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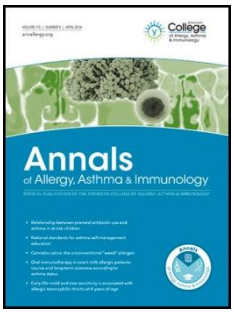

Title: Abnormal lung function at preschool age – asthma in adolescence?

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Title Page

Title: Abnormal Lung Function at Preschool Age – Asthma in Adolescence?

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Authorship contribution: Study desing and implementation were conducted by M.J.M., A.S.P., S.K., and L.P.M. S.K. and L.P.M. collected the data. K.L. and S.K. had full access to all the data and executed the tabulating. K.L., A.K-S., S.S. and L.P.M. take responsibility for data integrity and analysis. K.L. prepared the first version of the manuscript and M.J.M., A.S.P., A.K-S., and L.P.M. gave substantial contribution to the development of the manuscript. K.L. and M.J.M. are the guarantors of the article and share final responsibility for the decision to submit for publication.

Keywords: Adolescence, childhood asthma, exercise challenge, impulse oscillometry, longitudinal study, lung function testing, and spirometry.

Abbreviations: BDT, bronchodilation test; dR/df frequency dependent resistance; IOS, impulse oscillometry; CI, confidence interval; EIB, exercise-induced

bronchoconstriction; ETS, environmental tobacco smoke; FEV1, forced expiratory volume in 1 s; FEV1/FVC, forced expiratory ratio; FVC, forced vital capacity; mAPI, modified asthma predictive index; MEF50, maximal flow when 50% of FVC has been exhaled; PPV, positive predictive value; R5, respiratory resistance at 5 Hz; R20, respiratory resistance at 20 Hz; Fres, resonance frequency; R5-20, difference between R5 and R20; X5, reactance at 5 Hz; X10, reactance at 10 Hz.

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Figures: Figure 1, Figure 2a-b, Figure 3a-d

Tables: Table 1, Table 2, and Table 3

Introduction

Diagnosis of asthma among small children is based on specific respiratory symptoms, history of atopic diseases and exclusion of alternative diagnosis as defined in international guidelines for early childhood asthma (such as ICON,[1] GINA,[2] and NAEEP).[3] Asthma is a diagnosis that has to be made also in small children,[4] while, conversely, the current diagnostic approach falls short in objectiveness. Long-term prospective studies have shown that the origin of asthma in adulthood lies in early childhood.[5-7] 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,[8] Isle of Wight Birth Cohort,[9] Prevention and Incidence of Asthma and Mite Allergy birth cohort,[10] and modified Asthma Predictive Index (mAPI)[11] 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 at schoolage.[12] Reference values for younger children are available,[13] but the success rate in children below six years of age is at most 50%.[14] The advantage of impulse oscillometry (IOS) over spirometry is that measurements are performed during normal tidal breathing, and are suitable for children from 2-3 years of age on.[15] With a skilled technician the method is easily combined to routine clinical practice.[16] Even though spirometry and IOS results are shown to correlate with each other,[17] these techniques provide different kind of information on the lung function. Spirometry measures the flow of air volumes out of the respiratory system,[18] while oscillometry

uses sound waves to detect pulmonary mechanics given as resistance (R) and reactance (X) of the airways.[19] Diagnostic features of preschool IOS can further be improved by combining it to outdoor exercise challenge.[20,21].

The primary aim was to evaluate whether IOS at preschool can predict subjective signs of asthma as well as lung function at teenage.

Methods

Design

The children aged median 5 year with asthma symptoms (n=255) were enrolled to a prospective study of childhood asthma. (Figure 1). These children reported wheezing, persistent cough outside discrete flu periods, dyspnoea or cough under exertion.[22] The follow-up visit 10 years later were participated by 121 children (47%). Both the enrollment and the follow-up visits included physical examination, detailed questionnaire, skin prick tests, laboratory tests and lung function measurements. The use of corticosteroids or leukotriene antagonists were prohibited 2 months prior, and bronchodilators 12 hours prior to the lung function measurements at teenage.

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 prior to the enrollment. One child had low birth weight (<2500 g) and one extremely low birth weight (<1000 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). The increase of ≥35% in respiratory resistance at 5 Hz (R5) was considered indicative of exercise-induced bronchoconstriction (EIB), and a decrease of ≥35% in R5 of positive BDT.[23] The children with EIB and/or positive BDT are referred as the cases in this study, and those with normal lung function as the controls. The cases were treated with asthma

medication. At the 10-year follow-up visit, lung function was re-evaluated 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 the enrollment, and again at the follow-up visit with addition to 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.[24] Measurements were carried out at baseline and repeated 1, 4 and 10 min after the exercise. BDT was done immediately after the exercise challenge, including inhalation of 300 µg salbutamol (Ventoline, GSK, UK) via spacer (Babyhaler), followed by a post-bronchodilator measurement 15 min later. At 10-year follow-up the BDT was done straight after baseline measurement and with salbutamol dose of 400 µg. The detailed protocol and principles of IOS are described elsewhere.[25] 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), the frequency where X cuts zero level, referred as the resonance frequency (Fres).

At the 10-year follow-up visit spirometry manoeuvres were measured in triplicate with Masterscreen Pneumo, Jaeger GmbH (Würzburg, Germany) spirometer in

accordance to European Society guidelines.[18] After the baseline measurements, patients inhaled 400 µg salbutamol (Ventoline, GSK, UK) via spacer (Babyhaler), followed with post-bronchodilator 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).

Sensitisation 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 was considered positive. Atopy was defined as skin prick test positivity.

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

End Points

Appearance of asthma symptoms and the use of asthma medication during the time period between the 2 study visits was retraced using a questionnaire. Asthma symptoms (cough, wheezing, rhonchi, dyspnoea) or the use of any asthma medication (long or short acting ß2-agonists, oral and/or inhaled corticosteroids, combinations, or leukotriene antagonists) 2 months prior to the 10-year follow-up visit were chosen as primary end points.

Oscillometry indices at preschool age and spirometry indices at teenage were expressed as age/sex/height-matched z-scores based on reference values for healthy Finnish children.[21,26] Increased z-score (≥1.645 SD) for R5, R20, R5-20, Fres, and decreased z-score (≤-1.645 SD) for dR/df, X5 and X10, FVC, FEV1 and MEF50 and FEV1/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 McNemar test. Equality of Variances was ensured with Levene's test. A *P*-value of <0.05 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 (analysed using Pearson's R) were considered sufficient.

Results

Study population

There were no significant differences in age, gender, 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.[27] Parental asthma was more prevalent in the controls, while the cases were more often exposed to environmental tobacco smoke (ETS) (Table 1). The difference in ETS between the groups disappeared at teenage.

Symptoms and Medication

The children reported to have wheezed at preschool age had lower FEV1/FVC(%) values at teenage as compared to those who did not report any wheezing (*P*=0.018). Nevertheless, wheezing at preschool age was not associated with abnormal lung function (z-score of ≤-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 ß2-agonists, and 67% corticosteroids. Only 8 (33%) of the teenagers reporting symptoms and needing medication had abnormal FEV1 or FEV1/FVC(%).

Baseline IOS and lung function at teenage

Baseline R5 was comparable in the groups at preschool age, but higher among the cases at teenage (Table 2). In the children exposed to ETS the level of baseline R5 was significantly increased (*P*=0.021, data not shown), and there was a trend towards significance at teenage (*P*=0.052). Abnormal baseline R5 values were more

frequent among the cases, and their FEV1/FVC(%) baseline level was increased in adolescence when compared to the controls (Table 2). Those with abnormal baseline R5 at preschool age continued to have asthma symptoms, needed medication (Figure 2a), and showed poor lung function in adolescence (Figure 2b). All preschool IOS baseline variables except R20 significantly predicted abnormal FEV1/FVC(%) in adolescence (range of positive predictive value (PPV) 38-62%, $P<0.01$).

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, $P<0.01$ for all parameters). Poor R5 at preschool age predicted low spirometry values (Figures 3a-3d) and poor IOS values at teenage. All IOS indices correlated significantly with R5, except for X5, in adolescence (r=0.305-0.543, $P<0.01$ 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, $P<0.05$ for all parameters).

In 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 to all other IOS indices, EIB, BDT, mAPI or wheezing (partially illustrated in Table 3, Figures 2a, and 2b).

EIB, BDT, and mAPI

At preschool age, 78% of the asthma diagnoses were based on EIB, while BDT was positive only in 27%. PPV of EIB for asthma symptoms and the use of medication in adolescence was 35% (Figure 2a). BDT showed PPV of 37% for FEV1/FVC (*P*=0.049), but EIB failed to predict abnormal lung function in adolescence (Figure 2b).

EIB in preschool produced odds ratios of over 5 for asthma symptoms and the need for asthma medication continuing into teenage (Table 3). Combining EIB and abnormal baseline R5 yielded odds ratios of 14.6 (95%CI 1.4;147.1) for symptoms, of 13.7 (95%CI 1.4;138,4) for medication and of 28.9 (95%CI 2.7;302.2) for abnormal FEV1. The combination resulted PPV of 100% for abnormal FEV1/FVC (*P*>0.001) as well as for MEF50 (*P*=0.002). PPV for asthma symptoms (*P*=0.021), medication (*P*=0.024) and abnormal FEV1 (*P*=0.005) was 75%. All these children were exposed to ETS at preschool age.

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 teenage (Figure 2a and Table 3). However, it failed to predict abnormal lung function at teenage (Figure 2b and 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 FEV1, 96% for abnormal FEV1/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 teenage. Second, preschool children with abnormal baseline R5 and EIB have poorer prognosis in adolescence. Third, neither mAPI nor EIB alone predict abnormal lung function.

Impairment of lung function in adulthood is evident already in early childhood[5,6,28] and the baseline lung function is the strongest predictor of this pattern.[28] 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 showed nearly a 10-fold risk of lung function impairment, asthma symptoms and the need for asthma medication continuing into teenage with moderate sensitivity (33%) and excellent specificity (95%).

Early childhood bronchial hyperreactivity assessed by methacholine in childhood predicts persistence of asthma.[29] Bronchial hyperreactivity to indirect stimuli such as exercise challenge, more closely associates with eosinophilic airway inflammation.[30,31] 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%).[4] Similarly, in the present 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.

IOS is a feasible method for lung function testing in preschoolers. Measuring baseline IOS parameters only is in most cases in a clinical setting not sensitive enough to find the true asthmatics. As shown earlier, sensitivity improves by combining IOS with BDT or preferably EIB.[20,21] Clinically relevant difference between asthmatics and healthy controls has been reported to be 35-40% change in R5 after exercise test or BDT.[32,20] Based on our results, combining abnormal baseline R5 with EIB resulted in 100% specificity in detecting persistent asthma. It could be speculated that this combination 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,[8] Isle of Wight Birth Cohort,[9] mAPI,[11] and Prevention and Incidence of Asthma and Mite Allergy birth cohort[10] are useful tools for asthma diagnostics. Nevertheless, previous studies showed no connection between positive (stringent) API at preschool age and abnormal baseline or post-bronchodilator IOS, FEV1 or FEV1/FVC.[33] In the present study, mAPI successfully predicted symptoms and the need for medication at teenage. 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 diagnosis, 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 to the longitudinal

trajectory of lung function. Although the data do not allow estimates at what exact moment deficits in lung function originate, there is evidence 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 multi-factorial origin of asthma. Additionally, the use of different IOS indices and detailed questionnaire enable 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, where lung function is measured from symptomatic preschoolers. Also, the sample size limits extensive multi-factorial 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 teenage followed by a gradual fall through adulthood.[34] 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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Figure legends

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 teenage.

Figure 2a. 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 teenage. **2b.** PPV of abnormal forced expiratory volume in 1 s (FEV1) (the first *P*-value), and abnormal forced expiratory ratio (FEV1/FVC) (the second *P*-value). The increase of ≥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 z-score ≥1.645 SD and FEV1 and FEV1/FVC are abnormal when z-score ≤-1.645 SD. NS: Not significant.

Figure 3. Pearson correlation. Comparing of preschool baseline respiratory resistance at 5 Hz (R5) z-score to teenage baseline forced expiratory volume in 1 s (FEV1) (**3a**) and forced expiratory ratio (FEV1/FVC) (**3b**) z-scores including post-bronchial correlations (**3c** and **3d**).

Table 1. Baseline characteristics of 121 individuals. Cases n=64, controls n=57.

	PRESCHOOL			10-YEAR FOLLOW-UP		
	Cases	**Controls**	***P*-value**	**Cases**	**Controls**	***P*-value**
Age, y	5.06 (0.92)	5.00 (0.91)	0.753	14.22 (1.61)	14.23 (0.95)	0.962
Male	43 (67)	34 (60)	0.451			
Birth weight, kg	3.65 (0.48)	3.48 (0.63)	0.145			
Birth length, cm	50.57 (1.95)	49,95 (2.82)	0.614			
Height, cm	116 (7.62)	114 (7.87)	0.272	167.1 (9.75)	169.3 (8.77)	0.424
Weight, kg	21.93 (4.26)	21.17 (5.12)	0.392	60.1 (12.77)	60.7 (13.95)	0.802
ISO-BMI	22.9 [18.0;27.8]	21.9 [17.9;25.9]	0.181	23.08 [19.0;27.2]	22.43 [17.6;27.3]	0.690
Overweight[a]	16 (25)	9 (16)	0.362	15 (23)	14 (25)	0.999
Obesity[b]	4 (6)	3 (5)	0.999	4 (6)	4 (7)	0.999
Parental smoking	21 (33)	6 (11)	**0.008**	13 (20)	14 (25)	0.664
Pets	10 (16)	6 (11)	0.592	40 (63)	37 (65)	0.855
SPT positive[c]	45 (70)	32 (56)	0.182	59 (92)	42 (74)	**0.007**
IgE mediated food allergy[d]	16 (25)	22 (39)	0.117	15 (23)	15 (26)	0.999
Wheezing[e]	53 (83)	9 (16)	**<0.001**	7 (11)	2 (4)	0.166

Parental asthma	15 (23)	25 (44)	**0.032**	18 (28)	27 (47)	**0.038**
Atopic eczema[d]	37 (58)	24 (42)	0.143	38 (59)	21 (37)	**0.011**
Atopic rhinitis[d]	37 (58)	24 (42)	0.102	30 (47)	17 (30)	0.064
Blood eosinophilia[f]	47/61 (77)	9/19 (47)		28 (45)	18 (32)	0.187
mAPI positive	49 (77)	9 (16)	**<0.001**			
Use of any asthma medication during last 2 months				23 (36)	1 (2)	**<0.001**
Asthma symptoms during last 2 months				22 (34)	1 (2)	**<0.001**

Values are presented as mean (SD), n (%) or as median [IQR].

[a]Overweight: ISO-BMI >25 kg/m^2 and [b]obesity: ISO-BMI >30 kg/m^2.

[c]Skin prick testing of aeroallergens, wheal diameter of ≥3 mm (birch, timothy-grass, meadow fescue, mugwort, Cladosporium herbarum, dog, cat, horse, cow and house dust mite).

[d]Doctor diagnosed eczema, rhinitis, and IgE-mediated food allergies were based on questionnaire answers.

[e]Wheezing during last year

[f]Eosinophilia if eosinophil level is ≥4% of all leucocytes in blood.

Abbreviations: IgE, immunoglobulin E; ISO-BMI, sex and age specific body mass index for children (kg/m^2); mAPI, modified asthma predictive index; SPT skin prick test.

Table 2. Baseline lung function measurements.

PRESCHOOL	**Cases, n=64**	**Controls, n=57**	***P*-value**
R5 (kPas/L)	0.89 (0.22)	0.85 (0.19)	0.331
R5 z-score	0.31 (1.35)	-0.09 (1.05)	0.080
Abnormal R5	11 (17)	2 (4)	**0.014**
10-YEAR FOLLOW-UP			
R5 (kPas/L)	0.29 (0.08)	0.26 (0.06)	**0.015**
FEV1 % predicted	95.83 (12.11)	96.95 (10.79)	0.459
FEV1 z-score	-0.45 (1.16)	-0.17 (1.29)	0.223
Abnormal FEV1[e]	9 (14)	5 (9)	0.268
FEV1/FVC % predicted	82.97 (7.49)	86.67 (5.90)	**0.003**
FEV1/FVC z-score	-0.98 (1.28)	-0.35 (0.99)	**0.003**
Abnormal FEV1/FVC[d]	16 (25)	8 (14)	0.099

Values are presented as mean (SD) or n (%). R5 is abnormal when z-score ≥1.645 SD and FEV1 and FEV1/FVC are abnormal when z-score ≤-1.645 SD.

Abbreviations: FEV1/FVC, forced expiratory ratio; FEV1, forced expiratory volume in 1 s; R5, resistance at 5 Hz; Fres, resonance frequency.

Table 3. 10-year outcome after the abnormal preschool test results.

	10-YEAR FOLLOW-UP			
PRESCHOOL	**Abnormal FEV1**, n=14	**Abnormal FEV1/FVC**, n=24	**Symptoms** n=23	**Medication** n=24
Abnormal R5 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)
Abnormal Fres 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)
EIB n=49	NS	NS	5.3 (1.9;14.6)	5.7 (2.1;15.8)
Positive mAPI n=59	NS	NS	13.7 (1.4;147.1)	14.6 (1.4;147.10)

Data presented as odds ratios (95% confidence interval). Analyses were performed using logistic regression for abnormal FEV1 and FEV1/FVC, asthma symptoms, and the use of asthma medication during the last 2 months at teenage. Adjusted for birth weight, gender, obesity, wheezing, and exposure to environmental tobacco smoke. The increase of ≥35% in R5 is considered indicative of EIB. R5 and Fres are abnormal when z-score ≥1.645 SD and FEV1 and FEV1/FVC are abnormal when z-score ≤-1.645 SD.

Abbreviations: EIB, exercise induced bronchoconstriction; FEV1, forced expiratory volume in 1 s; FEV1/FVC, forced expiratory ratio; Fres, resonance frequency; mAPI, modified asthma predictive index; NS, not significant; R5, resistance at 5 Hz.

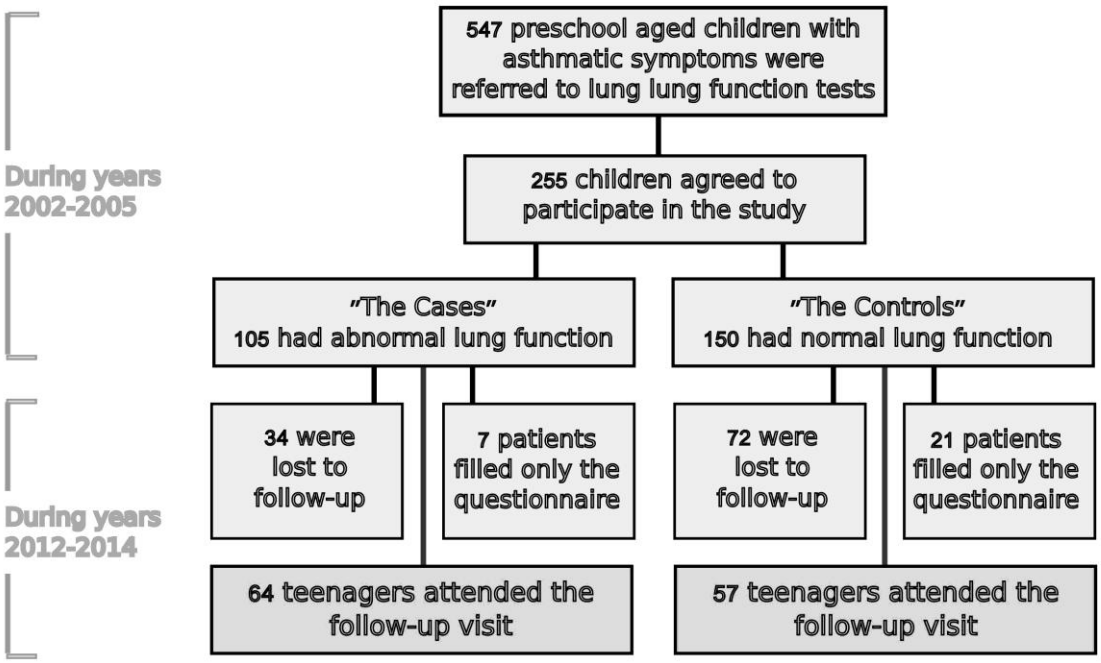

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Figure 3a.

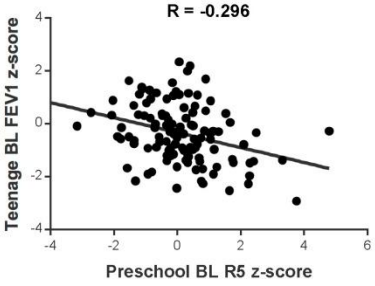


Figure 3b.

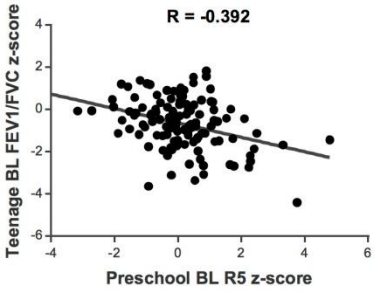


Figure 3c.

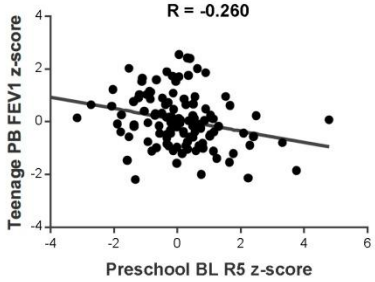
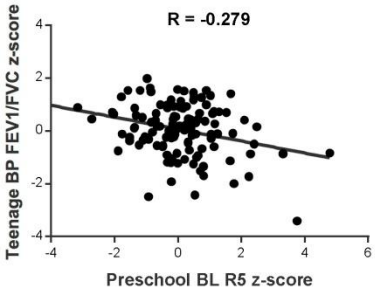


Figure 3d.



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471 Figure 3a-d (TIFF).tiff