

## Abnormal lung function at preschool age asthma in adolescence?



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### ABSTRACT

**Background:** Asthma often begins early in childhood. However, the risk for persistence is challenging to evaluate. **Objective:** This longitudinal study relates lung function assessed with impulse oscillometry (IOS) in preschool children to asthma in adolescence.

**Methods:** Lung function was measured with IOS in 255 children with asthma-like symptoms aged 4–7 years. Baseline measurements were followed by exercise challenge and bronchodilation tests. At age 12–16 years, 121 children participated in the follow-up visit, when lung function was assessed with spirometry, followed by a bronchodilation test. Asthma symptoms and medication were recorded by a questionnaire and atopy defined by skin prick tests.

**Results:** Abnormal baseline values in preschool IOS were significantly associated with low lung function, the need for asthma medication, and asthma symptoms in adolescence. Preschool abnormal R5 at baseline (z-score  $\geq 1.645$  SD) showed 9.2 odds ratio (95%CI 2.7;31.7) for abnormal FEV1/FVC, use of asthma medication in adolescence, and 9.9 odds ratio (95%CI 2.9;34.4) for asthma symptoms. Positive exercise challenge and modified asthma-predictive index at preschool age predicted asthma symptoms and the need for asthma medication, but not abnormal lung function at teenage.

**Conclusion:** Abnormal preschool IOS is associated with asthma and poor lung function in adolescence and might be utilised for identification of asthma persistence.

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### Introduction

Diagnosis of asthma among small children is based on specific respiratory symptoms, history of atopic diseases, and exclusion of alternative diagnoses as defined in international guidelines for early childhood asthma (such as ICON,<sup>1</sup> GINA,<sup>2</sup> and NAEEP<sup>3</sup>). Asthma also may be diagnosed in small children,<sup>4</sup> in whom current diagnostic approaches may fall short. Long-term prospective studies have shown that adulthood asthma originates in early childhood.<sup>5–7</sup> Criteria important in early identification of preschool asthma have emerged from several follow-up studies of different cohorts. Based on these

criteria, predictive indexes such as Leicester tool,<sup>8</sup> Isle of Wight Birth Cohort,<sup>9</sup> Prevention and Incidence of Asthma and Mite Allergy birth cohort,<sup>10</sup> and modified Asthma Predictive Index (mAPI)<sup>11</sup> have been created. The predictive power of these diagnostic guidelines has been validated for symptoms, the use of medication, and doctor-diagnosed asthma, but not for lung function.

Spirometry is the gold standard for measuring lung function in school-aged children.<sup>12</sup> Reference values for younger children are available,<sup>13</sup> but the success rate in children younger than 6 years of age is at most 50%.<sup>14</sup> The advantage of impulse oscillometry (IOS) over spirometry is that measurements are performed during normal tidal breathing and are suitable for children from 2 to 3 years of age and older.<sup>15</sup> With a skilled technician the method is easily integrated into routine clinical practice.<sup>16</sup> Even though spirometry and IOS results are shown to correlate with each other,<sup>17</sup> these techniques provide different kinds of information on lung function. Spirometry measures the flow of air volumes out of the respiratory system,<sup>18</sup> and oscillometry uses sound waves to detect pulmonary mechanics, such as resistance (R) and reactance (X) of the airways.<sup>19</sup> Diagnostic features of preschool IOS can further be improved by combining it with an outdoor exercise challenge.<sup>20,21</sup>

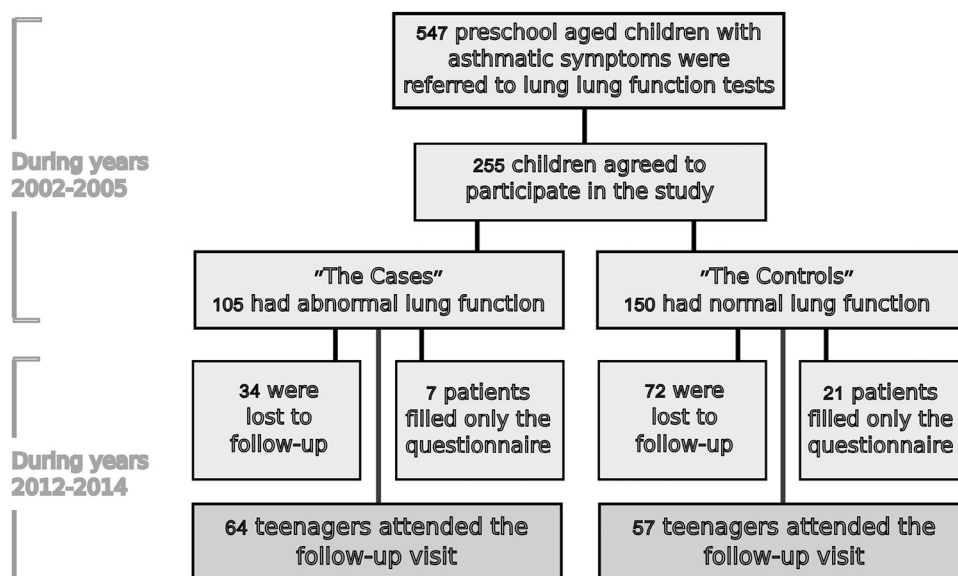
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**Figure 1.** Flow chart of the 121 study subjects, who underwent lung function testing at preschool age, and who participated in the follow-up visit at adolescence.

The primary aim of this study was to evaluate whether IOS in preschool-aged children can predict subjective signs of asthma as well as lung function in their teenage years.

## Methods

### Design

Children (median age 5 years) with asthma symptoms ( $n = 255$ ) were enrolled in a prospective study of childhood asthma (Fig 1). These children reported wheezing, persistent cough outside of discrete flu periods, dyspnea, or cough under exertion.<sup>22</sup> Follow-up visits 10 years later included 121 children (47%). Both the enrollment and the follow-up visits included a physical examination, detailed questionnaire, skin prick tests, laboratory tests, and lung function measurements. The use of corticosteroids or leukotriene antagonists were prohibited for 2 months before, and bronchodilators 12 hours before the lung function measurements at the teenage examination.

Patients were excluded from the study if they had seasonal asthma symptoms only, had received systemic or inhaled corticosteroids in the previous 6 months, or had signs of a respiratory tract infection 2 weeks before enrollment. One child had low birth weight ( $<2,500$  g) and one extremely low birth weight ( $<1,000$  g). Both had normal lung function at preschool age.

At preschool age, lung function was measured with IOS combined with an outdoor exercise challenge test and a bronchodilation test (BDT). An increase of 35% or more in respiratory resistance at 5 Hz (R5) was considered indicative of exercise-induced bronchoconstriction (EIB), and a decrease of 35% or more in R5 of positive BDT.<sup>23</sup> The children with EIB or positive BDT comprised the cases in this study, and those with normal lung function served as controls. The cases were treated with asthma medication. At the 10-year follow-up visit, lung function was reevaluated with IOS and spirometry.

The study was approved by the Research Ethics Committee of Helsinki University Hospital (139/13/03/03/2011). Written informed consents were obtained from the parents before enrollment and again at the follow-up visit, with the addition of the child's own assent.

### Procedures

IOS was measured in triplicate using Jaeger GmbH (Würzburg, Germany) apparatus at both study visits. Exercise challenge at preschool age was performed as a free-running test outdoors according to a validated protocol.<sup>24</sup> Measurements were carried out at baseline and repeated 1, 4, and 10 minutes after the exercise. BDT was performed immediately after the exercise challenge, including inhalation of 300  $\mu$ g salbutamol (Ventoline, GSK, United Kingdom) via spacer (Babyhaler, GlaxoSmithKline, Middlesex, United Kingdom), followed by a postbronchodilator measurement 15 minutes later. At the 10-year follow-up, the BDT was performed immediately after baseline measurement, with a salbutamol dose of 400  $\mu$ g. The detailed protocol and principles of IOS are described elsewhere.<sup>25</sup> Oscillometry indices evaluated were R5 and resistance at 20 Hz (R20), the difference between R5 and R20 (R5-20), frequency-dependent resistance (dR/df), reactance at 5 Hz (X5) and 10 Hz (X10), and the frequency at which X crosses the zero level, referred as the resonance frequency (Fres).

At the 10-year follow-up visit, spirometry maneuvers were measured in triplicate with a Masterscreen Pneumo, Jaeger GmbH (Würzburg, Germany) spirometer in accordance with European Society guidelines.<sup>18</sup> After the baseline measurements, patients inhaled 400  $\mu$ g salbutamol via spacer (Babyhaler), followed by postbronchodilator measurements 15 minutes later. Spirometry indices evaluated were forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), forced expiratory ratio (FEV1/FVC), and the maximal flow when 50% of FVC has been exhaled (MEF50).

Sensitization to local aeroallergens (birch, timothy-grass, meadow fescue, mugwort, *Cladosporium herbarum*, dog, cat, horse, cow, and house dust mite) was evaluated with skin prick tests. A wheal diameter of 3 mm or larger was considered positive. Atopy was defined as skin prick test positivity.

The mAPI was applied to evaluate clinical risk for persistent asthma. Positive mAPI requires infrequent wheezing during the first 3 years of life, and one of the following main criteria: eczema or parental asthma, or two of three minor criteria: blood eosinophilia, allergic rhinitis, or symptoms outside discrete flu periods.<sup>11</sup>

## End Points

Appearance of asthma symptoms and the use of asthma medication during the period between the 2 study visits was retraced using a questionnaire. Asthma symptoms (cough, wheezing, rhonchi, dyspnea) or the use of any asthma medication (long- or short-acting  $\beta_2$ -agonists, oral or inhaled corticosteroids, combinations, or leukotriene antagonists) 2 months before the 10-year follow-up visit were chosen as primary end points.

Oscillometry indices at preschool age and spirometry indices 10 years later were expressed as age/sex/height-matched z-scores based on reference values for healthy Finnish children.<sup>21,26</sup> Increased z-score ( $\geq 1.645$  SD) for R5, R20, R5–20, Fres, and decreased z-score ( $\leq -1.645$  SD) for dR/df, X5 and X10, FVC, FEV<sub>1</sub>, and MEF50 and FEV<sub>1</sub>/FVC at baseline were indicative of abnormal lung function. Lung function measured with spirometry was chosen as a secondary end point. All end points were included as dichotomous dummy variables.

## Statistics

Statistical analyses were performed with SPSS 23. Proportions of dichotomous variables were compared with Fisher's exact test, continuous variables with univariate *t*-test, and paired variables with the McNemar test. Equality of variances was ensured with Levene's test. *P* < .05 was considered significant. Multivariate analyses were performed by binary logistic regression. Analyses of association between abnormal teenage lung function and preschool indices was estimated using stepwise logistic regression. Tolerance over 0.8 and linear correlations over 0.3 (analyzed using Pearson's R) were considered sufficient.

## Results

### Study Population

No significant differences were seen in age, sex, birth weight, birth length, weight, or height between the groups. The number of household pets from preschool to adolescence increased; however, the phenomenon was similar in both groups.<sup>27</sup> Parental asthma was more prevalent in the controls, and the cases were more often exposed to environmental tobacco smoke (ETS) (Table 1). No difference in ETS between the groups was found at the 10-year visit.

### Symptoms and Medication

The children reported to have wheezed at preschool age had lower FEV<sub>1</sub>/FVC(%) values as teenagers compared with those who did not report any wheezing (*P* = .018). Nevertheless, wheezing at preschool age was not associated with abnormal lung function (z-score of  $\leq -1.645$  SD) in adolescence (data not shown). The teenagers who reported asthma symptoms (*n* = 24) (Table 1), most frequently shortness of breath (33%), were the same who needed asthma medication: 96% used  $\beta_2$ -agonists, and 67% corticosteroids. Only 8 (33%) of the teenagers reporting symptoms and needing medication had abnormal FEV<sub>1</sub> or FEV<sub>1</sub>/FVC(%) .

### Baseline IOS and Lung Function at 10-Year Follow-Up

Baseline R5 was comparable in the groups at preschool age, but higher among the cases at adolescence (Table 2). In the children exposed to ETS, the level of baseline R5 was significantly increased

**Table 1**  
Baseline Characteristics of 121 Individuals<sup>a</sup>

	Preschool			10-year follow-up		
	Cases	Controls	<i>P</i>	Cases	Controls	<i>P</i>
Age, y	5.06 (0.92)	5.00 (0.91)	.753	14.22 (1.61)	14.23 (0.95)	.962
Male	43 (67)	34 (60)	.451			
Birth weight, kg	3.65 (0.48)	3.48 (0.63)	.145			
Birth length, cm	50.57 (1.95)	49.95 (2.82)	.614			
Height, cm	116 (7.62)	114 (7.87)	.272	167.1 (9.75)	169.3 (8.77)	.424
Weight, kg	21.93 (4.26)	21.17 (5.12)	.392	60.1 (12.77)	60.7 (13.95)	.802
ISO-BMI	22.9 [18.0;27.8]	21.9 [17.9;25.9]	.181	23.08 [19.0;27.2]	22.43 [17.6;27.3]	.690
Overweight <sup>b</sup>	16 (25)	9 (16)	.362	15 (23)	14 (25)	.999
Obesity <sup>c</sup>	4 (6)	3 (5)	.999	4 (6)	4 (7)	.999
Parental smoking	21 (33)	6 (11)	<b>.008</b>	13 (20)	14 (25)	.664
Pets	10 (16)	6 (11)	.592	40 (63)	37 (65)	.855
SPT positive <sup>d</sup>	45 (70)	32 (56)	.182	59 (92)	42 (74)	<b>.007</b>
IgE mediated food allergy <sup>e</sup>	16 (25)	22 (39)	.117	15 (23)	15 (26)	.999
Wheezing <sup>f</sup>	53 (83)	9 (16)	<b>&lt;.001</b>	7 (11)	2 (4)	.166
Parental asthma	15 (23)	25 (44)	<b>.032</b>	18 (28)	27 (47)	<b>.038</b>
Atopic eczema <sup>e</sup>	37 (58)	24 (42)	.143	38 (59)	21 (37)	<b>.011</b>
Atopic rhinitis <sup>e</sup>	37 (58)	24 (42)	.102	30 (47)	17 (30)	.064
Blood eosinophilia <sup>g</sup>	47/61 (77)	9/19 (47)		28 (45)	18 (32)	.187
mAPI positive	49 (77)	9 (16)	<b>&lt;.001</b>			
Use of any asthma medication during last 2 months				23 (36)	1 (2)	<b>&lt;.001</b>
Asthma symptoms during last 2 months				22 (34)	1 (2)	<b>&lt;.001</b>

Abbreviations: IgE, immunoglobulin E; ISO-BMI, sex- and age-specific body mass index for children (kg/m<sup>2</sup>); mAPI, modified asthma predictive index; SPT skin prick test; SD, standard deviation; IQR, interquartile range.

NOTE: Bold values indicate significance.

<sup>a</sup>Cases *n* = 64, controls *n* = 57. Values are presented as mean (SD), *n* (%), or as median [IQR].

<sup>b</sup>Overweight: ISO-BMI >25 kg/m<sup>2</sup>.

<sup>c</sup>Obesity: ISO-BMI >30 kg/m<sup>2</sup>.

<sup>d</sup>Skin prick testing of aeroallergens, wheal diameter of  $\geq 3$  mm (birch, timothy-grass, meadow fescue, mugwort, *Cladosporium herbarum*, dog, cat, horse, cow, and house dust mite).

<sup>e</sup>Doctor-diagnosed eczema, rhinitis, and IgE-mediated food allergies were based on questionnaire answers.

<sup>f</sup>Wheezing during last year.

<sup>g</sup>Eosinophilia if eosinophil level is  $\geq 4\%$  of all leukocytes in blood.

**Table 2**  
Baseline Lung Function Measurements

Preschool	Cases, n = 64	Controls, n = 57	P
R5 (kPas/L), mean (SD)	0.89 (0.22)	0.85 (0.19)	.331
R5 z-score, mean (SD)	0.31 (1.35)	-0.09 (1.05)	.080
Abnormal R5, n (%)	11 (17)	2 (4)	<b>.014</b>
10-Year follow-up			
R5 (kPas/L), mean (SD)	0.29 (0.08)	0.26 (0.06)	<b>.015</b>
FEV <sub>1</sub> % predicted, mean (SD)	95.83 (12.11)	96.95 (10.79)	.459
FEV <sub>1</sub> z-score, mean (SD)	-0.45 (1.16)	-0.17 (1.29)	.223
Abnormal FEV <sub>1</sub> , n (%)	9 (14)	5 (9)	.268
FEV <sub>1</sub> /FVC % predicted, mean (SD)	82.97 (7.49)	86.67 (5.90)	<b>.003</b>
FEV <sub>1</sub> /FVC z-score, mean (SD)	-0.98 (1.28)	-0.35 (0.99)	<b>.003</b>
Abnormal FEV <sub>1</sub> /FVC, n (%)	16 (25)	8 (14)	.099

Abbreviations: FEV<sub>1</sub>/FVC, forced expiratory ratio; FEV<sub>1</sub>, forced expiratory volume in 1 second; R5, resistance at 5 Hz; Fres, resonance frequency.

NOTE. Values are presented as mean (SD) or n (%). R5 is abnormal when z-score  $\geq 1.645$ . Bold values indicate significance. SD, and FEV<sub>1</sub> and FEV<sub>1</sub>/FVC are abnormal when z-score  $\leq -1.645$  SD.

( $P = .021$ , data not shown), and a trend toward significance was seen at adolescence ( $P = .052$ ). Abnormal baseline R5 values were more frequent among the cases, and their FEV<sub>1</sub>/FVC(%) baseline level was increased in adolescence when compared with controls (Table 2). Those with abnormal baseline R5 at preschool age continued to have asthma symptoms, needed medication (Fig 2A), and showed poor lung function in adolescence (Fig 2B). All preschool IOS baseline variables except R20 significantly predicted abnormal FEV<sub>1</sub>/FVC(%) in adolescence (range of positive predictive value [PPV], 38%–62%,  $P < .01$ ).

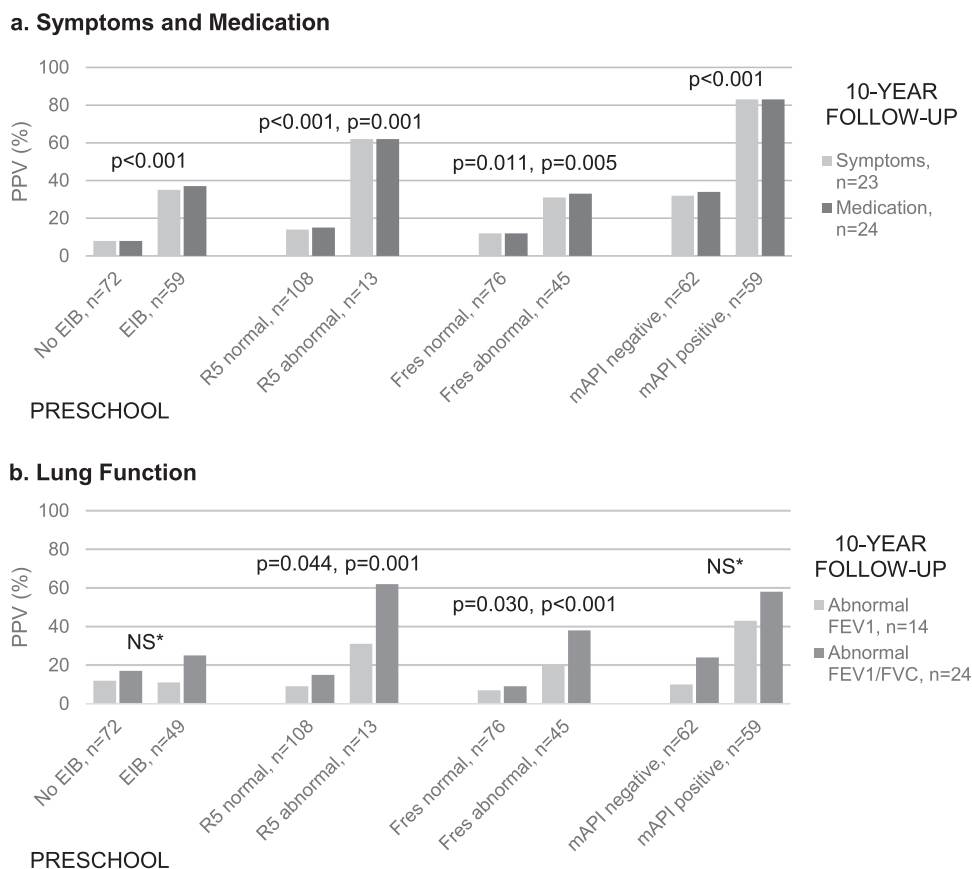
To test comparability of preschool IOS and teenage spirometry indices, they were converted into z-scores and tested for correlation. Except for FVC and X10, all parameters correlated significantly. Best correlations were between Fres, dR/df, R5-20, and MEF50 ( $r = 0.372$ – $0.416$ ,  $P < .01$  for all parameters). Poor R5 at preschool age predicted low spirometry values (Fig 3A–D), and poor IOS values at adolescence. All IOS indices correlated significantly with R5, except for X5, in adolescence ( $r = 0.305$ – $0.543$ ,  $P < .01$  for all parameters). Other preschool IOS indices correlated significantly, yet not as prominently, with teenage Fres, dR/df, and R5-20 ( $r = 0.197$ – $0.467$ ,  $P < .05$  for all parameters).

In a logistic regression model, preschool R5, R5-20, and BDT were associated with each other, and consequently, only R5 and Fres were included in further analyses. As a single variable, R5 presented superior PPV of abnormal lung function in adolescence when compared with all other IOS indices, EIB, BDT, mAPI, or wheezing (partially illustrated in Table 3 and Fig 2A and B).

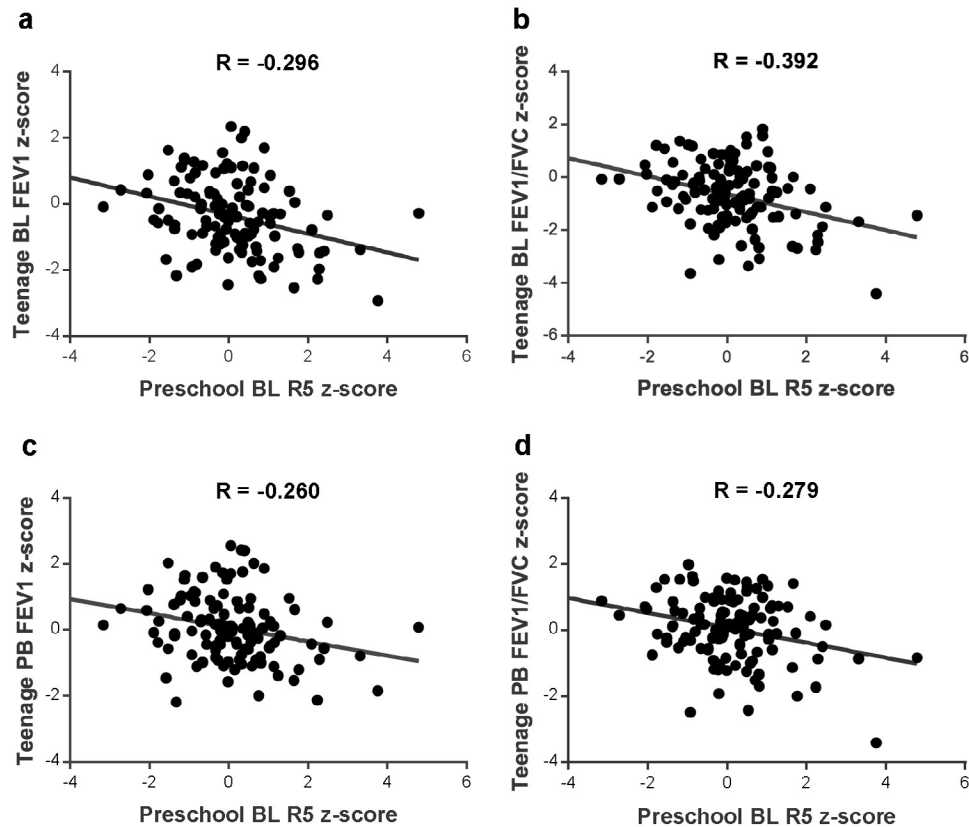
#### EIB, BDT, and mAPI

At preschool age, 78% of the asthma diagnoses were based on EIB, whereas BDT was positive only in 27%. The PPV of EIB for asthma symptoms and the use of medication in adolescence was 35% (Fig 2A). The BDT showed PPV of 37% for FEV<sub>1</sub>/FVC ( $P = .049$ ), but EIB failed to predict abnormal lung function in adolescence (Fig 2B).

The EIB in preschool produced odds ratios of over 5 for asthma symptoms and the need for asthma medication continuing into



**Figure 2.** (A) Positive predictive values (PPV) of patient-reported asthma symptoms (the first P-value) and the use of any asthma medication (the second P-value) during last 2 months at adolescence. (B) PPV of abnormal forced expiratory volume in 1 second (FEV<sub>1</sub>) (the first P-value), and abnormal forced expiratory ratio (FEV<sub>1</sub>/FVC) (the second P-value). The increase of  $\geq 35\%$  in respiratory resistance at 5 Hz (R5) is considered indicative of exercise-induced bronchoconstriction (EIB). R5 and the resonance frequency (Fres) are abnormal when the z-score  $\geq 1.645$  SD, and FEV<sub>1</sub> and FEV<sub>1</sub>/FVC are abnormal when the z-score  $\leq -1.645$  SD. NS, not significant.



**Figure 3.** Pearson correlations. Comparison of preschool baseline respiratory resistance at 5 Hz (R5) z-score with teenage baseline forced expiratory volume in 1 second (FEV<sub>1</sub>) (A) and forced expiratory ratio (FEV<sub>1</sub>/FVC) (B), and z-scores, including postbronchial (PB) correlations (C, D).

adolescence (Table 3). Combining EIB and abnormal baseline R5 yielded odds ratios of 14.6 (95%CI 1.4; 147.1) for symptoms, 13.7 (95%CI 1.4; 138.4) for medication, and 28.9 (95%CI 2.7; 302.2) for abnormal FEV<sub>1</sub>. The combination resulted in a PPV of 100% for abnormal FEV<sub>1</sub>/FVC ( $P > .001$ ) as well as for MEF50 ( $P = .002$ ). The PPV for asthma symptoms ( $P = .021$ ), medication ( $P = .024$ ), and abnormal FEV<sub>1</sub> ( $P = .005$ ) was 75%. All of these children were exposed to ETS at preschool age.

The mAPI was more often positive among the cases (Table 1) at preschool age, with sensitivity of 83% and specificity of 75%, and it had a good PPV with subjective signs of asthma at adolescence (Fig 2A, Table 3). However, it failed to predict abnormal lung function at adolescence (Fig 2B, Table 3). Combining mAPI with EIB, BDT, R5, or other baseline IOS indices in logistic regression model did not increase PPV for abnormal lung function, medication, or symptoms. In contrast, if R5 was normal and mAPI negative, the negative

predictive value was 94% for abnormal FEV<sub>1</sub>, 96% for abnormal FEV<sub>1</sub>/FVC, and for symptoms and medication 97%.

## Discussion

This communication reports three essential findings. First, abnormal preschool IOS baseline parameters predict asthma symptoms, the need for asthma medication, and abnormal lung function at adolescence. Second, preschool children with abnormal baseline R5 and EIB have a poorer prognosis in adolescence. Third, neither mAPI nor EIB alone predicted abnormal lung function.

Impairment of lung function in adulthood is evident in early childhood<sup>5,6,28</sup> and the baseline lung function is the strongest predictor of this pattern.<sup>28</sup> Our findings with early childhood baseline IOS parameters and their link to teenage asthma are in accordance with this concept. Abnormal baseline R5 at preschool age

**Table 3**  
10-Year Outcome After the Abnormal Preschool Test Results

10-year follow-up				
Preschool	Abnormal FEV <sub>1</sub> , n = 14	Abnormal FEV <sub>1</sub> /FVC, n = 24	Symptoms, n = 23	Medication, n = 24
<b>Abnormal R5</b> n = 13	4.4 (1.1;16.7)	9.2 (2.7;31.7)	9.9 (2.9;34.4)	9.2 (2.7;31.7)
<b>Abnormal Fres</b> n = 45	3.5 (1.1;11.2)	5.9 (2.2;15.8)	3.3 (1.3;8.5)	3.7 (1.4;9.3)
<b>EIB</b> n = 49	NS	NS	5.3 (1.9;14.6)	5.7 (2.1;15.8)
<b>Positive mAPI</b> n = 59	NS	NS	13.7 (1.4;147.1)	14.6 (1.4;147.10)

Abbreviations: EIB, exercise-induced bronchoconstriction; FEV<sub>1</sub>, forced expiratory volume in 1 second; FEV<sub>1</sub>/FVC, forced expiratory ratio; Fres, resonance frequency; mAPI, modified asthma predictive index; NS, not significant; R5, resistance at 5 Hz.

NOTE. Data presented as odds ratios (95% confidence interval). Analyses were performed using logistic regression for abnormal FEV<sub>1</sub> and FEV<sub>1</sub>/FVC, asthma symptoms, and the use of asthma medication during the last 2 months at adolescence. Adjusted for birth weight, sex, obesity, wheezing, and exposure to environmental tobacco smoke. The increase of  $\geq 35\%$  in R5 is considered indicative of EIB. R5 and Fres are abnormal when z-score  $\geq 1.645$  SD, and FEV<sub>1</sub> and FEV<sub>1</sub>/FVC are abnormal when z-score  $\leq -1.645$  SD. Bold values indicate significance.

showed nearly a 10-fold risk of lung function impairment, asthma symptoms, and the need for asthma medication continuing into adolescence, with moderate sensitivity (33%) and excellent specificity (95%).

Early childhood bronchial hyperreactivity assessed by methacholine in childhood predicts persistence of asthma.<sup>29</sup> Bronchial hyperreactivity to indirect stimuli such as exercise challenge more closely associates with eosinophilic airway inflammation.<sup>30,31</sup> Previous studies of asthma persistence have demonstrated that EIB in childhood was associated with doctor-diagnosed asthma in adolescence with modest predictive value (sensitivity 31% and specificity 29%).<sup>4</sup> Similarly, in the current study, childhood EIB was a prognostic factor for asthma symptoms and the use of asthma medication in adolescence, with a 75% sensitivity and 68% specificity, but not for lung function.

The IOS is a feasible method for lung function testing in pre-schoolers. Measuring baseline IOS parameters only is in most cases in a clinical setting not sensitive enough to find the true asthmatic patients. As shown earlier, sensitivity improves by combining IOS with BDT or preferably EIB.<sup>20,21</sup> Clinically relevant differences between asthmatic patients and healthy controls has been reported to be a 35% to 40% change in R5 after exercise test or BDT.<sup>20,32</sup> Based on our results, combining abnormal baseline R5 with EIB resulted in 100% specificity in detecting persistent asthma. This combination possibly could identify those with early lung volume deficits and predisposition to eosinophilic inflammation, emphasizing the need for clinical follow-up of these children.

Predictive models created from Leicester study,<sup>8</sup> Isle of Wight Birth Cohort,<sup>9</sup> mAPI,<sup>11</sup> and Prevention and Incidence of Asthma and Mite Allergy birth cohort<sup>10</sup> are useful tools for asthma diagnostics. Nevertheless, previous studies showed no connection between positive (stringent) API at preschool age and abnormal baseline or postbronchodilator IOS, FEV<sub>1</sub>, or FEV<sub>1</sub>/FVC.<sup>33</sup> In the current study, mAPI successfully predicted symptoms and the need for medication at adolescence. Reported symptoms and the use of asthma medication, however, were poorly associated with lung function. In this setting, symptom-based clinical indexes may lead to false-positive diagnoses, and the use of objective diagnostic methods such as IOS should be encouraged in preschool asthma diagnostics.

To the best of our knowledge, this study is the first to compare IOS and spirometry prospectively between two time points, providing new insight into the longitudinal trajectory of lung function. Although the data do not allow estimates of at what exact moment deficits in lung function originate, evidence indicates that persistent defects are already apparent at preschool age. Combining lung function with symptom load and the use of medication as outcome measures links the results more reliably to the multifactorial origin of asthma. Additionally, the use of different IOS indices and a detailed questionnaire enables identification and elimination of several confounding factors.

One of the shortcomings of the study is the selected cohort including only symptomatic children, although this setting reflects more accurately the real-world situation, in which lung function is measured from symptomatic preschoolers. Also, the sample size limits extensive multifactorial analyses and the strength of the conclusions. Additional clinical studies are required to further verify the findings. Furthermore, loss to follow-up exposed the study to selection bias of more severe cases. In contrast, the study population of this research suffered only from mild to moderate asthma. One potential explanation behind this incongruity is the peak of lung function at adolescence, followed by a gradual decrease through adulthood.<sup>34</sup> Bearing this in mind, the results of this study appear even more meaningful. A longer follow-up might offer more accurate perspective to the development of lung function.

Positive mAPI and aberrant lung function measured with IOS before school age predict asthma symptoms and the need for asthma medication in adolescence. As an additional benefit to clinical evaluation, IOS predicts the persistence of abnormal lung function until adolescence, providing a comprehensive and objective assessment of recurrent respiratory symptoms at preschool age. Based on this communication, lung function measurement with IOS could be considered as an important tool in predicting prognosis of childhood asthma.

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