OsmohalerTM). The following dosing steps were used: 0 mg (empty capsule acting as a placebo to measure baseline $FEV_1$), 5, 10, 20, 40, 80, 160, 160, and 160 mg. We administered multiples of 40 mg capsules to achieve doses of 80 mg and more. After each dose, children performed a 5-sec breath-hold, followed one minute later by spirometry in duplicate, and the higher FEV1 was recorded. If the children had a decrease in $FEV_1$ >10%, then the dose producing this was repeated for safety reasons. This process was repeated until either $FEV_1$ had fallen by 15% or the subject had reached the maximum dose (cumulative dose of 635 mg mannitol). We reported the results of the mannitol provocation test as provocation dose causing a 15% decrease of $FEV_1$ from baseline (PD-15).

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## Supplementary tables and figure

**Table S1.** Diagnoses in children with suspected asthma N=111

| | Diagnoses pre-BPTs[1] n (%) | | Diagnoses post-BPTs[1] n (%) | |
|---|---|---|---|---|
| **Definite diagnoses** | 79 | (71) | 97 | (87) |
| Asthma | 65 | (59) | 68 | (61) |
| Cough not due to asthma | 9 | (8) | 14 | (13) |
| ILO[2]/vocal cord dysfunction | 3 | (3) | 6 | (5) |
| Functional symptoms / hyperventilation | 0 | (0) | 7 | (6) |
| Adenoid hyperplasia with OSAS[3] | 1 | (1) | 1 | (1) |
| Recurrent colds | 1 | (1) | 1 | (1) |
| **Probable diagnoses** | 32 | (29) | 14 | (13) |
| Asthma | 29 | (26) | 12 | (11) |
| ILO[2]/vocal cord dysfunction | 3 | (3) | 2 | (2) |

[1] Bronchial Provocation Tests

[2] Inducible Laryngeal Obstruction

[3] Obstructive Sleep Apnoea Syndrome

**Table S2.** Diagnostic test results in patients with and without asthma N=111

| | Asthma | | | | | |
|---|---|---|---|---|---|---|
| | **Definite asthma** | | **Other diagnosis** | | **Probable asthma** | |
| | N=68 | | N=31 | | N=12 | |
| **Diagnostic tests** | median (IQR) | | median (IQR) | | median (IQR) | |
| Skin prick test (N=107) | | | | | | |
| ≥1 positive test n(%) | 29 | (43) | 7 | (23) | 5 | (42) |
| Number of positive tests* | 3 | (2-4) | 2 | (0-3) | 2 | (1-3) |
| Cum wheel size in mm± | 9 | (5-14) | 5 | (0-8) | 7 | (0-9) |
| FeNO (N=111) | | | | | | |
| Parts per billion | 30 | (14-62) | 10 | (6-16) | 14 | (9-22) |
| Spirometry (N=111) | | | | | | |
| FEV1, z-scores | -0.5 | (-1.2-0.3) | -0.1 | (-0.5-0.4) | -1.0 | (-2.2--0.2) |
| FEV1/FVC | 83 | (75-89) | 87 | (83-90) | 78 | (71-89) |
| Bronchodilator rev. (N=103) | | | | | | |
| Increase in FEV1 in % | 4 | (-5-14) | 1 | (-5-8) | 3 | (-1-6) |
| Bronchial provocation test | | | | | | |
| Exercise (N=99) | | | | | | |
| Decrease in FEV1 in %° | 12 | (6-19) | 4 | (1-7) | 5 | (1-6) |
| Methacholine (N=104) | | | | | | |
| Provocation dose in mg“ | 0.1 | (0.1-0.3) | 2.4 | (0.3-3.2) | 0.3 | (0.1-1.6) |
| Mannitol (N=111) | | | | | | |
| Provocation dose in mg# | 635 | (190-635) | 635 | (635-635) | 635 | (635-635) |

° median (and inter quartile range) fall in FEV1 during exercise

“ median (and inter quartile range) provocation dose for a fall of ≥ 20% in FEV1 (PD-20)

# median (and inter quartile range) provocation dose for a fall of ≥ 15% in FEV1 (PD-15)

* Wheal size ≥3mm

± Cumulative wheel size in mm

Bronchodilator rev. = Bronchodilator reversibility

**Table S3.** Sensitivity analysis of diagnostic accuracy of respiratory symptoms to diagnose asthma pre-BPTs N=111

| | **A+S+** n | **A-S+** n | **A+S-** n | **A-S-** n | **Sens** % (95%CI) | **Spec** % (95%CI) | **PPV** % (95%CI) | **NPV** % (95%CI) | **YI** |
|---|---|---|---|---|---|---|---|---|---|
| **Respiratory symptoms in the past 12 months** | | | | | | | | | |
| Any wheeze | 69 | 11 | 25 | 6 | 73 (63-82) | 35 (14-62) | 86 (77-93) | 19 (7-37) | 0.08 |
| > 3 attacks of wheeze | 36 | 2 | 58 | 15 | 38 (28-49) | 88 (64-99) | 95 (82-99) | 21 (12-32) | 0.26 |
| Wheeze with colds | 36 | 7 | 58 | 10 | 38 (28-49) | 59 (33-82) | 84 (69-93) | 15 (7-25) | -0.03 |
| Wheeze apart from colds | 59 | 8 | 35 | 9 | 63 (52-73) | 53 (28-77) | 88 (78-95) | 20 (10-35) | 0.16 |
| Exercise-induced wheeze | 62 | 8 | 32 | 9 | 66 (55-75) | 53 (28-77) | 89 (79-95) | 22 (11-38) | 0.19 |
| Wheeze triggered by | | | | | | | | | |
| Pollen | 34 | 2 | 47 | 14 | 42 (31-53) | 88 (62-98) | 94 (81-99) | 23 (13-35) | 0.30 |
| House dust | 20 | 1 | 58 | 14 | 26 (16-37) | 93 (68-99) | 95 (76-99) | 19 (11-30) | 0.19 |
| Pets | 20 | 0 | 57 | 10 | 26 (17-37) | 99 (69-99) | 99 (83-99) | 15 (7-26) | 0.25 |
| Awakening due to wheeze | 33 | 3 | 61 | 14 | 35 (26-46) | 82 (57-96) | 92 (78-98) | 19 (11-29) | 0.17 |
| Cough > 4 weeks | 14 | 7 | 79 | 10 | 15 (8-24) | 59 (33-82) | 67 (43-85) | 11 (6-20) | -0.26 |
| Night cough | 45 | 3 | 49 | 13 | 48 (37-58) | 81 (54-96) | 94 (83-99) | 21 (12-33) | 0.29 |
| Cough more than others | 32 | 5 | 61 | 12 | 34 (25-45) | 71 (44-90) | 86 (71-95) | 16 (9-27) | 0.05 |
| Dyspnoea | 23 | 2 | 69 | 15 | 25 (17-35) | 88 (64-99) | 92 (74-99) | 18 (10-28) | 0.13 |
| Hay fever | 46 | 3 | 46 | 14 | 50 (39-61) | 82 (57-96) | 94 (83-99) | 23 (13-36) | 0.32 |
| Eczema | 24 | 2 | 68 | 15 | 26 (17-36) | 88 (64-99) | 92 (75-99) | 18 (10-28) | 0.14 |

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, Sens = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value YI = Youden's-Index = Sensitivity + Specificity -1

**Table S4.** Sensitivity analysis of diagnostic accuracy of clinical tests to diagnose asthma pre BPTs N=111

| | A+T+ n | A-T+ n | A+T- n | A-T- n | Sens % (95%CI) | Spec % (95%CI) | PPV % (95%CI) | NPV % (95%CI) | YI | AUC |
|---|---|---|---|---|---|---|---|---|---|---|
| **Clinical tests** | | | | | | | | | | |
| Skin prick test[1] | | | | | | | | | | 0.69 |
| ≥1 positive test | 79 | 8 | 12 | 8 | 87 (78-93) | 50 (25-75) | 91 (83-96) | 40 (19-64) | 0.37 | |
| ≥2 positive tests* | 70 | 5 | 21 | 11 | 77 (67-85) | 69 (41-89) | 93 (85-98) | 34 (19-53) | 0.46 | |
| Skin prick test[2] | | | | | | | | | | 0.69 |
| ≥4 mm* | 73 | 6 | 16 | 10 | 82 (72-89) | 63 (35-85) | 92 (84-97) | 38 (20-59) | 0.45 | |
| ≥8 mm | 49 | 4 | 40 | 12 | 55 (44-66) | 75 (48-93) | 92 (82-98) | 23 (13-37) | 0.30 | |
| FeNO | | | | | | | | | | 0.78 |
| ≥21ppb | 49 | 2 | 45 | 15 | 52 (42-63) | 88 (64-99) | 96 (87-99) | 25 (15-38) | 0.40 | |
| ≥22ppb | 46 | 2 | 48 | 15 | 49 (38-59) | 88 (64-99) | 96 (86-99) | 24 (14-36) | 0.37 | |
| ≥25ppb* | 42 | 0 | 52 | 17 | 45 (34-55) | 99 (80-99) | 99 (91-99) | 25 (15-36) | 0.44 | |
| ≥35ppb | 33 | 0 | 61 | 17 | 35 (26-46) | 99 (80-99) | 99 (89-99) | 22 (13-33) | 0.34 | |
| Spirometry | | | | | | | | | | |
| FEV1/FVC | | | | | | | | | | 0.71 |
| <70% | 6 | 0 | 88 | 16 | 6 (2-13) | 99 (79-99) | 99 (54-99) | 15 (9-24) | 0.06 | |
| <80% | 39 | 0 | 55 | 16 | 41 (31-52) | 99 (79-99) | 99 (91-99) | 23 (13-34) | 0.41 | |
| <81%* | 40 | 0 | 54 | 16 | 43 (32-53) | 99 (79-99) | 99 (91-99) | 23 (14-34) | 0.43 | |
| <90% | 77 | 11 | 17 | 5 | 82 (73-89) | 31 (11-59) | 88 (79-94) | 23 (8-45) | 0.13 | |
| FEV1 | | | | | | | | | | 0.65 |
| ≤-0.6* | 45 | 2 | 49 | 15 | 48 (38-58) | 88 (64-99) | 98 (85-99) | 23 (14-36) | 0.36 | |
| ≤-0.8 | 40 | 2 | 54 | 15 | 43 (32-53) | 88 (64-99) | 95 (84-99) | 22 (13-33) | 0.31 | |
| ≤-1.0 | 31 | 2 | 63 | 15 | 33 (24-43) | 88 (64-99) | 94 (80-99) | 19 (11-30) | 0.21 | |
| Bronchodilator rev. | | | | | | | | | | 0.72 |
| ≥2% increase $FEV_1$* | 55 | 3 | 32 | 13 | 63 (52-73) | 81 (54-96) | 95 (86-99) | 29 (16-44) | 0.44 | |
| ≥10% increase $FEV_1$ | 23 | 0 | 64 | 16 | 26 (18-37) | 99 (79-99) | 99 (85-99) | 20 (12-30) | 0.26 | |
| ≥12% increase $FEV_1$ | 19 | 0 | 68 | 16 | 22 (14-32) | 99 (79-99) | 99 (82-99) | 19 (11-29) | 0.22 | |
| BPT | | | | | | | | | | |
| Exercise | | | | | | | | | | 0.70 |
| ≥6% decrease $FEV_1$* | 57 | 3 | 29 | 10 | 66 (55-76) | 77 (46-95) | 95 (86-99) | 26 (13-42) | 0.43 | |
| ≥8% decrease $FEV_1$ | 49 | 3 | 37 | 10 | 57 (46-68) | 77 (46-95) | 94 (84-99) | 21 (11-36) | 0.34 | |
| ≥10% decrease $FEV_1$ | 40 | 3 | 46 | 10 | 47 (36-58) | 77 (46-95) | 93 (81-99) | 18 (9-30) | 0.24 | |
| ≥12% decrease $FEV_1$ | 32 | 3 | 54 | 10 | 37 (27-48) | 77 (46-95) | 91 (77-98) | 16 (8-27) | 0.14 | |
| Methacholine | | | | | | | | | | 0.68 |
| PD-20 <0.6mg* | 65 | 5 | 23 | 11 | 74 (63-83) | 69 (41-89) | 93 (84-98) | 32 (17-51) | | |
| PD-20 <0.7mg | 67 | 6 | 21 | 10 | 76 (66-85) | 63 (35-85) | 92 (83-97) | 32 (17-51) | 0.43 | |
| PD-20 <1mg | 67 | 6 | 21 | 10 | 76 (66-85) | 63 (35-85) | 92 (83-97) | 32 (17-51) | 0.39 | |
| Mannitol | | | | | | | | | | 0.60 |
| PD-15 <635 mg* | 30 | 2 | 64 | 15 | 32 (23-42) | 88 (64-99) | 94 (79-99) | 19 (11-29) | 0.20 | |

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, Sens = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value, YI = Youden's-Index = Sensitivity + Specificity -1, AUC = area under the curve, FeNO = fractional exhaled nitric oxide, ppb = parts per billion, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, Bronchodilator rev. = bronchodilator reversibility, BPT = bronchial provocation test

Cut-offs chosen based on proposed cut-offs from previous publications

*Cut-off with maximum combined sensitivity and specificity (highest Youden's-Index)

[1] Number allergens for which the skin prick test is positive: wheel size ≥3

[2] Cumulative wheel size

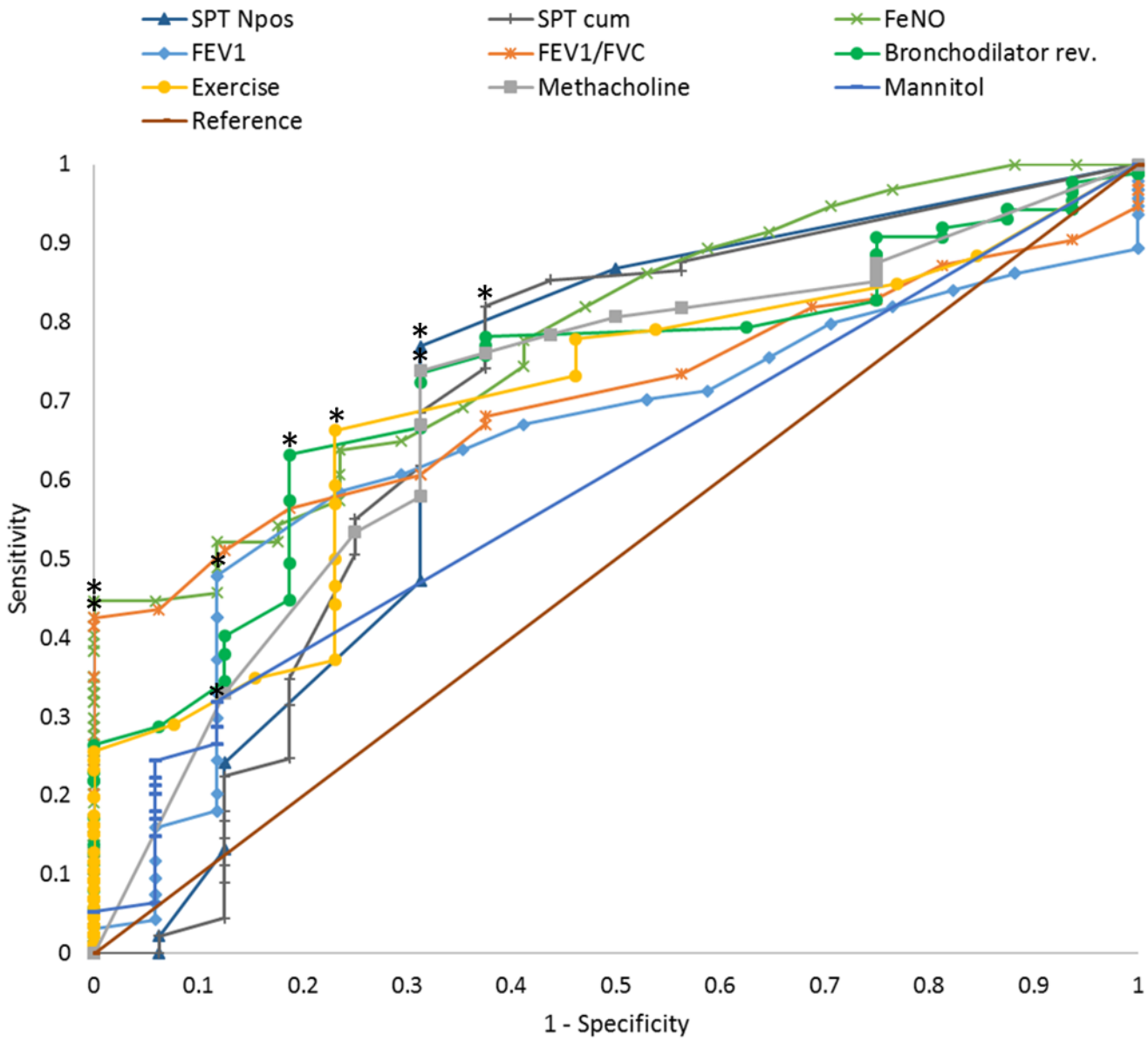


**Figure S1** Receiver operating characteristics (ROC) curve of clinical tests to diagnose asthma. (Sensitivity analysis: pre-BPTs) * Cut-off with maximum combined sensitivity and specificity

| **Test** | **Unit** |
|---|---|
| SPT number positive | decrease of 1 positive skin prick test |
| SPT cumulative wheel size | decrease of 1 mm cumulative wheel size |
| FeNO | decrease of 1 parts per billion (ppb) |
| FEV1 | increase of 0.1 z-score |
| FEV1/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 |

# Supplementary questionnaire 2
# Baseline questionnaire, English translation

# Questionnaire on breathing and allergies

How to fill it in? yes ☐ no ☐ = please, tick the appropriate box
|15 |10 |1998| = please, fill out
_____ = please, write words

## General questions

Date questionnaire completed: |___|___|____|
day month year

Person completing questionnaire: mother ☐ father ☐ child ☐ other ☐ _____
(tick all who helped to fill in)

Last name _____
First name _____
Birthdate |___|___|____| Sex male ☐ female ☐
day month year

## Part 1

1. In the last 12 months, how many times have you had a cold or flu?

None ☐ 1-3 ☐ 4-6 ☐ 7-9 ☐ 10 or more ☐

2. How long does a cold usually last?

Less than a week ☐ 1-2 weeks ☐ 2-4 weeks ☐ More than 4 weeks ☐

3. In the last 12 months, have you had a cough that lasted more than 4 weeks?

yes ☐ no ☐

4. In the last 12 months, have you had a dry cough at night, apart from a cough associated with a cold or a chest infection?

yes ☐ no ☐

5. Do you think that you cough more than other children your age?

yes ☐ no ☐

## Part 2

6. Have you ever had wheezing or whistling in the chest at any time in the past?

yes ☐ no ☐

7. Have you had wheezing or whistling in the chest in the last 12 months?

yes ☐ no ☐

**If you answered "no" to both questions, please skip to part 3.**

8. How many attacks of wheezing have you had during the last 12 months?

None ☐ 1-3 times ☐ 4-12 times ☐ More than 12 times ☐

9. In the last 12 months, have you had wheezing or whistling in the chest during or soon after a cold or flu?

yes ☐ no ☐

10. In the last 12 months, have you had wheezing or whistling in the chest without having a cold or flu?

yes ☐ no ☐

11. In the last 12 months, has your chest sounded wheezy during or after exercise?

yes ☐ no ☐

12. In the last 12 months, which of the following things caused you to wheeze

| | | | |
|---|---|---|---|
| - Exercise (running, sports) | yes ☐ | no ☐ | Don't know ☐ |
| - Laughing or crying | yes ☐ | no ☐ | Don't know ☐ |
| - Pollen (grass, hay, trees, flowers) | yes ☐ | no ☐ | Don't know ☐ |
| - House dust | yes ☐ | no ☐ | Don't know ☐ |
| - Contact with pets or other animals | yes ☐ | no ☐ | Don't know ☐ |
| - Foods or drinks | yes ☐ | no ☐ | Don't know ☐ |

13. In the last 12 months, how often, on average, has your sleep been disturbed due to wheezing?

Never woken up ☐ Less than one night per week ☐ One or more nights per week ☐

14. In the last 12 months, has wheezing ever been severe enough to limit your speech to only one or two words at a time between breaths?

yes ☐ no ☐

15. Have you ever had asthma?

yes ☐ no ☐

16. Do you need to use medication because of these breathing problems?

yes ☐ no ☐

- If yes, how regularly?

Sometimes (less than once per week) ☐ Regularly (1-6 times per week) ☐ Daily ☐

- If yes, which medication? _____

17. In the last 12 months, how much did cough, wheezing or breathlessness interfere with your daily activities (at home or while playing with other kids)

Practically daily ☐ About once a week ☐ About once per month ☐

Less than once per month ☐ Never ☐ Don't know ☐

18. In the last 12 months, how much did cough, wheezing or breathlessness interfere with your sport activities?

Practically daily ☐ About once a week ☐ About once per month ☐

Less than once per month ☐ Never ☐ Don't know ☐

**Part 3**

19. In the last 12 months, have you had a problem with sneezing or a runny or blocked nose when you did not have a cold or flu?

yes ☐ no ☐

20. In the last 12 months, has this nose problem been accompanied by itchy-watery eyes?

yes ☐ no ☐

21. In which of the last 12 months, did these problems occur?

| | | | |
|---|---|---|---|
| January ☐ | February ☐ | March ☐ | April ☐ |
| May ☐ | June ☐ | July ☐ | August ☐ |
| September ☐ | October ☐ | November ☐ | December ☐ |

22. In the last 12 months, how much did these problems interfere with your daily activities?

Not at all ☐ A little ☐ Moderately ☐ Very much ☐

23. Have you ever had hay fever?

yes ☐ no ☐

**Part 4**

24. Have you ever had an itchy rash, which was coming and going for at least six months?

yes ☐ no ☐

25. Have you had this itchy rash at any time in the last 12 months?

yes ☐ no ☐

26. Has this itchy rash affected any of the following places: the folds of the elbows, behind the knees or around the neck, ears or eyes?

yes ☐ no ☐

-If yes, which places were affected by this itchy rash? _____

27. Has this rash cleared completely at any time during the last 12 months?

yes ☐ no ☐

28. In the last 12 months, how often, on average, have you been kept awake at night by this itchy rash?

Never in the last 12 months ☐ Less than 1 night per week ☐ One or more nights per week ☐

29. Have you ever had eczema?

yes ☐ no ☐

**Part 5**

30. Did you ever have problems with your heart?

yes ☐ no ☐

31. What kind of heart problems?

Arrhythmia ☐ Congenital heart defect ☐ Other ☐ _____

32. Did you ever have to take medication for your heart?

yes ☐ no ☐

33. Did you ever have a heart surgery?

yes ☐ no ☐

34. Do your heart problems still interfere with your daily activities?

yes ☐ no ☐

**Part 6**

35. Who smokes in your household?

| | | |
|---|---|---|
| Father | yes ☐ | no ☐ |
| Mother | yes ☐ | no ☐ |
| Other adult | yes ☐ | no ☐ |
| Children | yes ☐ | no ☐ |

36. How many cigarettes in total are being smoked in your house per day?

None ☐ 1-10 ☐ 11-20 ☐ 21-40 ☐ Über 40 ☐

37. Do you smoke yourself?

Yes, I smoke sometimes ☐ Yes, I have tried it once or twice, but I don't smoke regularly ☐ No, I have never smoked ☐

- If yes, how many packages do you smoke per week? _____
- If yes, since how many months do you smoke? _____

Comment box

**Thank you for completing the questionnaire!**