Early childhood lower-airway symptoms and airway hyperresponsiveness linked to school-age small-airway dysfunction

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Background: The role of early airway hyperresponsiveness (AHR) in the subsequent small-airway lung function remains unclear.
Objective: We assessed via a prospective follow-up study the small-airway lung function of schoolchildren with early childhood lower-airway symptoms and AHR to methacholine and compared the findings to the measurements of reference children with no previous or current lung diseases.
Methods: During 2004-11, we measured atopic markers, lung function, and airway responsiveness to methacholine in 193 symptomatic children <3 years old. In 2016-18, a follow-up sample of 84 schoolchildren and 40 reference children were assessed for atopic parameters, spirometry, and small-airway lung function. Analysis was performed on the basis of early childhood AHR, early childhood atopy (defined as a positive skin prick test result), and exposure to parental smoking reported in a questionnaire. All the results were compared with those of the reference group.
Results: Schoolchildren with early childhood lower-airway symptoms and AHR had higher prebronchodilator area under the reactance curve (AX) *z* score, lower forced expiratory flow at 50% of forced vital capacity ($FEF_{50\%}$) *z* score, and higher lung clearance index (LCI) 2.5% compared with those without early childhood AHR and reference children. Moreover, AX and $FEF_{50\%}$ *z* scores only partly improved after bronchodilation. Early childhood atopy and exposure to parental smoking were not associated with school-age small-airway dysfunction.
Conclusion: AHR in symptomatic young children associated with subsequent persistent small-airway dysfunction. Further studies with larger samples of symptomatic young children are warranted to determine whether this connection predicts the development of asthma or other obstructive pulmonary diseases as the children grow. (J Allergy Clin Immunol Global 2025;4:100454.)

Key words: *Airway hyperresponsiveness, atopy, maternal smoking, parental smoking, preschool children, school-age children, skin prick test, small airways, small-airway dysfunction*

Airway hyperresponsiveness (AHR) is a typical characteristic of asthma, which is the most common chronic disease in children.[1] Increasing evidence suggests that small-airway dysfunction (SAD) may be a more sensitive sign of pediatric asthma than common spirometry indexes, such as forced expiratory volume in 1 second (FEV_1).[2]

Small airways are traditionally defined as the distal part of the bronchial tree with an internal diameter of <2 mm.[3] Currently, no single lung function or imaging parameter is completely specific to small-airway lung function, which is usually investigated using several different lung function tests, such as impulse oscillometry (IOS), multiple-breath nitrogen washout (MBNW), or spirometry.[4,5] In children aged 5-15 years with well-controlled asthma and normal FEV_1, the lung clearance index (LCI) at 2.5% measured with MBNW is higher than in controls, and remains high after bronchodilation, indicating persistent small-airway disease undetected by FEV_1.[6] Alveolar nitric oxide (NO) concentration (C_{ALV}) describes inflammation in the alveolar compartment and can be investigated using the 2-compartment model of pulmonary NO dynamics, which also estimates the bronchial flux of NO from bronchial wall to luminal air (J_{NO}).[7]

In ATLANTIS, a large ongoing prospective cohort study investigating adults with asthma, the prevalence of SAD depended on the lung function parameter that was used; it was linked to asthma severity, history of exacerbations, and AHR.[5] In children aged 5-10 years with recurrent wheeze, baseline small-airway IOS indexes, such as area under the reactance curve (AX), the difference between respiratory resistance at 5 Hz and 20 Hz (Rrs5-20), and C_{ALV} were elevated, in contrast to healthy children.[8] In children 7-17 years old with mild-to-moderate controlled asthma, increased prebronchodilator AX and Rrs5-20 associated with decreasing asthma control at the 8- to 12-week follow-up visit; baseline FEV_1/forced vital capacity (FVC) ratio was also slightly lower in the uncontrolled asthma group.[9]

Early childhood sensitization to food and inhalant allergens precedes later atopic diseases and asthma.[10] It is unclear if atopy is associated with SAD. In ATLANTIS, atopy prevalence was similar in both asthma patient groups with distinct differences in their SAD parameters.[5] Because SAD may precede asthma, there is increasing interest in its relationship with atopy.

Exposure to environmental tobacco smoke[11] and especially prenatal maternal smoking[12] increases the risk of childhood asthma. Prenatal exposure to maternal smoking is associated with school-age reduced small-airway lung function measured with forced expiratory flow between 25% and 75% of vital

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Abbreviations used

AHR: Airway hyperresponsiveness
AX: Area under the reactance curve
C-ACT: Childhood Asthma Control Test
C_{ALV}: Alveolar NO concentration
$FEF_{25-75\%}$: Forced expiratory flow between 25% and 75% of vital capacity
$FEF_{50\%}$: Forced expiratory flow at 50% of FVC
FEV_1: Forced expiratory volume in 1 second
FRC: Functional residual capacity
FVC: Forced vital capacity
IOS: Impulse oscillometry
J_{NO}: Bronchial flux of NO from bronchial wall to luminal air
LCI: Lung clearance index
$LCI_{2.5\%/5\%}$: Number of lung turnovers required to wash out nitrogen to 1/40th (2.5%) or 1/20th (5%) of initial concentration
mAPI: Modified Asthma Predictive Index
MBNW: Multiple-breath nitrogen washout
NO: Nitric oxide
PD40 $V'_{max,FRC}$: Dose of methacholine causing 40% decrease in maximal flow at FRC
Rrs5: Respiratory resistance at 5 Hz
Rrs5-20: Difference between respiratory resistance at 5 Hz and 20 Hz
S_{acin}: Acinar airway ventilation heterogeneity
SAD: Small-airway dysfunction
S_{cond}: Conducting airway ventilation heterogeneity
SPT: Skin prick test
Xrs5: Respiratory reactance at 5 Hz

capacity ($FEF_{25-75\%}$) and forced expiratory flow at 75% of FVC.[13] In adults with adult-onset asthma, regular smoking associated with decreased $FEF_{25-75\%}$ and forced expiratory flow at 50% of FVC ($FEF_{50\%}$).[14] In a birth cohort study of South African children, environmental tobacco smoke exposure during the postnatal period resulted in increased LCI at 1 year of age.[15]

We hypothesized that AHR in children younger than 3 years old with persistent or recurrent lower-airway symptoms would be associated with SAD at 7-12 years of age, henceforth referred to as school age. To test this, we compared schoolchildren with early childhood lower-airway symptoms and AHR, their peers without AHR, and reference children. As a secondary objective, we investigated subsequent small-airway lung function in the study children with and without early childhood atopic parameters and exposure to parental smoking and the reference children.

METHODS

Study participants

We enrolled 84 children who had been initially studied at age 6-26 months (median, 15 months) and referred for the examination of persistent or recurrent lower-airway symptoms to the Skin and Allergy Hospital of the Helsinki University Hospital, Finland, between September 22, 2004, and September 14, 2011.[16] The initial exclusion criteria included inhaled corticosteroid use in the previous 4 weeks and respiratory infection symptoms in the preceding 7 days.[16]

Between April 1, 2016, and March 8, 2018, the children attended follow-up visits at age 7.3-13.1 years and discontinued their inhaled corticosteroid medication 4 weeks before and oral antihistamine medication at least 5 days before the lung function measurements. During the weeks preceding the study visits, the study children and their families were instructed to treat symptoms with short-acting bronchodilators and local antihistamine medication. Bronchodilators were discontinued at least 12 hours before the lung function measurements.

Additionally, 40 reference children aged 7.2-12.9 years participated in the study between April 20, 2017, and November 21, 2018. The inclusion criteria were (1) birth at ≥36 weeks of gestation, (2) no diagnosis of acute or chronic respiratory disease, (3) no systemic disease with possible direct or indirect respiratory effects, and (4) no hemodynamically relevant heart disease. All the reference children who met these inclusion criteria were included in the study.[16]

Ethical considerations

The institutional review board of the Helsinki University Hospital approved the study (reference number 211/13/03/03/2015, date of approval August 27, 2015), and written informed consent was obtained from the children's parents at both visits (and written assent obtained from the children themselves at school age) before any tests were performed or samples were drawn.

Methacholine challenge in early childhood

The methacholine challenge in early childhood has previously been described in detail.[17,18] Early childhood AHR was assessed using a dosimetric bronchial methacholine challenge test.[17,18] There were two end points in the challenge test: a decrease of 40% in maximal flow at functional residual capacity (PD40 $V'_{max,FRC}$) or reaching the maximal dose of methacholine.[17,18] AHR in early childhood was defined as PD40 $V'_{max,FRC}$ of ≤300 μg.[16,19]

Skin prick tests in early childhood

In early childhood, skin prick tests (SPTs) for common food and inhalant allergens were conducted as previously described.[17,20] A positive test result was SPT with a wheal diameter of ≥3 mm.[21]

Measurements at school age

Childhood Asthma Control Test questionnaire. To assess the current lower-airway symptoms, all the schoolchildren completed a Childhood Asthma Control Test (C-ACT) questionnaire together with their parents.[22] A C-ACT score of ≤19 indicated insufficient asthma control.[22]

IOS. At school age, respiratory resistance at 5 Hz (Rrs5) and at 20 Hz, respiratory reactance at 5 Hz (Xrs5), and AX were determined using IOS as previously described,[8] according to international guidelines.[23] Briefly, lung function was measured with IOS at baseline and after a 0.4 mg dose of salbutamol. To minimize pressure losses in IOS, the investigator or the parent used their hands to support the cheeks of the child. The measurement was accepted when 3 or more regular tidal breathing patterns lasting at least 20 seconds without signs of artifacts, such as air leak, apnea, swallowing, or speaking, were recorded. The z scores for the IOS parameters were calculated using previously published reference values for Rrs5, Xrs5,[24] Rrs5-20, and AX.[25]

Spirometry. School-age spirometry has been described previously in detail with its published results.[16] In brief, spirometry was conducted using at least 3 successful measurements. Flow indexes, including FVC, FEV_1, and $FEF_{50\%}$, were obtained from the curve with the largest sum of FVC and FEV_1. Because the Global Lung Function Initiative 2012 reference values for spirometry underestimate lung volumes for the native Finnish population,[26] *z* scores were calculated using local reference values for children with at least one ethnic Finnish parent.[27] The Global Lung Function Initiative 2012 reference values were used for children from any other ethnic background.[28] Ethnicity for spirometry *z* score calculation was classified on the basis of the parental reports.

MBNW. MBNW was performed as previously described[8] according to international guidelines[29] by analyzing the washout pattern of endogenous nitrogen during tidal breathing of 100% oxygen. A minimum of two successful recordings were required, and mean values of functional residual capacity (FRC) and LCI illustrating the number of lung turnovers required to wash out the nitrogen to 1/40th ($LCI_{2.5\%}$) and 1/20th ($LCI_{5\%}$) of the initial concentration were used in the analyses. The upper limit of normal values for $LCI_{2.5\%}$ and $LCI_{5\%}$ were defined and FRC *z* scores calculated as previously recommended.[30] Conducting airway ventilation heterogeneity (S_{cond}) and acinar airway ventilation heterogeneity (S_{acin}) were defined according to international guidelines.[29]

Measurement of alveolar nitric concentration and bronchial NO flux

At school age, exhaled NO fraction was measured as previously described[8] at 4 different flow rates (30, 50, 100, and 200 mL/s) with two or more successful measurements required for each flow rate. A 2-compartment linear model[7] with 3 flow rates (100, 200, and 50 mL/s for achieving the best goodness of fit [r^2]) was used to calculate C_{ALV} and J_{NO}.

Definitions

Information on participant sex was obtained from parents and self-reports of the investigated children. Early childhood recurrent wheeze was defined as 3 or more physician-confirmed wheezing episodes during acute respiratory infection before the age of 24 months.[31] Severe wheeze was defined as detailed in Table E4 in the Online Repository. Loose modified Asthma Predictive Index (mAPI) was defined as originally recommended,[31] with the modification that eosinophilia was defined as an eosinophil count of $\geq 0.3 \times 10^9$/L in peripheral blood.[32] Children with early childhood parental smoking had at least one smoking parent living in the same household on the first study visit. Children with prolonged parental smoking had at least one smoking parent living in the same household during both the first and second study visits.

Statistical analysis

The chi-square test or the Fisher exact test (if the expected frequency for over 20% of the cells was <5) was used for group comparisons of independent variables. The unpaired *t* test or 1-way ANOVA was used for analysis of independent continuous variables with normal distribution, and Mann-Whitney *U* test or Kruskal-Wallis test was used for the other continuous or ordinal variables. Correlations were determined by the Spearman rank correlation test. Two-tailed tests were used in all analyses. $P < .05$ was considered statistically significant. The data were analyzed by SPSS v28 for Windows (IBM, Armonk, NY).

RESULTS

Descriptive characteristics and the pre- and postbronchodilator spirometry results of all the investigated children have been previously published. The overall small-airway lung function parameters, baseline spirometry values, and the number of children who participated in each measurement are summarized in Table I. All children were able to perform a technically successful prebronchodilator IOS measurement; however, in the other lung function tests, the number of children with successful measurements was smaller as a result of technical difficulties (Table I). Additionally, 2 study children and 1 reference child did not undergo postbronchodilator IOS measurements.

Early childhood AHR, C-ACT scores, and subsequent prebronchodilator small-airway lung function

Although the originally symptomatic children with or without early childhood AHR had slightly lower school-age C-ACT scores than the reference children, only 9 of 84 study children reported low C-ACT scores indicating insufficient asthma control (Table I). In the prebronchodilator small-airway lung function measurements, the study children with early childhood symptoms and AHR had significantly higher school-age AX *z* score, lower $FEF_{50\%}$ *z* score, and higher $LCI_{2.5\%}$ than their peers without early childhood AHR and the reference children (Fig 1, *A, C,* and *D*). In the baseline Rrs5-20 *z* scores, the difference was not statistically significant between the two study groups, although their values were significantly higher than in the reference children (Fig 1, *B*).

The study children with AHR also had higher prebronchodilator $LCI_{5\%}$ than the study children without AHR and the reference children. There were no statistically significant differences in S_{cond} or S_{acin} among the 3 groups. In a subgroup analysis, the levels of C_{ALV} were similar in the study children with or without AHR and the reference children. However, the study children with AHR had significantly higher $\ln(J_{NO})$ values than their peers without AHR and the reference children (Table I).

Early childhood PD40 $V'_{max,FRC}$ seemed to correlate negatively with school-age prebronchodilator AX *z* score and J_{NO} values, and positively with school-age prebronchodilator FEV_1/FVC and $FEF_{50\%}$ (see Table E1 in the Online Repository available at www.jaci-global.org). In the correlation analyses stratified by the early AHR group, only school-age S_{cond} correlated weakly, which may be due to confounding effect of the study groups or reflect lack of power (see Table E2 in the Online Repository).

Early childhood AHR and subsequent postbronchodilator small-airway lung function

In postbronchodilator measurements, the difference in the AX *z* scores disappeared between the study children with and without early childhood AHR; however, in the children with early

TABLE I. Small-airway lung function measurements at school age

Characteristic	PD40 $V'_{max,FRC} \leq 300$ μg in early childhood		Reference children (group 3)	*P*
	Yes (group 1)	No (group 2)		
Demographic data				
No. of subjects	30	54	40	
C-ACT score, median (IQR)	24 (22, 25)[aaa]	25 (21, 26)[bbb]	27 (26, 27)[aaa,bbb]	<.001*
C-ACT score ≤ 19	2 (7)	7 (13)[b]	0[b]	.034*
IOS				
Rrs5, kPa L^{-1} s^{-1}, mean (SD)	0.56 (0.14)	0.56 (0.14)	0.57 (0.10)	.970
Baseline Rrs5 *z* score, SD, mean (SD)	0.24 (0.51)	0.19 (0.55)	−0.03 (0.53)	.071
Baseline Rrs5 *z* score > 1.65 SD	0	1 (2)	0	1.000
Xrs5, kPa L^{-1} s^{-1}, median (IQR)	−0.17 (−0.19, −0.13)	−0.15 (−0.20, −0.12)	−0.18 (−0.20, −0.15)	.283
Baseline Xrs5 *z* score, SD, median (IQR)	0.21 (−0.29, 0.54)	0.47 (−0.12, 0.83)	0.51 (−0.15, 1.11)	.209
Baseline Xrs5 *z* score < −1.65 SD	2 (7)	4 (7)	0	.199
Baseline √(Rrs5-20, kPa L^{-1} s^{-1}), geometric mean (95% CI)	0.14 (0.12, 0.18)	0.11 (0.09, 0.14)	0.10 (0.08, 0.12)	.103
Baseline Rrs5-20 > 0.15 kPa L^{-1} s^{-1} (75th percentile of controls)	13 (43)	18 (33)	9 (23)	.181
Baseline Rrs5-20 > 0.248 kPa L^{-1} s^{-1} (95th percentile of controls)	5 (17)	6 (11)	2 (5)	.293
Baseline √(AX, kPa L^{-1}), geometric mean (95% CI)	1.01 (0.77, 1.27)	0.82 (0.66, 1.01)	0.84 (0.76, 0.92)	.102
Baseline AX > 1.005 kPa L^{-1} (75th percentile of controls)	14 (47)	19 (35)	10 (25)	.180
Baseline AX > 1.677 kPa L^{-1}(95th percentile of controls)	6 (20)	7 (13)	2 (5)	.150
Baseline AX *z* score > 1.65 SD	6 (20)[aa]	8 (15)[b]	0[aa,b]	.006*
Postbronchodilator change in Rrs5 ≤ −40%	2 (7)	0	0	.059
Postbronchodilator change in AX ≤ −80%	3 (10)	3 (6)	2 (5)	.723
Spirometry	(n = 30)	(n = 52)	(n = 33)	
Baseline FVC, L, mean (SD)	2.83 (0.55)[aa]	2.73 (0.49)[bb]	2.41 (0.55)[aa,bb]	.004*
Baseline FVC *z* score, SD, mean (SD)	−0.56 (0.96)	−0.34 (0.93)	−0.31 (1.04)	.534
Baseline FVC *z* score < −1.65 SD	3 (10)	3 (6)	3 (9)	.741
Baseline FEV_1, L, mean (SD)	2.22 (0.46)	2.24 (0.40)	2.07 (0.43)	.191
Baseline FEV_1 *z* score, SD, mean (SD)	−1.64 (1.23)[aaa,c]	−1.11 (1.10)[b,c]	−0.63 (0.96)[aaa,b]	.002*
Baseline FEV_1 *z* score < −1.65 SD	13 (43)	14 (27)	7 (21)	.135
Baseline FEV_1/FVC, mean (SD)	0.78 (0.05)[aaa,cc]	0.82 (0.06)[bbb,cc]	0.86 (0.05)[aaa,bbb]	<.001*
Baseline FEV_1/FVC *z* score, SD, mean (SD)	−1.85 (0.93)[aaa,c]	−1.30 (1.07)[bb,c]	−0.59 (0.86)[aaa,bb]	<.001*
Baseline FEV_1/FVC *z* score < −1.65 SD	17 (56)[aaa]	21 (40)[b]	5 (15)[aaa,b]	.003*
Baseline $FEF_{50\%}$, L s^{-1}, median (IQR)	2.09 (1.90, 2.52)	2.52 (2.06, 3.01)	2.38 (1.97, 2.90)	.094
Multiple breath nitrogen washout	(n = 26)	(n = 45)	(n = 20)	
FRC *z* score, SD, mean (SD)	0.43 (1.38)	0.30 (1.11)	1.01 (0.96)	.080
$LCI_{2.5\%}$ > 7.91	2 (7)	1 (2)	0	.433
$LCI_{5\%}$, median (IQR)	4.97 (4.67, 5.20)[aaa,c]	4.87 (4.57, 4.99)[bb,c]	4.60 (4.45, 4.72)[aaa,bb]	<.001*
$LCI_{5\%}$ > 5.73	2 (7)	1 (2)	0	.433
S_{cond}, median (IQR)	0.024 (0.012, 0.029)	0.022 (0.018, 0.032)	0.024 (0.015, 0.030)	.812
S_{acin}, median (IQR)	0.066 (0.038, 0.094)	0.060 (0.038, 0.082)	0.053 (0.033, 0.101)	.541
NO measurements	(n = 9)	(n = 31)	(n = 18)	
C_{ALV}, ppb, median (IQR)	2.56 (1.12, 6.19)	1.44 (0.87, 1.75)	1.41 (0.92, 2.17)	.225
ln(J_{NO}), nL/s, geometric mean (95% CI)	0.67 (0.33, 1.36)[aa,c]	0.33 (0.25, 0.44)[c]	0.27 (0.21, 0.35)[aa]	.011*

Data are presented as n (%) unless otherwise indicated. Same letter denotes significant difference in pairwise comparison: [a]group 1 versus 3, [b]group 2 versus 3, and [c]group 1 versus 2. Number of symbols refers to level of significance: [a]$P < .05$, [aa]$P < .01$, and [aaa]$P < .001$.

CI, Confidence interval; *IQR,* interquartile range; *SD,* standard deviation.

*Statistically significant.

childhood AHR, the postbronchodilator AX *z* scores remained higher than those of the reference children (Fig 2, *A*). In study children with early childhood AHR, the postbronchodilator $FEF_{50\%}$ *z* scores remained decreased, in contrast to both their counterparts without AHR and the reference children (Fig 2, *B*).

Early childhood wheeze, atopic markers, and subsequent small-airway lung function

In the study children with and without early childhood recurrent wheeze, with and without history of wheeze-related hospitalization, or with and without severe wheeze, there were no differences in their subsequent pre- or postbronchodilator

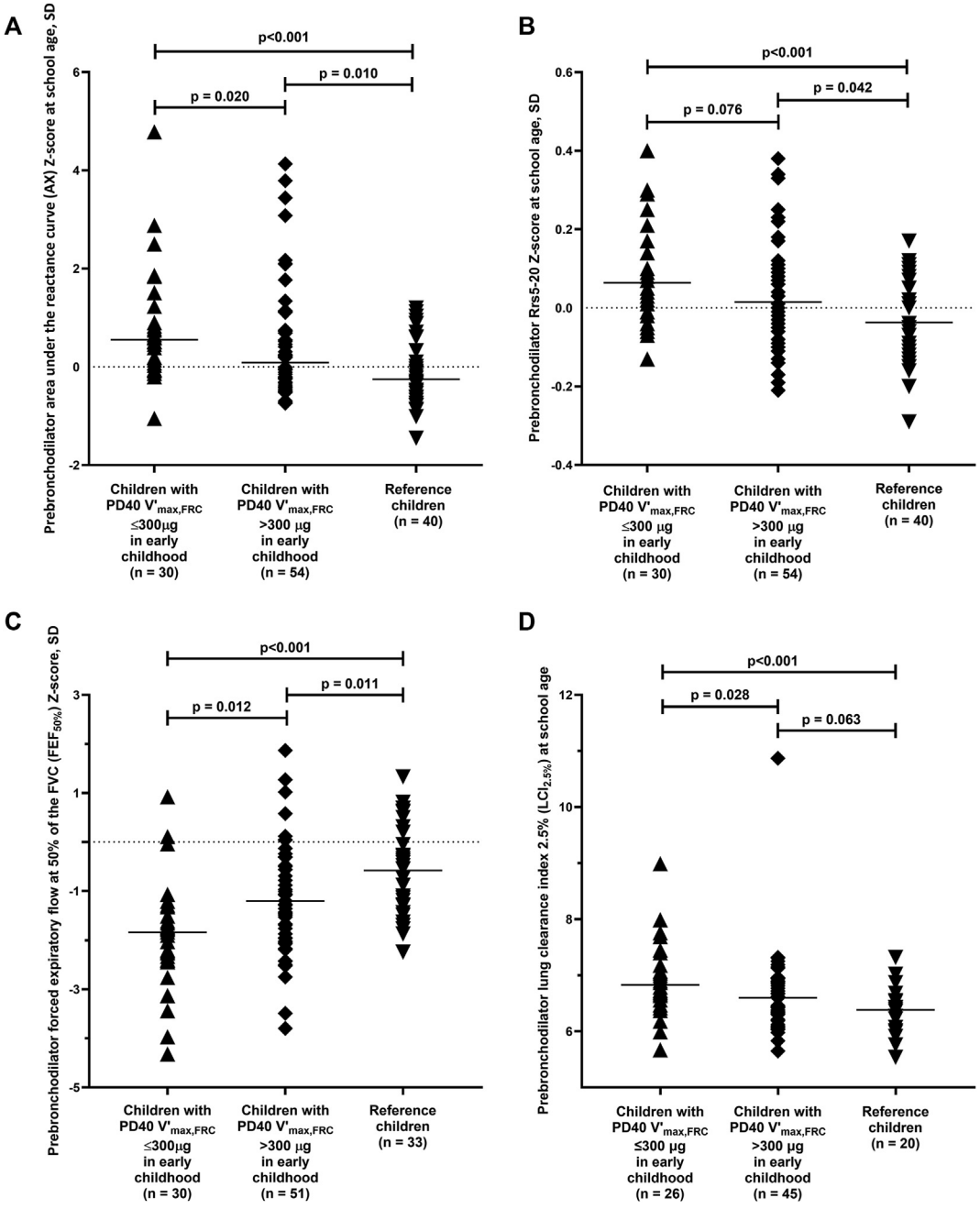

FIG 1. Relationship between AHR (defined as PD40 $V'_{max,FRC} \leq 300$ µg) in early childhood and subsequent prebronchodilator AX, Rrs5-20, and $FEF_{50\%}$ *z* scores **(A-C),** and $LCI_{2.5\%}$ **(D)**. *Horizontal lines* indicate median *(A)* or mean *(B-D)* values.

small-airway lung function (see Tables E3-E5 in the Online Repository available at www.jaci-global.org). However, the study children with early childhood positive loose mAPI exhibited slightly lower school-age prebronchodilator Rrs5-20 *z* score than those without (see Table E6 in the Online Repository). Investigation of the study children with early childhood blood eosinophilia revealed a higher proportion of boys, and the children with early blood eosinophilia had slightly greater FRC *z* scores than the study children without blood eosinophilia; however, no differences in subsequent small-airway lung function emerged between the two groups (see Table E7 in the Online Repository).

The C-ACT scores were clearly lower in the children with early childhood positive SPT results than their peers without and the reference children; moreover, the decreased C-ACT score indicating insufficient asthma control was most frequent in children with early childhood positive SPT. When compared with the reference children, neither the study children with nor their peers without early childhood positive SPT showed statistically significant differences in their subsequent

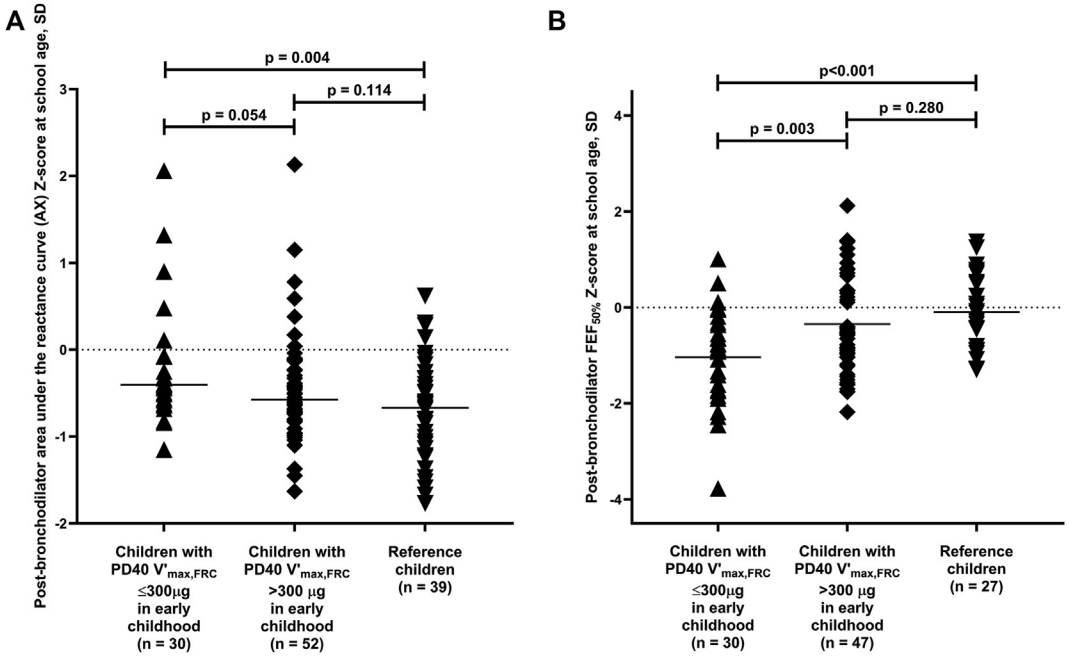

FIG 2. Relationship between AHR (defined as PD40 $V'_{max,FRC} \leq 300$ μg) in early childhood and subsequent postbronchodilator AX *z* score **(A)** and $FEF_{50\%}$ *z* score **(B)**. *Horizontal lines* indicate median *(A)* or mean *(B)* values.

pre- or postbronchodilator small-airway lung function. In the subgroup analysis, those with early childhood positive SPT had significantly higher subsequent J_{NO} than those without early childhood positive SPT or the reference children (Table II).

Parental smoking in early childhood and subsequent small-airway lung function

The study children with (n = 25) or without (n = 52) early childhood parental smoking exhibited no significant differences compared with the reference children in their subsequent small-airway lung function (Table III). Likewise, early childhood exposure to maternal smoking or exposure to prolonged parental smoking was not associated with subsequent altered small-airway function (see Tables E8 and E9 in the Online Repository available at www.jaci-global.org).

DISCUSSION

In this novel prospective follow-up study of children with persistent or recurrent early childhood lower-airway symptoms, the children with early symptoms and AHR had higher school-age prebronchodilator AX and lower $FEF_{50\%}$ *z* scores than their peers without AHR and the reference children. Additionally, in the prebronchodilator MBNW measurements, individuals with early childhood lower-airway symptoms and AHR had elevated LCI at both 2.5% and 5% of the washout, indicating compromised ventilation homogeneity. Interestingly, the children with early childhood symptoms and AHR had higher postbronchodilator AX *z* scores than the reference children as well as lower $FEF_{50\%}$ *z* scores than both their peers without early childhood AHR or the reference children. Our results indicate that early childhood AHR is linked to subsequent SAD, which persists at least partly after bronchodilatation. Our secondary analysis did not show discernible associations between atopic markers in early childhood, exposure to maternal or parental smoking during early childhood, or even prolonged parental smoking and the manifestation of SAD in school-age children.

To the best of our knowledge, there is limited evidence on the association between early childhood AHR and subsequent SAD. In our study, we observed that children with lower-airway symptoms and AHR during early childhood had marked modifications in school-age small-airway lung function. Specifically, these modifications were characterized by elevated prebronchodilator AX *z* score, reduced $FEF_{50\%}$ *z* score, and increased $LCI_{2.5\%}$ compared with their counterparts without AHR and the reference children. Our results are partly consistent with a prior study where children aged 6-18 years with asthma, atopic sensitization, and AHR had higher baseline tidal volume corrected S_{cond} values than their peers without AHR, and slightly higher baseline LCI and clearly higher tidal volume–corrected S_{cond} and S_{acin} than controls.[33]

Previously, we reported that early childhood AHR in our study children was associated with subsequent decreased prebronchodilator FEV_1 and FEV_1/FVC *z* score and that this obstructive lung function improved after bronchodilation.[16] However, in the current study, the same children with early childhood AHR had higher postbronchodilator AX *z* scores than the reference children and lower $FEF_{50\%}$ *z* scores than their peers without early childhood AHR or the reference children. This is consistent with a previous study in which children aged 5-15 years with well-controlled asthma and normal FEV_1 had higher $LCI_{2.5\%}$ than controls also after bronchodilation, indicating persistent SAD undetected by FEV_1.[6] Our findings may indicate partly persistent ventilation heterogeneity in the small airways that is linked with AHR originating already in early childhood.

TABLE II. SPT-positive results in early childhood in relation to subsequent small-airway lung function

Characteristic	SPT positive in early childhood		Reference children	P
	Yes (group 1)	No (group 2)	(group 3)	
Demographic data				
No. of subjects	22	57	40	
Male sex	17 (77)	40 (70)	23 (58)	.229
Age, years, mean (SD)	11.7 (1.0)^{aa}	11.1 (1.4)^{b}	10.4 (1.8)^{aa,b}	.002*
Height, cm, mean (SD)	149.5 (7.5)^{aa}	146.7 (9.4)^{b}	141.9 (11.8)^{aa,b}	.011*
C-ACT score, median (IQR)	22 (20, 25)^{aaa,cc}	25 (23, 26)^{bbb,cc}	27 (26, 27)^{aaa,bbb}	<.001*
C-ACT score ≤ 19	5 (23)^{aa,c}	3 (5)^{c}	0^{aa}	.003*
IOS				
Rrs5 z score, SD, mean (SD)	0.10 (0.43)	0.26 (0.57)^{b}	−0.03 (0.53)^{b}	.034*
Baseline Rrs5 z score > 1.65 SD	0	1 (2)	0	1.000
Xrs5 z score, SD	0.20 (−0.24, 0.71)	0.34 (−0.19, 0.79)	0.51 (−0.15, 1.11)	.423
Baseline Xrs5 z score < −1.65 SD	1 (5)	5 (9)	0	.133
Baseline Rrs5-20 z score, SD, median (IQR)	−0.02 (−0.08, 0.09)	0.01 (−0.05, 0.09)^{bb}	−0.05 (−0.12, 0.06)^{bb}	.021*
Baseline AX z score, SD, median (IQR)	0.16 (−0.20, 0.69)^{a}	0.46 (−0.27, 1.11)^{bbb}	−0.26 (−0.60, 0.27)^{a,bbb}	<.001*
Baseline AX z score > 1.65 SD	4 (18)^{a}	10 (18)^{bb}	0^{a,bb}	.005*
Postbronchodilator change in Rrs5, %, mean (SD)	−20 (8)^{a}	−21 (10)^{bbb}	−12 (13)^{a,bbb}	<.001*
Postbronchodilator change in Rrs5 < −40%	0	2 (4)	0	.678
Postbronchodilator change in AX < −80%	2 (9)	4 (7)	2 (5)	.892
Spirometry	(n = 22)	(n = 55)	(n = 33)	
Baseline FVC, z score, SD, mean (SD)	−0.40 (0.99)	−0.41 (0.96)	−0.31 (1.04)	.894
Baseline FVC z score < −1.65 SD	2 (9)	4 (7)	3 (9)	1.000
Baseline FEV_1, z score, SD, median (IQR)	−1.23 (−2.11, −0.79)^{aa}	−1.14 (−2.07, −0.48)^{b}	−0.47 (−1.48, 0.17)^{aa,b}	.013*
Baseline FEV_1 z score < −1.65 SD	7 (32)	19 (35)	7 (21)	.409
Baseline FEV_1/FVC z score, SD, mean (SD)	−1.88 (1.03)^{aaa}	−1.41 (1.02)^{bbb}	−0.59 (0.86)^{aaa,bbb}	<.001*
Baseline FEV_1/FVC z score < −1.65 SD	14 (64)^{aaa}	23 (42)^{bb}	5 (15)^{aaa,bb}	.001*
Baseline $FEF_{50\%}$ z score, SD, mean (SD)	−1.79 (1.12)^{aaa}	−1.33 (1.18)^{bb}	−0.58 (0.94)^{aaa,bb}	<.001*
Postbronchodilator change in FEV_1, %, median (IQR)	7 (5, 10)^{aaa}	5 (2, 9)^{bb}	3 (1, 5)^{aaa,bb}	<.001*
Postbronchodilator change in FEV_1 ≥12% and ≥0.20 L	4 (19)^{a}	10 (19)^{b}	0^{a,b}	.022*
MBNW	(n = 21)	(n = 46)	(n = 20)	
FRC z score, SD, mean (SD)	0.50 (1.39)	0.41 (1.05)	1.01 (0.96)	.137
$LCI_{2.5\%}$, median (IQR)	6.79 (6.36, 7.17)^{a}	6.64 (6.31, 6.94)^{b}	6.39 (6.03, 6.55)^{a,b}	.019*
$LCI_{2.5\%}$ > 7.91	2 (10)	0	0	.107
$LCI_{5\%}$, median (IQR)	4.96 (4.67, 5.16)^{aaa}	4.88 (4.62, 4.98)^{bb}	4.60 (4.45, 4.72)^{aaa,bb}	<.001*
$LCI_{5\%}$ > 5.73	2 (10)	0	0	.107
S_{cond}, median (IQR)	0.022 (0.012, 0.037)	0.023 (0.017, 0.029)	0.024 (0.015, 0.030)	.978
S_{acin}, median (IQR)	0.081 (0.048, 0.095)	0.054 (0.038, 0.073)	0.053 (0.033, 0.101)	.195
NO measurements	(n = 7)	(n = 30)	(n = 18)	
C_{ALV}, ppb, median (IQR)	1.75 (1.31, 8.29)	1.42 (0.85, 2.02)	1.42 (0.92, 2.17)	.215
J_{NO}, nL/s, median (IQR)	1.48 (0.51, 1.92)^{aa,cc}	0.29 (0.20, 0.49)^{cc}	0.27 (0.19, 0.42)^{aa}	.016*

Data are presented as n (%) unless otherwise indicated. Same letter denotes significant difference in pairwise comparison: [a]group 1 versus 3, [b]group 2 versus 3, and [c]group 1 versus 2. Number of symbols refers to level of significance: $^{a}P < .05$, $^{aa}P < .01$, and $^{aaa}P < .001$. *IQR,* Interquartile range; *SD,* standard deviation.
*Statistically significant.

In our study sample, the levels of both prebronchodilator S_{acin} and S_{cond} were similar in both study children with and without AHR and the reference children. Currently, S_{acin} is considered likely to be the most specific of the indexes of ventilation heterogeneity. Acinar structure is expected to be normal when S_{acin} is unchanged.[4] In contrast, elevated S_{cond} can result from both proximal and peripheral airway alterations and should always be combined with spirometry.[4] In adults with asthma, SAD is associated particularly with severe asthma, and baseline S_{acin} is elevated most frequently in patients with the most severe symptoms.[5] Our study children had persistent or recurrent lower-airway symptoms in early childhood that were generally well controlled. Accordingly, these children often reported mild or no asthma symptoms at school age, which was also reflected in their only slightly decreased C-ACT scores. This symptom remission may explain why the baseline levels of S_{acin} and S_{cond} in our study children were no different from the reference children.

TABLE III. Parental smoking during early childhood in relation to subsequent small-airway lung function

Characteristic	Parental smoking in early childhood		Reference children	P
	Yes (group 1)	No (group 2)	(group 3)	
Demographic data				
No. of subjects	25	52	40	
Male sex	16 (64)	39 (75)	23 (58)	.214
Age, years	11.2 (1.3)	11.3 (1.4)	10.4 (1.8)	.052
Height, cm	147.8 (9.8)^{aa}	147.2 (8.3)^{b}	141.9 (11.8)^{aa,b}	.011*
C-ACT score, median (IQR)	24 (20, 26)^{aaa}	24 (22, 26)^{bbb}	27 (26, 27)^{aaa,bbb}	<.001*
C-ACT score ≤ 19	5 (20)^{aa}	3 (6)	0^{aa}	.010*
IOS				
Rrs5 z score, SD, mean (SD)	0.20 (0.73)	0.23 (0.43)	−0.03 (0.53)	.069
Baseline Rrs5 z score > 1.65 SD	1 (4)	0	0	.214
Xrs5 z score, SD, median (IQR)	0.22 (−0.75, 0.75)	0.38 (0.07, 0.77)	0.51 (−0.15, 1.11)	.295
Baseline Xrs5 z score < −1.65 SD	4 (16)^{a}	2 (4)	0^{a}	.017*
Baseline Rrs5-20 z score, SD, median (IQR)	0.00 (−0.06, 0.09)	0.00 (−0.06, 0.09)	−0.05 (−0.12, 0.06)	.050
Baseline AX z score, SD, median (IQR)	0.08 (−0.39, 1.03)^{a}	0.32 (−0.20, 1.05)^{bbb}	−0.26 (−0.60, 0.27)^{a,bbb}	<.001*
Baseline AX z score > 1.65 SD	5 (20)^{aa}	9 (17)^{bb}	0^{aa,bb}	.004*
Postbronchodilator change in Rrs5, %, mean (SD)	−20 (10)^{aa}	−21 (9)^{bbb}	−12 (13)^{aa,bbb}	<.001*
Postbronchodilator change in Rrs5 < −40%	1 (4)	1 (2)	0	.488
Postbronchodilator change in AX < −80%	2 (9)	4 (8)	2 (5)	.804
Spirometry	(n = 24)	(n = 52)	(n = 33)	
Baseline FVC z score, SD	−0.44 (1.13)	−0.42 (0.89)	−0.31 (1.04)	.852
Baseline FVC z score < −1.65 SD	3 (13)	3 (6)	3 (9)	.486
Baseline FEV_1 z score, SD	−1.42 (1.59)^{a}	−1.28 (0.99)^{b}	−0.63 (0.96)^{a,b}	.009*
Baseline FEV_1 z score < −1.65 SD	9 (38)	17 (33)	7 (21)	.373
Baseline FEV_1/FVC z score, SD	−1.63 (1.28)^{aaa}	−1.49 (0.94)^{bbb}	−0.59 (0.86)^{aaa,bbb}	<.001*
Baseline FEV_1/FVC z score < −1.65 SD	11 (46)^{a}	25 (48)^{bb}	5 (15)^{a,bb}	.006*
Baseline $FEF_{50\%}$ z score, SD, mean (SD)	−1.50 (1.53)^{aa}	−1.43 (1.03)^{bb}	−0.58 (0.94)^{aa,bb}	<.001*
Postbronchodilator change in FEV_1, %, median (IQR)	5 (4, 9)^{a}	6 (4, 10)^{bbb}	3 (1, 5)^{a,bbb}	.002*
Postbronchodilator change in FEV_1 ≥12% and ≥0.20 L	4 (17)^{a}	10 (20)^{b}	0^{a,b}	.022*
MBNW	(n = 21)	(n = 45)	(n = 20)	
FRC z score, SD, mean (SD)	0.14 (1.01)^{a}	0.47 (1.22)	1.01 (0.96)^{a}	.049*
$LCI_{2.5\%}$, median (IQR)	6.70 (6.24, 7.02)	6.64 (6.33, 6.95)^{b}	6.39 (6.03, 6.55)^{b}	.047*
$LCI_{2.5\%}$ > 7.91	1 (5)	2 (5)	0	1.000
$LCI_{5\%}$, median (IQR)	4.70 (4.55, 5.01)^{a}	4.89 (4.64, 5.01)^{bbb}	4.60 (4.45, 4.72)^{a,bbb}	.003*
$LCI_{5\%}$ > 5.73	1 (5)	2 (4)	0	1.000
S_{cond}, median (IQR)	0.025 (0.015, 0.036)	0.022 (0.018, 0.029)	0.024 (0.015, 0.030)	.549
S_{acin}, median (IQR)	0.051 (0.038, 0.070)	0.065 (0.045, 0.089)	0.053 (0.033, 0.101)	.572
NO measurements	(n = 9)	(n = 27)	(n = 18)	
C_{ALV}, ppb, median (IQR)	1.44 (0.89, 2.64)	1.39 (0.87, 2.06)	1.41 (0.92, 2.17)	.988
$ln(J_{NO})$, nL/s, geometric mean (95% CI)	0.35 (0.19, 0.64)	0.64 (0.40, 0.28)	0.27 (0.21, 0.35)	.253

Data are presented as n (%) unless otherwise indicated. Same letter denotes significant difference in pairwise comparison: [a]group 1 versus 3, [b]group 2 versus 3, and [c]group 1 versus 2. Number of symbols refers to level of significance: $^{a}P < .05$, $^{aa}P < .01$, and $^{aaa}P < .001$.

CI, Confidence interval; *IQR,* interquartile range; *SD,* standard deviation.

*Statistically significant.

Even though we did not observe any differences in the values of C_{ALV} in the subgroup analysis, the children with early childhood symptoms and AHR had clearly higher $ln(J_{NO})$ values than their peers without AHR and the reference children. In a recent meta-analysis, adults with asthma had higher baseline C_{ALV} and J_{NO} than healthy controls.[34] The children aged 5-10 years with recurrent wheeze also had higher C_{ALV} than healthy children.[8] Possibly our small subgroup size, caused by technical difficulties in the measurement of C_{ALV}, prevented us from entirely duplicating these findings.

In the secondary analyses, the study children with early childhood positive SPT result had at school age similar small-airway lung function as that of their peers without early childhood positive SPT. Likewise, early childhood positive loose mAPI or eosinophilia were not associated with subsequent SAD. In children aged 4-6 years with multiple-trigger wheeze, LCI and S_{cond} were higher than in their peers with episodic wheeze or controls, independent of positive SPT, current eczema, or both.[35] Moreover, when children aged 7-10 years with asthma were investigated using a longitudinal trajectory clustering method, a cluster

of children with frequent early childhood exacerbations, relatively high asthma treatment rates, and SAD measured with decreased $FEF_{25-75\%}$ z score was identified, without any significant differences in the rates of atopy (>1 positive response in SPT) or allergic sensitization in comparison with other asthma clusters.[36]

Previously, postnatal exposure to environmental tobacco smoke was associated with decreased school-age $FEF_{25-75\%}$ and forced expiratory flow at 75% of FVC, but these changes were significantly reduced after adjusting for prenatal smoking exposure, which seemed to have an independent association with subsequent SAD.[13] This is consistent with our findings, as in our study children, early childhood parental or maternal smoking or prolonged parental smoking were not associated with subsequent SAD.

The strength of our study is that at school age, all the investigated children discontinued inhaled corticosteroid medication at least 4 weeks before and oral antihistamines at least 5 days before undergoing comprehensive small-airway lung function tests, thus reducing the effect of anti-inflammatory medication on the measurements. Moreover, we used several different methods to investigate school-age small-airway lung function. Even though technical difficulties meant that not every child could perform all the selected lung function tests, IOS measurements were successful and of high quality in all the schoolchildren. To our knowledge, no previous studies have used similar methods to describe the relationship between early childhood AHR and subsequent small-airway lung function.

Our results are limited by the generally recognized fact that current methods of assessing small-airway lung function rely on at-the-mouth noninvasive measurements, despite aiming to interpret the function of a complex, cyclically changing cul-de-sac structure several airway generations away.[4] Nonetheless, as the link between early childhood AHR and subsequent lung function was observed in several methods proposed to reflect small airways, their association seems plausible. Further studies are required to determine whether early AHR predicts small-airway disease later in life.

In conclusion, current guidelines recommend primarily pre- and postbronchodilator spirometry in diagnosing[37] and managing[38] asthma during school age. However, conventional spirometry often fails to detect SAD despite its potential impact on asthma control and severity. Our longitudinal study showed that the children experiencing lower-airway symptoms and AHR before the age of 3 years had altered small-airway lung function at school age, characterized by elevated prebronchodilator AX z score, diminished $FEF_{50\%}$ z score, and heightened $LCI_{2.5\%}$. Moreover, these differences in AX and $FEF_{50\%}$ z scores persisted at least partly after bronchodilation. Future studies are warranted to determine whether this connection can be used to predict the development of asthma or other obstructive pulmonary diseases.

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Key messages

- **Symptomatic early childhood AHR is linked with subsequent SAD, which only partially improves after bronchodilatation.**
- **Further studies with larger samples are warranted to determine whether this connection predicts future development of asthma or other obstructive pulmonary diseases.**

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