

## Supplementary tables and figure

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

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

<sup>1</sup> Bronchial Provocation Tests

<sup>2</sup> Inducible Laryngeal Obstruction

<sup>3</sup> Obstructive Sleep Apnoea Syndrome

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

| Diagnostic tests            | Asthma                                  |            |   |            |   |             |
|-----------------------------|---|------------|---|------------|---|-------------|
|                             | Definite asthma<br>N=68<br>median (IQR) |            | Other diagnosis<br>N=31<br>median (IQR) |            | Probable asthma<br>N=12<br>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+<br>n | A-S+<br>n | A+S-<br>n | A-S-<br>n | Sens<br>%<br>(95%CI) | Spec<br>%<br>(95%CI) | PPV<br>%<br>(95%CI) | NPV<br>%<br>(95%CI) | YI    |
|---|-----------|-----------|-----------|-----------|----------------------|----------------------|---------------------|---------------------|-------|
| <b>Respiratory symptoms in the past 12 months</b> |           |           |           |           |                      |                      |                     |                     |       |
| 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+<br>n | A-T+<br>n | A+T-<br>n | A-T-<br>n | Sens<br>%<br>(95%CI) | Spec<br>%<br>(95%CI) | PPV<br>%<br>(95%CI) | NPV<br>%<br>(95%CI) | YI   | AUC  |
|---------------------------------|-----------|-----------|-----------|-----------|----------------------|----------------------|---------------------|---------------------|------|------|
| <b>Clinical tests</b>           |           |           |           |           |                      |                      |                     |                     |      |      |
| Skin prick test <sup>1</sup>    |           |           |           |           |                      |                      |                     |                     |      | 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 <sup>2</sup>    |           |           |           |           |                      |                      |                     |                     |      | 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 <sub>1</sub> * | 55        | 3         | 32        | 13        | 63 (52-73)           | 81 (54-96)           | 95 (86-99)          | 29 (16-44)          | 0.44 |      |
| ≥10% increase FEV <sub>1</sub>  | 23        | 0         | 64        | 16        | 26 (18-37)           | 99 (79-99)           | 99 (85-99)          | 20 (12-30)          | 0.26 |      |
| ≥12% increase FEV <sub>1</sub>  | 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 <sub>1</sub> * | 57        | 3         | 29        | 10        | 66 (55-76)           | 77 (46-95)           | 95 (86-99)          | 26 (13-42)          | 0.43 |      |
| ≥8% decrease FEV <sub>1</sub>   | 49        | 3         | 37        | 10        | 57 (46-68)           | 77 (46-95)           | 94 (84-99)          | 21 (11-36)          | 0.34 |      |
| ≥10% decrease FEV <sub>1</sub>  | 40        | 3         | 46        | 10        | 47 (36-58)           | 77 (46-95)           | 93 (81-99)          | 18 (9-30)           | 0.24 |      |
| ≥12% decrease FEV <sub>1</sub>  | 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 |      |

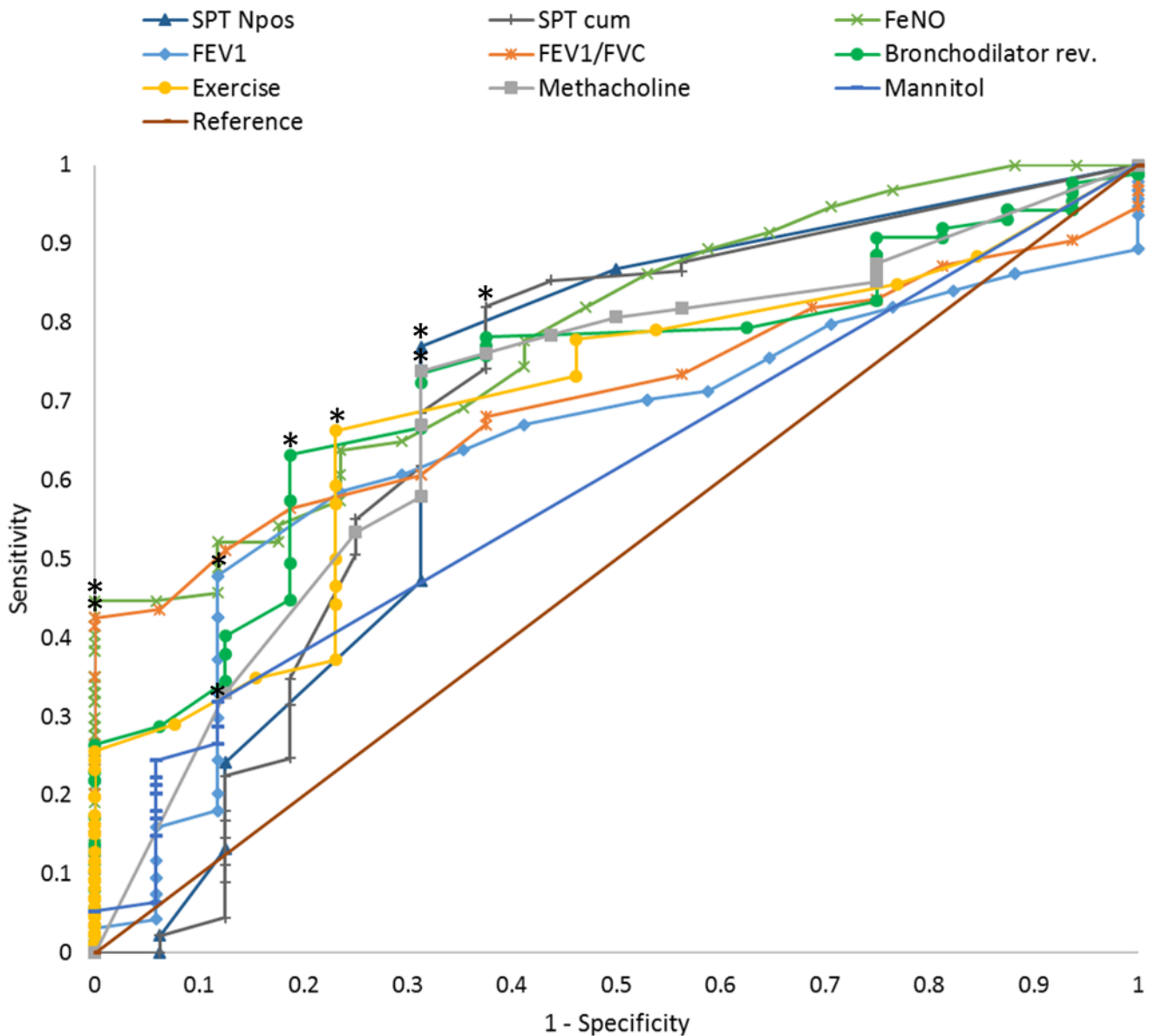
A+T+ = children with asthma diagnosis and positive test result, A-T+ = children without asthma diagnosis but positive test result, A+T- = children with asthma diagnosis but negative test result, A-T- = children without asthma and negative test result, Sens = sensitivity, Spec = specificity, PPV = positive 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, FEV<sub>1</sub> = 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)

<sup>1</sup> Number allergens for which the skin prick test is positive: wheel size ≥3

<sup>2</sup> 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 <sub>1</sub>     |
| Exercise                     | decrease of 1% in FEV <sub>1</sub>     |
| Methacholine                 | increase of 0.1 mg methacholine        |
| Mannitol                     | increase of 5 mg mannitol              |

