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Recurrent wheeze and its relationship with lung function and airway inflammation in preschool children: a cross-sectional study in South Korea

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ABSTRACT

Background Relationship between recurrent wheeze and airway function and inflammation in preschool children is not fully known.

Objective To investigate the relationship between recurrent wheeze and airway inflammation, lung function, airway hyper-reactivity (AHR) and atopy in preschool children.

Design Observational study, comparing forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and mid-forced expiratory flow ($FEF_{25\%–75\%}$), dose–response slope (DRS), exhaled nitric oxide (eNO) and atopic sensitisation between children with recurrent wheeze and those without.

Setting Population-based, cross-sectional study in Seoul and the Gyeonggi province of Korea conducted as a government-funded programme to perform standardised measurement of the prevalence of allergic diseases, and related factors, in preschool children.

Participants 900 children aged 4–6 years.

Primary and secondary outcome measures eNO, FEV_1/FVC, $FEF_{25\%–75\%}$, DRS, atopic sensitisation and allergic diseases.

Methods Children completed the modified International Study of Asthma and Allergies in Childhood questionnaire and underwent eNO assessments, spirometry, methacholine bronchial provocation tests and skin prick tests. Recurrent wheeze was defined as having a lifetime wheeze of more than three episodes, based on the questionnaire. The frequency of hospitalisation and emergency room visits was also obtained by means of the questionnaire. 'Current' wheeze was defined as having symptoms or treatments within the past 12 months.

Results The prevalence of recurrent wheeze was 13.4%. Children with recurrent wheeze showed a higher prevalence of lifetime or current allergic rhinitis (p=0.01 and p=0.002, respectively) and lifetime atopic dermatitis (p=0.007). Children with recurrent wheeze showed lower FEV_1/FVC (p=0.033) and $FEF_{25\%–75\%}$ (p=0.004), and higher eNO levels (p=0.013) than those without recurrent wheeze. However, the DRS, prevalence of atopic sensitisation and serum IgE levels were not significantly different between the two groups.

Conclusions Recurrent wheeze in preschool children may be associated with airway inflammation and diminished airway function, but not with AHR or atopy.

Strengths and limitations of this study

- This was a large-scale, population-based epidemiologic study to investigate the relationship between recurrent wheeze of more than three episodes and airway inflammation, lung function, airway hyper-reactivity and atopic sensitisation using objective parameters in preschool children aged 4–6 years.
- We measured forced expiratory volume in 1 s/forced vital capacity, mid-forced expiratory flow, exhaled nitric oxide and PC_{20} to evaluate lung function, airway inflammation and airway hyper-reactivity in preschool children.
- Since this was a cross-sectional study, we could not evaluate the cause-and-effect relationship between recurrent wheeze and development of asthma or airway function.
- Prevalence of allergic diseases was evaluated based on parents' report using ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire, and not based on chart review or doctor's examination.

INTRODUCTION

Wheezing is common among preschool children and infants, and can be related to many medical conditions. However, persistent recurrent wheezing has a considerable impact on health and may lead to asthma.

The concept of wheezing phenotypes, that is, transient early wheezing, late-onset wheezing and persistent wheezing, has been proposed.[1] Even though approximately 40% of infants show wheezing in their first

year of life, only 30% of them persistently wheeze by the age of 6 years.[2]

According to the newly revised Global Initiative for Asthma (GINA) guideline, the frequency and severity of wheezing episodes and the temporal pattern of symptoms should be taken into account in the diagnosis of asthma in children, 5 years and younger.[3] Despite a great deal of research focusing on predicting wheezing phenotypes before the age of 6, no attempt has yet been successful; therefore, such prospective allocation of individual children to wheezing phenotypes has been unreliable in clinical situations.[4]

Airway inflammation, reversible airway obstruction and airway hyper-reactivity (AHR) are the main pathophysiological factors of asthma. Documenting these findings using lung function tests, bronchial provocation tests or fractional exhaled nitric oxide (FeNO) is helpful in establishing a diagnosis of asthma. However, due to the limitations of these procedures, diagnosis of asthma in preschool children is mostly based on the assessment of symptoms, risk factors and therapeutic responses.

Risk factors such as eczema, allergic rhinitis (AR), wheeze apart from cold, parental asthma and blood eosinophilia are used as predictive tools of asthma.[5] However, it is still challenging to distinguish asthma from transient wheeze, which has been predicted to have a better prognosis in preschool children, because measurement of lung function or airway inflammation is not easy and cannot be performed routinely in preschool-aged children.

Therefore, in order to diagnose, manage and predict a prognosis of wheezy infants, it is important to explore the relationship between recurrent wheezing and asthma, and the relationship between recurrent wheezing and airway function or other allergic characteristics. However, there are little data on airway function parameters, such as reversible airway obstruction, airway inflammation or AHR, in preschool children, and their relationship with recurrent wheeze.

This study aimed to investigate the association between recurrent wheeze and airway inflammation, lung function and AHR, as well as asthma-related risk factors such as AR, atopic dermatitis (AD) and parental asthma, in preschool children.

METHODS

Study design

We performed a population-based, cross-sectional study among 933 children aged 4–6 years between July 2010 and August 2010 in 16 child care centres from Seoul and the Gyeonggi province, which were metropolitan city and the most densely populated urban areas in Korea. Child care centres were randomly selected from among middle-class homes of average household income in Korea. This study was conducted as a government-funded programme to perform standardised measurement of the prevalence of allergic diseases, and related factors, in preschool children.

Parents of all 933 children completed a modified International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. Of this, 900 children whose parents answered the frequency of lifetime wheeze were eligible for inclusion in the study. The questionnaire was based on the Korean version of ISAAC.[6 7] Key questions included the history of symptoms suggestive of asthma, especially wheezing episodes, physician-diagnosed asthma, AR or AD, as in the original ISAAC questionnaire. To interpret the results, recurrent wheeze was defined as a lifetime wheeze of more than three episodes, based on the questionnaire. The frequency of hospital admissions and emergency room (ER) visits was obtained by means of the questionnaire. The 'current' was defined as having symptoms or treatments within the last 12 months and 'lifetime' was defined as having symptoms or treatments at any point in a lifetime.

eNO assessments (n=379), spirometry (n=491), methacholine bronchial provocation (n=214) and skin prick tests (n=659) were performed on children who could afford the tests and had not taken any medication or shown symptoms of respiratory infections within 1 month of the tests. All the tests were done at the child care centres by trained field technicians. All the tests were conducted by the same researchers to ensure standardisation of the survey results.

Outcome variables were prevalence of asthma, AR or AD according to 'current' (within 1 year) or 'lifetime' status, and atopic sensitisation, as well as serum total IgE, blood eosinophil counts and lung function parameters such as forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), mid-forced expiratory flow ($FEF_{25\%–75\%}$), dose–response slope (DRS) and eNO.

Written informed consent was obtained from all participants' parents or guardians after they were fully informed of the details of the study.

Exhaled nitric oxide

The level of fraction of eNO was measured using a Niox Mino device (Aerocrine, Solna, Sweden) as described in our previous study.[6] Children inhaled through a nitric oxide scrubbing filter and immediately exhaled at a constant flow rate of 50 mL/s. Three exhalations were performed with at least 30 s intervals between repetitions, and the mean FeNO was recorded. Children did not wear a nose clip to avoid nasal contamination.[8 9]

Pulmonary function and methacholine bronchial provocation tests

Pulmonary function tests were performed using a portable Micro Plus spirometer (Micro Medical, UK) according to the guidelines of the American Thoracic Society.[10] Predicted values were calculated using reference equations from European Community for Coal and Steel. We measured FEV_1, FVC and $FEF_{25\%–75\%}$. All technically satisfactory manoeuvres were recorded, and the best of three

forced expiratory volume curves was used to determine the % predicted value of FEV_1, $FEF_{25\%-75\%}$ and the FEV_1/FVC ratio.

Methacholine challenge tests were performed using the same method as described in our previous study.[11] In short, methacholine (Sigma Chemicals, St Louis, MO) solutions were prepared at concentrations of 0.625, 1.25, 2.5, 5, 10 and 25 mg/mL in buffered saline solution (pH 7.4), and each subject inhaled five inspiratory breaths of each of the solutions, from the lowest to a higher concentration, until the highest concentration of methacholine was reached (25 mg/mL) or there was a ≥20% decrease from baseline FEV_1. Airway responsiveness was expressed as the concentration of methacholine required to induce a 20% fall in FEV_1 (PC_{20}), and AHR was defined as a PC_{20} value of ≤8 mg/mL.

The DRS was defined as the percentage decline of FEV_1, from the postsaline value to the value measured after the final methacholine dose administered, divided by the final cumulative methacholine dose administered.

Serum total IgE concentrations and blood eosinophils

Serum total IgE concentrations were measured via fluorescent enzyme immunoassay (Pharmacia CAP System; Pharmacia Diagnostics AB, Uppsala, Sweden). Blood eosinophil levels were counted using an automatic blood cell counter (XE-100, Sysmex, Kobe, Japan),[12] and each result was converted to a logarithmic value for analysis.

Atopic sensitisation

A skin prick test (Allergopharma, Reinbek, Germany) was performed on each participant using 16 common allergens: house dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*), animal dander (cat and dog epithelia), pollen (mugwort, ragweed, grass and tree pollen mix 1 and 2), moulds (*Aspergillus fumigatus* and *Alternaria alternata*), cockroaches (*Blattella germanica*) and food (milk, soybean, egg white and peanut). Histamine was used as a positive control and isotonic saline was used as a negative control. The skin prick test was considered positive when the mean wheal size in response to an allergen was greater than 3 mm and at least equal to or greater than the mean wheal size in response to histamine. Atopy was defined as a positive skin prick test for any allergen.

Statistical analysis

Statistical analyses were performed using STATA V.11.0 (StataCorp, College Station, TX). Mean values were compared between two different groups using Student's t-test, and between three different groups using one-way analysis of variance. Post hoc multiple comparisons were carried out using Bonferroni corrections. The significance of between-group differences of categorical variables was explored using χ^2 tests.

Multivariate logistic regression was used to determine the associations between lung function tests and asthma-related risk factors with recurrent wheeze. Adjusted ORs and 95% CIs were derived after adjusting for age, sex, height and weight. All data were expressed as means±SDs and significance was defined as a p value less than 0.05.

Table 1 Clinical characteristics of study subjects

Variable	Mean±SD or n (%)
Age (years)	4.9±1.1
Male	463 (51.4)
Recurrent wheeze	121 (13.4)
Lifetime wheeze	228 (25.3)
Lifetime asthma	78 (8.7)
Current asthma	40 (4.4)
Lifetime AR	403 (44.8)
Current AR	321 (35.7)
Lifetime AD	315 (35.0)
Current AD	149 (16.5)
Atopic sensitisation	201 (22.3)
Parental history of asthma	101 (11.2)
Parental history of AR	484 (53.8)
Parental history of AD	254 (28.2)
AHR*	75 (35.1)

Atopic sensitisation: positive skin prick test for any allergen.
Wheeze, asthma, AR, AD: based on the questionnaire.
*AHR, PC_{20} value of ≤8 mg/mL in methacholine provocation test.
AD, atopic dermatitis; AHR, airway hyper-reactivity; AR, allergic rhinitis.

RESULTS

Clinical characteristics of study subjects

The mean age of the study subjects was 4.9 years; 51.4% were male with no significant difference in gender. Prevalence results were as follows: lifetime wheeze and recurrent wheeze were present in 25.3% and 13.4% of the children, respectively; physician-diagnosed current asthma within the last 1 year and lifetime asthma were present in 4.4% and 8.7% of the children, respectively; current AR and AD were present in 35.7% and 16.5% of the children, and lifetime AR and AD in 44.8% and 35.0% of the children, respectively; parental asthma, AR and AD were present in 11.2%, 53.8% and 28.2% of the children, respectively; atopic sensitisation and AHR were present in 22% and 35.1% of the children, receptively (table 1).

We compared the clinical characteristics of children who had undergone at least one objective test, including spirometry, methacholine bronchial provocation test and eNO measurement (n=531), with those who had not (n=369). The average age (mean±SD) of children who underwent eNO, spirometry, methacholine bronchial provocation and skin prick tests was 5.4±0.7, 5.3±0.7, 5.9±0.3 and 4.9±0.9 years, respectively. Children who had undergone the tests were older (5.4±0.8 years) than children who had not (4.1±0.9 years). However, there were no significant differences in terms of gender, prevalence of recurrent wheeze, asthma, AR, AD, or parental history of

Table 2 Comparison between clinical characteristics of children who underwent (+) and did not undergo (–) lung function tests

	Lung function tests (–) (n=369)	Lung function tests (+)* (n=531)	p Value
Age (years)	4.1±0.9	5.4±0.8	<0.001
Male (%)	52.8	50.2	0.44
Recurrent wheeze (%)	15.8	11.5	0.06
Lifetime asthma (%)	8.0	8.8	0.64
Current asthma (%)	5.1	3.5	0.23
Lifetime AR (%)	21.5	26.4	0.09
Current AR (%)	17.3	20.4	0.24
Lifetime AD (%)	33.4	35.9	0.43
Current AD (%)	17.1	16.3	0.75
Atopic sensitisation (%)	17.3	23.7	0.10
Parental history of asthma (%)	11.5	10.8	0.78
Parental history of AR (%)	56.2	51.9	0.26
Parental history of AD (%)	25.3	30.2	0.14
logTEC (/μL)	5.4±0.9	5.4±0.8	0.66
logIgE (IU/mL)	4.2±1.4	4.4±1.3	0.16

*Children who underwent at least one test among spirometry, exhaled nitric oxide assessment or the methacholine bronchial provocation test.
AD, atopic dermatitis; AR, allergic rhinitis; logIgE, logarithmic transformation of IgE; logTEC, logarithmic transformation of blood total eosinophil count.

asthma, AR or AD between children who had performed the tests and those who had not. In addition, prevalence of atopic sensitisation, blood levels of total eosinophil counts and serum total IgE levels showed no differences between the two groups (table 2).

Comparison between clinical and laboratory characteristics of children with and without recurrent wheeze

We compared the prevalence of allergic diseases, atopic sensitisations, hospital admissions or ER visits due to wheezing, and familial history of allergic diseases between preschool children with and without recurrent wheeze. There were no differences in age or gender between the two groups. Children with recurrent wheeze showed a higher prevalence of lifetime and current asthma or AR, and lifetime AD. Prevalence of parental asthma or AR was higher in children with recurrent wheeze than those without. In children with recurrent wheeze, the prevalence of lifetime ER visits or current hospital admissions due to wheezing was higher than those without wheeze. There were no differences in blood eosinophil counts or serum total IgE levels between the two groups (table 3).

Table 3 Comparison between clinical characteristics of preschool children with (+) and without (–) recurrent wheeze

	Recurrent wheeze (–) (n=779)	Recurrent wheeze (+) (n=121)	p Value
Age (years)	4.9±1.0	4.8±1.1	0.390
Male (%)	51.1	56.2	0.284
Lifetime asthma (%)	4.0	39.0	<0.001
Current asthma (%)	1.4	23.7	<0.001
Lifetime AR (%)	22.9	33.8	0.010
Current AR (%)	17.6	29.7	0.002
Lifetime AD (%)	26.2	38.0	0.007
Current AD (%)	15.8	18.3	0.482
Lifetime ER visit due to wheezing (%)	16.8	38.8	0.001
Current ER visit due to wheezing (%)	6.6	12.2	0.240
Lifetime admission due to wheezing (%)	35.7	50.5	0.058
Current admission due to wheezing (%)	17.6	82.4	0.020
Atopic sensitisation (%)	21.8	25.9	0.408
Parental history of asthma (%)	9.6	20.0	0.002
Parental history of AR (%)	51.4	69.5	0.001
Parental history of AD (%)	28.0	29.5	0.748
logTEC (/μL)	5.4±0.8	5.6±0.8	0.069
logIgE (IU/mL)	4.34±1.32	4.56±1.30	0.16

AD, atopic dermatitis; AR, allergic rhinitis; ER, emergency room; logIgE, logarithmic transformation of IgE; logTEC, logarithmic transformation of blood total eosinophil count.

Pulmonary function, bronchodilator response, AHR and eNO were compared between children with and without recurrent wheeze (table 4). There were no differences in height or weight between the two groups. Children with recurrent wheeze showed lower FEV_1 (% predicted), FEV_1/FVC, $FEF_{25\%-75\%}$ (% predicted) and higher eNO compared with children without recurrent wheeze. However, the methacholine test DRS, prevalence of AHR and postbronchodilator responses were not significantly different between the two groups (table 4). The recurrent wheezing group with atopy showed higher eNO levels (16.8±9.9 ppb) than those with recurrent wheezing group but without atopy (10.5±6.8 ppb; p<0.05 data not shown).

Association between clinical and lung function parameters with recurrent wheeze

Multivariate logistic regression analyses were carried out after adjusting for age, sex, height and weight. The results showed that recurrent wheeze was significantly associated

Table 4 Comparison between laboratory characteristics of preschool children with (+) and without (–) recurrent wheeze

	Recurrent wheeze (–)	Recurrent wheeze (+)	p Value
Height (cm)	108.7±7.8	108.8±9.4	0.909
Weight (kg)	18.8±3.5	18.9±4.2	0.786
FEV_1 (% predicted)	96.6±15.0	92.3±15.8	0.044
FVC (% predicted)	90.1±42.9	86.0±15.1	0.165
FEV_1/FVC (%)	94.7±6.64	92.4±7.5	0.033
$FEF_{25\%–75\%}$ (% predicted)	97.5±25.8	85.1±24.6	0.004
Change of FEV_1 after bronchodilator	1.05±0.57	4.19±1.73	0.062
Dose–response slope	1.80±0.57	1.78±0.64	0.933
Positive AHR (%)	34.0	34.8	0.945
eNO (ppb)	10.2±5.7	12.7±8.5	0.013

AHR, airway hyper-reactivity; eNO, exhaled nitric oxide; $FEF_{25\%–75\%}$, mid-forced expiratory flow; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

with higher eNO levels and lower FEV_1, FEV_1/FVC and $FEF_{25\%–75\%}$ levels. The results also demonstrated that recurrent wheeze was strongly associated with a higher prevalence of lifetime and current asthma or AR, lifetime AD, lifetime ER visits and current admissions due to wheezing. However, recurrent wheeze was not associated with atopic sensitisation, AHR or bronchodilator response (table 5).

Table 5 Association of asthma-related risk factors and lung function parameters to recurrent wheeze

	OR	95% CI
Lifetime asthma	15.65	8.91 to 27.50
Current asthma	21.0	9.62 to 45.84
Lifetime AR	1.94	1.26 to 2.99
Current AR	2.29	1.46 to 3.58
Lifetime AD	1.71	1.13 to 2.57
Current AD	1.27	0.76 to 2.14
Lifetime ER visit due to wheezing	3.30	1.63 to 6.67
Lifetime admission due to wheezing	1.91	0.98 to 3.71
Current ER visit due to wheezing	2.61	0.71 to 9.54
Current admission due to wheezing	6.17	1.29 to 29.38
Atopic sensitisation	1.56	0.81 to 2.98
Dose–response slope	0.96	0.44 to 2.11
Positive AHR	1.68	0.61 to 4.66
FEV_1 (% predicted)	0.98	0.96 to 0.99
FVC (% predicted)	0.99	0.97 to 1.01
FEV_1/FVC (%)	0.96	0.92 to 0.99
$FEF_{25\%–75\%}$ (% predicted)	0.98	0.96 to 0.99
Change of FEV_1 after bronchodilator	1.02	0.99 to 1.04
eNO (ppb)	1.05	1.01 to 1.10
logTEC (/µL)	1.31	0.97 to 1.74
logIgE	1.13	0.94 to 1.35

All values are adjusted for age, sex, height and weight.
AD, atopic dermatitis; AHR, airway hyper-reactivity; AR, allergic rhinitis; eNO, exhaled nitric oxide; ER, emergency room; $FEF_{25\%–75\%}$, mid-forced expiratory flow; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; logIgE, logarithmic transformation of IgE; logTEC, logarithmic transformation of blood total eosinophil count.

DISCUSSION

This study demonstrates that the recurrent wheezing group showed increased airway inflammation assessed by eNO, as well as airflow limitation. However, recurrent wheeze was not associated with AHR or atopic sensitisation. There are some well-executed studies that demonstrate the relationship between decreased lung function in infants and early wheeze. Martinez *et al* showed that diminished lung function was associated with the development of a first wheezing episode in infants.[13] Additionally, early transient wheeze led to diminished airway function both before the age of 1 and at the age of 6, and was not associated with elevated serum IgE levels or skin test reactivity.[14] Similarly, another prospective study has shown that pre-existing abnormalities in respiratory function are important determinants of wheezing and lower respiratory illness in the first year of life.[15] In the present study, we did not compare airway function with wheezing phenotype. We instead demonstrated that more than three wheezing episodes by the age of 4–6 years were associated with diminished airway function and airway inflammation, and not with AHR according to the methacholine bronchial provocation or atopic sensitisation tests. These results imply that wheezing in early life is more likely associated with structurally small airways since viral lower respiratory infections can easily induce wheezing by inducing airway inflammation and mucus production in the already narrowed airway. However, another birth cohort study showed that reduced airway function at 1 month of age was associated with persistent wheezing at 11 years of age that was independent of AHR and atopy.[15] This study suggests that diminished airway function in early life can be a risk factor for persistent wheezing by school age, regardless of atopic sensitisation or AHR.

In our study, recurrent wheezing was not associated with either atopic sensitisation or AHR. Both atopic sensitisation and AHR are the main hallmarks of asthma. Atopy has been found to be a risk factor for persistent wheezing in other prospective studies,[16 17] and more closely associated with AHR than wheeze.[18 19] Our results imply that early recurrent wheezing may not be related to atopic asthma in preschool children.

In the present study, preschool children with recurrent wheeze showed higher eNO levels than those without

recurrent wheeze. Previous studies have demonstrated the relationship between high eNO levels and asthma.[20 21] However, there are limited data on eNO levels in recurrent wheezing.[8 22 23] In a study that explored asthma prediction by school age, wheezy preschool children less than 4 years of age with a stringent asthma predictive index (API) had higher eNO levels compared with children with recurrent wheeze with loose API or recurrent cough but no wheeze.[24] In a prospective study of children with a high risk of asthma, children with asthma at 5 years of age showed significantly higher eNO levels as infants, even before any wheezing, and also showed a greater increase in eNO between infancy and follow-up at 5 years of age, compared with children without asthma.[25] This suggests that eNO can be used as a predictor for the development of asthma, when combined with other asthma-related risk factors.

In this study, it is difficult to clearly verify whether recurrent wheezing is an asthma predictor. We found that recurrent wheezing is associated with airway inflammation and function, and with lifetime and current AR, paternal asthma and lifetime AD, all of which were factors in the prediction of asthma. Recurrent wheeze implies diminished airway function due to both structurally small or abnormal airways such as malacic airway and airway inflammation due to viral infection or allergens.[26] Thus, the probability of developing asthma should be determined by considering other asthma-related risk factors.

Nevertheless, this study has some limitations. First, it was impossible to confirm whether the children developed asthma afterwards, because the study design was cross sectional. Second, assessments of recurrent wheezing were based on parental rather than physician reports. According to a study conducted by Mohangoo *et al*, the prevalence of wheezing estimated from questionnaire was significantly higher than from physician interview.[27] And in the newly revised GINA guideline, wheezing may be interpreted differently based on who observes it.[3] However, questionnaire-based parent-reported wheezing showed high concordance with physician-confirmed wheezing.[28 29] Third, we did not perform lung function tests, methacholine provocation tests or eNO assessments in all study subjects. Children who underwent the tests were older than those who did not. This presumably introduces a selection bias. However, there were no prevalence differences in recurrent wheeze, asthma, AR or AD, and parental history of allergic diseases between children who had or had not undergone these tests. Furthermore, we found the same association results after adjusting for age, sex, height and weight, all of which can affect lung function tests.

The major strength of this study was the relatively large number of preschool children enrolled from the general population in multiple regions. In addition, measurements of eNO or spirometry were performed, and methacholine bronchial provocation tests were carried out to evaluate airway inflammation, lung function and AHR in recurrent wheezing preschoolers. Furthermore, we evaluated atopy-related factors, such as atopic sensitisation or serum IgE levels.

CONCLUSIONS

Our results suggest that small airway calibre, low lung function and airway inflammation were more likely to be associated with recurrent wheeze in preschool children than atopy or AHR. We also found that recurrent wheeze was associated with asthma, AR or AD. New lines of prospective study which measures serial lung function, AHR and airway inflammation in preschool children with wheeze are required to understand the pathophysiological phenotypes of recurrent wheeze.

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