Lung function and bronchodilator response in 4-year-old children with different wheezing phenotypes

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ABSTRACT: Persistent wheeze is a common chronic disease in early childhood and later may progress to asthma. However, the association between pre- and post-bronchodilator lung function and the wheezing phenotype in preschool children is not known.

Children 4 yrs of age involved in a prospective birth cohort study (in Antwerp, Belgium) concerning perinatal factors and the occurrence of asthma and allergies, were invited to participate in lung function measurements with the forced oscillation technique. The wheezing phenotype was assessed via (bi)annual questionnaires.

Wheezing phenotype and baseline respiratory impedance data were available for 325 children, 96% of whom underwent bronchodilation tests. The baseline resistance at 4 Hz was higher in children with early transient (11.0 hPa·s·L^{-1}, n=127) or persistent wheeze (11.9 hPa·s·L^{-1}, n=54) than in children who never wheezed (10.3 hPa·s·L^{-1}, n=144). After bronchodilation, the resistance decreased on average by 22%. The decrease was greater among the persistent wheezers than among those who never wheezed (3.4 versus 2.3 hPa·s·L^{-1}).

The baseline lung function was poorer and the bronchodilator response was greater in 4-yr-old children with persistent wheeze than in those who never wheeze or who had early transient wheeze, implying a higher bronchomotor tone in the former group.

KEYWORDS: Childhood asthma, cohort studies, forced oscillations, preschool children, wheezing

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Persistent wheezing is a common chronic disease in young children and a major cause of preschool morbidity. The prevalence of recurrent days with cough, wheeze and/or breathlessness in children aged 1–5 yrs has been reported to be 32%, and as many as 24% of preschool children suffer from weekly symptoms despite current treatment [1].

Atopy and increased airway responsiveness in young children have been associated with persistent wheeze and asthma in later life [2–4]. Furthermore, abnormalities in pulmonary function during infancy have been demonstrated to be an important determinant of subsequent respiratory symptoms and lung function, independently of atopy and airway responsiveness [5–7]. It was recently reported that persistent wheeze and low airway function at school age are independently associated with chronic asthma in early adulthood [8]. These findings have increased our awareness of the impact of respiratory events in early life on the development of respiratory disease in adulthood.

At present, however, children at high risk of developing persistent asthma are still inadequately identified [9].

Recent advances in diagnostic technologies have led to the standardisation of a number of techniques for the assessment of lung function in the preschool age group [10]. The use of these techniques in preschool children with recurrent wheeze may have important implications for the correct identification of children at risk of developing severe asthma in later life. BRUSSEE et al. [11] recently reported that 4-yr-old children with persistent wheeze exhibited higher interruptor resistances than age-matched children who never wheezed or those with the early transient wheezing phenotype.

Asthma is at least partially defined by abnormalities in pulmonary function, including variable airway obstruction. In addition to reporting on baseline lung function measures (respiratory resistance and reactance, as determined with the forced

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oscillation technique) and the bronchodilator responsiveness in 4-yr-old children, the present study also aimed to determine the association between baseline and post-bronchodilator resistance and reactance, and the phenotypes of childhood wheezing.

METHODS

Study design and study population

The Prospective Cohort on the Influence of Perinatal Factors on the Occurrence of Asthma and Allergies (PIPO) study is a prospective birth cohort study involving 1,128 children. Between June 1997 and December 2001, pregnant females in the Antwerp region of Belgium were invited to participate by completing a screening questionnaire. Data on demography, respiratory symptoms and risk factors for asthma were collected through the use of postal questionnaires: the first questionnaire covered the first year of life, with subsequent questionnaires at 6-month intervals up to the age of 4 yrs. The questionnaires were based on validated International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires [12]. At 4 yrs of age, the children included in the PIPO study were invited for medical examination and lung function testing at the Antwerp University Hospital (Antwerp, Belgium). The children who regularly used bronchodilators were asked to abstain from their use on the examination day, whereas the use of inhaled corticosteroids was not interrupted. The atopic status of the child and parents was assessed from specific immunoglobulin (Ig)E levels against common food and inhalant allergens, determined from blood samples. All parts of the study were approved by the University Ethics Committee (University of Antwerp, Antwerp, Belgium), and written informed parental consent was obtained before each assessment.

Lung function measurements

Forced oscillation technique

Respiratory impedance (Z_{rs}) was measured in the frequency range 4–32 Hz, using a home-made setup that met the American Thoracic Society (ATS)/European Respiratory Society (ERS) requirements [10, 13]. Measurements were performed according to recent international guidelines [10]. Recordings lasted for 16 s, and the average of three to five acceptable Z_{rs} data was used for further analysis.

Measurement protocol

Children sitting upright on their parent's lap were measured with their head in a neutral position. The parent supported the child's chin and cheeks with both hands. The child was instructed to breathe normally while watching a video film.

Reversibility testing

After the baseline Z_{rs} measurement, 200 μg of salbutamol was administered through a spacer (OptiChamber; Respironics New Jersey Inc., Parsipanny, NJ, USA) without an additional face mask or a mouthpiece. The Z_{rs} measurement was repeated 15 min thereafter. The pre- and post-bronchodilator measurements were performed by the same technician.

Short-term reproducibility

In 50 children, chosen at random, the short-term reproducibility of the Z_{rs} data was assessed by repeating the baseline measurement after a 15-min time interval.

Wheezing phenotype

Symptoms of wheeze were assessed through core questions from the ISAAC questionnaire [12]. According to the history of wheeze reported by the parents in the (bi)annual questionnaires, the children were divided into those who never wheeze, and those with early transient, late-onset or persistent wheeze [2, 11].

Data analysis

From the measured respiratory reactance (X_{rs}) data, the "area under the reactance curve" (AX), i.e. the integrated area of all X_{rs} data below zero up to the resonance frequency (f_{res}), was determined. Data are expressed as mean $\pm$ SD, unless otherwise specified. Statistical analyses were performed using SPSS for Windows, Version 15.0 (SPSS Inc., Chicago, IL, USA).

After testing the data for normality, the difference between the two baseline measurements was analysed with paired t-tests. The differences between the four groups of wheezing phenotype were assessed with one-way ANOVA, post hoc least significant difference analysis or Mann–Whitney analysis (or Chi-squared test). Significance was accepted at p<0.05.

The online supplementary material provides additional details on the measurement technique, the questionnaires, the definitions of the wheezing phenotypes and the analysis of adjustment for potential confounders.

RESULTS

Baseline Z_{rs} data were obtained for 535 children and post-bronchodilator Z_{rs} data for 501 children (the online supplementary material includes a flowchart of the children participating in the study). In 203 children (38%), the wheezing phenotype could not be determined because of incomplete or missing questionnaires. These children were excluded from the study group. The remaining children (n=332) were divided into those who never wheeze (n=144, 43%), and those with an early transient (n=127, 38%), a late-onset (n=7, 2%) or a persistent (n=54, 16%) wheezing phenotype. The group of children with late-onset wheeze was considered too small for further analysis. In 313 of the remaining 325 children (96%), the post-bronchodilator response was also assessed. The general characteristics of the subgroups are listed in table 1. The anthropometric characteristics and sex distribution were not different in the children with the different wheezing phenotypes. In comparison with the group who never wheeze, a significantly higher proportion of the persistently wheezing children were atopic and had used antibiotics at 4 yrs of age, whereas the children with early transient or persistent wheeze suffered from lower respiratory tract infections at 4 yrs of age significantly more frequently.

The short-term reproducibility of Z_{rs} was assessed in 27 young males and 23 young females. This group of children did not differ significantly from the study group (n=325 children) in terms of the distribution of the wheezing phenotypes (in 12 children, the wheeze phenotype was undetermined; 18 children had never wheezed; 16 children had early transient wheeze phenotype; four children had a persistent wheeze phenotype), or the value of $R4$ (resistance at 4 Hz) or AX (see later). The results of the two baseline measurements of respiratory resistance (R_{rs}) and X_{rs} are depicted in figure 1. The R_{rs} data

TABLE 1	General characteristics of the study population			
	Total	**Wheezing phenotypes**		
		Never	**Early**	**Persistent**
Subjects n	325	144	127	54
Males	53	49	55	59
Age yrs		4.4 ± 0.2	4.4 ± 0.2	4.4 ± 0.2
Height cm		106.4 ± 4.5	106.1 ± 4.3	106.0 ± 3.4
Weight kg		17.6 ± 2.1	17.5 ± 2.3	17.6 ± 2.0
Education level of				
mother[#]				
Low	21	19	22	23
High	79	81	78	77
Atopy of mother[¶]	43	45	43	35
Parental smoking[+] at 4 yrs	5	6	4	6
Siblings at 4 yrs	87	85	87	92
Exposure to pets[§] at 4 yrs	57	58	55	59
Eczema of child[f]	53	50	55	58
Rhinitis of child[f]	76	73	75	86
Atopy of child[¶]	28	23	29	41*
LRTI at 4 yrs	15	7	15*	36***
Antibiotics at 4 yrs	46	39	46	65***

Data are presented as mean $\pm$ SD or %, unless stated otherwise. LRTI: lower respiratory tract infection (a serious lung or airways infection). [#]: high if the mother had completed a bachelor or master's degree, otherwise low; [¶]: defined as a specific immunoglobulin E level $\geqslant 0.35$ kU·L^{-1} at the medical examination at 1 or 4 yrs; [+]: regular exposure to tobacco smoke by either of the parents; [§]: regular exposure to a cat or dog; [f]: a positive answer to the following question in any of the questionnaires: ''Did your child suffer from eczema/rhinitis during the past 6 months?'' [12]. At 4 yrs: a positive answer in the questionnaire returned at 42 or 48 months.*: p<0.05, relative to those who never wheeze; ***: p<0.001, relative to those who never wheeze.

obtained 15 min apart were not significantly different, except that R_6 and R_8 were slightly lower (by ~0.4 hPa·s·L^{-1}) in the second baseline measurement (p<0.05). A small upward shift was noted in the second baseline X_{rs} curve relative to the first at almost all data points (p<0.01); the X_{rs} data from the second baseline measurement were on average 0.4 hPa·s·L^{-1} larger than those from the first measurement.

The baseline R_{rs} and X_{rs} in the groups of children with different wheezing phenotypes are reported in figure 2. R_{rs} displayed a slight negative frequency dependence in the children who never wheeze. R_{rs} increased in magnitude and the negative frequency dependence of R_{rs} became progressively more marked in the groups of children with the early transient or persistent wheezing phenotypes. In comparison with the children who never wheeze, X_{rs} became more negative and exhibited an ever-higher f_{res} in the sequence early transient and persistent wheezing phenotype (see table 1 of the online supplementary material). Since the largest differences in Z_{rs} at baseline between the wheezing phenotype groups were observed in the low-frequency range, our subsequent analysis was focused on those frequencies. R_4, R_6, R_8, reactance at 4 Hz (X_4), and X_6, X_8, and AX were analysed. Figure 3 presents the values of R_4 and AX at baseline
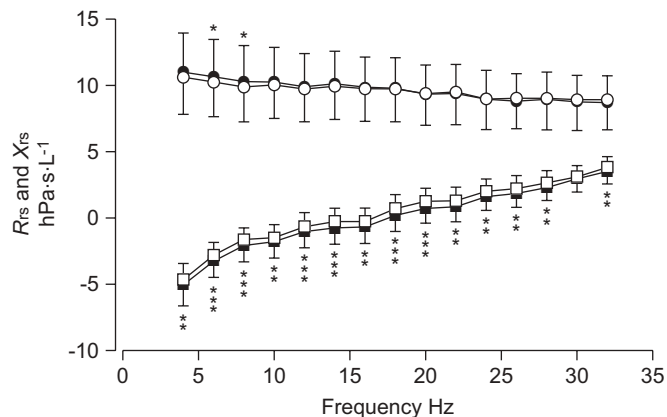

FIGURE 1. Short-term reproducibility of respiratory resistance (R_{rs}; ● and ○) and respiratory reactance (X_{rs}; ■ and □) data obtained from 50 4-yr-old children. The two baseline measurements (■ and ●: baseline 1; □ and ○: baseline 2) were made 15 min apart. Data points and error bars present average values $\pm$ SD. *: p<0.05; **: p<0.01; ***: p<0.001.

and after bronchodilation. The children with early transient, late-onset or persistent wheeze had baseline values of R_4 and AX that were significantly larger than those of the children who never wheeze. Further, the children with persistent wheeze had significantly larger baseline R_4 values than the children with early transient wheeze.

Bronchodilation significantly decreased the values of R_4 and AX in all the groups of children. On average, R_4 decreased 22% by bronchodilation. However, for the children with persistent wheeze, the decrease in R_4 after bronchodilation was significantly larger than the children who never wheeze and those with early transient wheeze (p<0.05). After bronchodilation, the values of R_4 were still significantly larger in the children with persistent wheeze than in those who never wheeze (p<0.02). Relative to the group who never wheeze, the decreases in AX were significantly larger in the children with early transient and persistent wheeze, and accordingly the post-bronchodilator values of AX were comparable in the three groups of children with the different wheezing phenotypes (fig. 3 and table 2).

The characteristics of the children who never wheeze were used to determine the cut-off values for a significant bronchodilator response. From the fifth percentiles, the cut-off points were set to be absolute decreases of 5.5 hPa·s·L^{-1} and 31.0 hPa·L^{-1} for R_4 and AX, respectively, and relative decreases of 43% and 81%, respectively. Compared with the relative change, expressing the bronchodilator response in absolute change proved to be a more sensitive means of differentiating between the groups (table 3). Significantly more children with a persistent wheeze (13%) than children who never wheeze (4%) responded positively to bronchodilation when the absolute change in R_4 was considered (p<0.05). When the absolute change in AX was used to define a positive response, significantly more children with an early transient (14%) or persistent wheeze (23%) responded significantly to bronchodilation than the children who never wheeze (4%). The combined changes in resistance and reactance at 4 Hz after
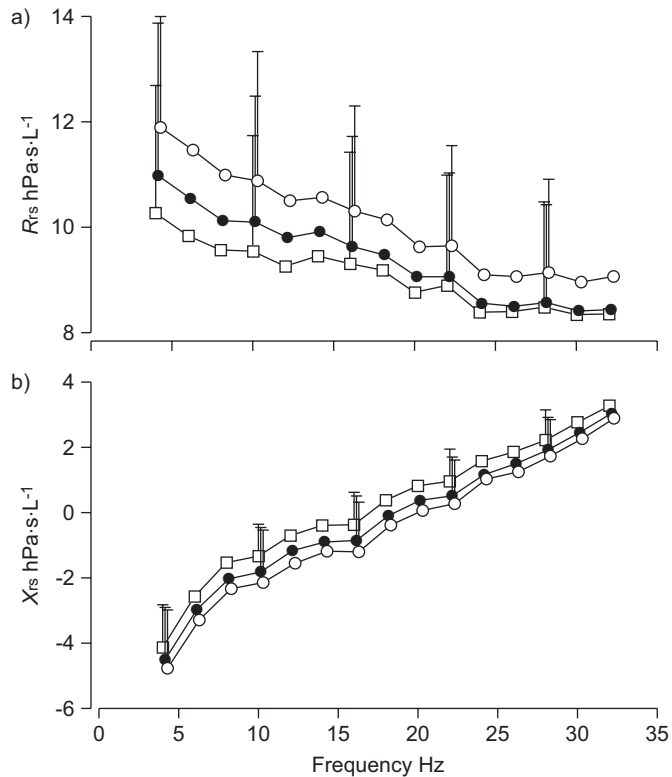
FIGURE 2. Average$\pm$SD of a) respiratory resistance (R_{rs}) and b) respiratory reactance (X_{rs}) in the groups of children with different wheezing phenotypes: those who never wheeze ($\square$; n=144), those with early transient wheeze ($\bullet$; n=127) and those with persistent wheeze ($\circ$; n=54).

FIGURE 3. Baseline ($\blacksquare$) and post-bronchodilator ($\blacksquare$) values of a) resistance at 4 Hz (R_4) and b) area under the reactance curve (AX) in the groups who never wheeze, or who have early transient or persistent wheeze. Bars and error bars present average values$\pm$SEM. *: p<0.05; **: p<0.01; ***: p<0.01. —: comparisons between baseline values; – – –: comparison between post-bronchodilator values.

bronchodilation in the different groups of wheeze phenotype followed the same path (fig. 4).

DISCUSSION

Although there was a considerable overlap in lung function data between the groups, our study did reveal significant differences both in the baseline respiratory function and in the bronchodilator response between preschool children with different wheezing phenotypes. At 4 yrs of age, the children with early transient wheeze yielded higher baseline resistance values than those who never wheezed, although 43% of the children with early transient wheeze had experienced only one wheezing episode during the first 3 yrs of life. The children with persistent wheeze, of whom two-thirds had experienced several episodes of wheeze during their fourth year of life, displayed a poorer baseline lung function than the children who never wheeze or those with early transient wheeze, and their bronchodilator response was larger.

There was a considerable dropout rate in our study: half of the children who entered the cohort at birth were not available for examination at 4 yrs of age and 38% of the remaining had incomplete or missing questionnaires. However, despite the loss of data, we feel that the dropout does not affect or limit the interpretation of our results. We did not intend to study lung function and wheeze phenotype in a representative sample of the population; the purpose of our study was rather to investigate the association between lung function and wheezing
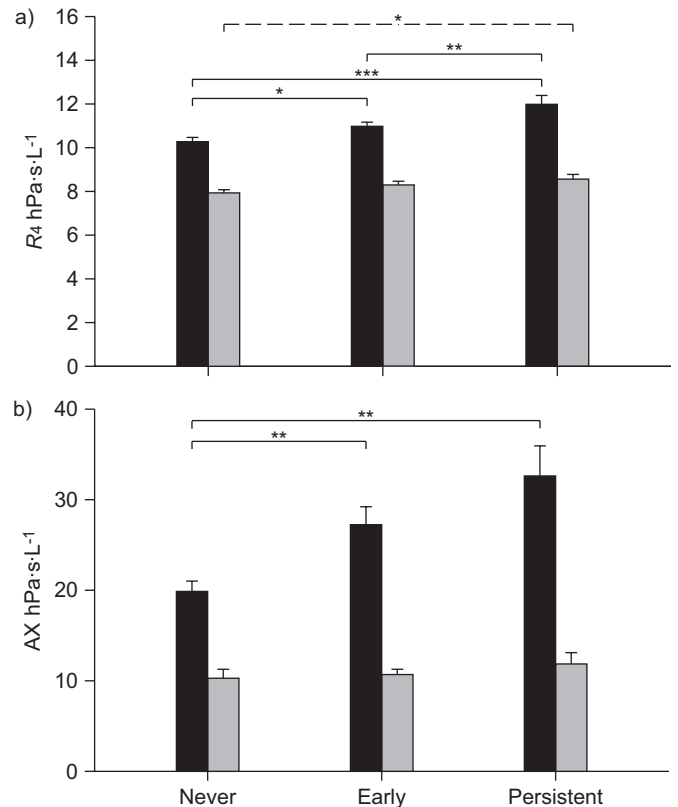
phenotype. From the description of our study population (table 1), it is clear that the mothers of the children were relatively highly educated (which may explain the low smoking incidence) and atopic mothers were more likely to enrol their child into our birth cohort. We do not consider this non-representative selection at entry as a drawback; on the contrary, it favoured a more homogeneous distribution of the children among the wheeze phenotype groups.

Following the Tucson definition [2], the ERS Task Force on wheezing disorders in preschool children recently described cut-off ages to define the wheeze phenotype of the child at 3 and 6 yrs of age [14], whereas we defined cut-off points at 3 and 4 yrs of age. Many previous epidemiological studies, however, employed different definitions of the wheeze phenotype: cut-off ages of 3 and 5 yrs [15, 16], 3 and 7 yrs [17], and 4 and 10 yrs [18] have been described. Our definition of wheeze phenotype was similar to that employed by BRUSSEE *et al.* [11].

The baseline reproducibility of R_{rs} indicated isolated, small decreases ($\sim$3%) in R_6 and R_8 and a significant upward shift of the X_{rs} curve throughout the whole frequency range at the second baseline measurement compared with the first (fig. 1). The most probable explanation appears to be a change in chest wall compliance due to a more relaxed state in the young

TABLE 2	Baseline resistance and reactance values and the change after bronchodilation in the groups of children with different wheezing phenotypes		
	Never	**Early**	**Persistent**
Baseline			
Subjects n	144	127	54
R_4 hPa·s·L^{-1}	10.3 (9.9–10.7)	11.0 (10.5–11.5)*	11.9 (11.1–12.7)***,#
R_6 hPa·s·L^{-1}	9.8 (9.5–10.2)	10.5 (10.1–11.0)*	11.5 (10.7–12.2)***,##
R_8 hPa·s·L^{-1}	9.6 (9.2–9.9)	10.1 (9.7–10.6)	11.0 (10.3–11.7)***,#
X_4 hPa·s·L^{-1}	-4.1 (-4.4– -3.9)	-4.5 (-4.8– -4.2)	-4.8 (-5.3– -4.3)*
X_6 hPa·s·L^{-1}	-2.6 (-2.7– -2.4)	-3.0 (-3.2– -2.7)*	-3.3 (-3.7– -2.9)**
X_8 hPa·s·L^{-1}	-1.5 (-1.7– -1.4)	-2.0 (-2.3– -1.8)**	-2.3 (-2.8– -1.9)**
AX hPa·L^{-1}	19.9 (17.6–22.1)	27.2 (23.4–31.1)**	32.6 (25.8–39.3)***
Bronchodilation			
Subjects n	139	121	53
ΔR_4 hPa·s·L^{-1}	-2.3 (-2.6– -2.0)	-2.6 (-3.1– -2.2)	-3.4 (-4.1– -2.7)*,#
ΔR_6 hPa·s·L^{-1}	-2.1 (-2.4– -1.9)	-2.5 (-2.9– -2.2)	-3.2 (-3.8– -2.5)**
ΔR_8 hPa·s·L^{-1}	-2.2 (-2.4– -1.9)	-2.4 (-2.8– -2.1)	-3.1 (-3.7– -2.5)**,#
ΔX_4 hPa·s·L^{-1}	1.0 (0.9–1.2)	1.2 (1.0–1.5)	1.4 (1.0–1.8)
ΔX_6 hPa·s·L^{-1}	0.9 (0.8–1.0)	1.1 (1.0–1.3)	1.4 (1.0–1.8)*
ΔX_8 hPa·s·L^{-1}	0.9 (0.7–1.0)	1.2 (1.0–1.4)**	1.5 (1.1–1.9)**
ΔAX hPa·L^{-1}	-9.8 (-11.6– -8.1)	-16.3 (-19.6– -13.0)**	-21.2 (-27.4– -15.1)***

Data are presented as mean (95% CI), unless stated otherwise. R_4, R_6, R_8 and X_4, X_6, X_8: resistance and reactance, respectively, at 4, 6 and 8 Hz; AX: area under the reactance curve; Δ: change after bronchodilation. *: $p<0.05$, relative to the children who never wheeze; **: $p<0.01$, relative to the children who never wheeze; ***: $p<0.001$, relative to the children who never wheeze; #: $p<0.05$, relative to the children with early transient wheeze; ##: $p<0.01$, relative to the children with early transient wheeze.

children, who had adapted somewhat to the new experimental situation. Although there was a systematic difference in X_{rs} between the two baseline measurements, the change was small relative to that induced by bronchodilation: the relative increases in X_4 and X_6 were 6% and 12%, respectively, whereas the changes induced by bronchodilation were 24% and 35%, respectively.

Besides the analysis of the raw R_{rs} and X_{rs} data points at low frequency, we also analysed AX, all X_{rs} data points below f_{res} thus being taken into account. As such, AX can be regarded as an index reflecting the elastance of the respiratory system, and it actually has the dimension of elastance. Its recent introduction was because AX is not greatly influenced by the measurement noise of the individual X_{rs} data points [19]. Indeed, AX discriminated between the groups with different wheezing phenotypes better or with more power (table 2) than X_4, X_6 or X_8.

In contrast with most previous forced oscillation technique (FOT) measurements in children, we obtained highly reproducible Z_{rs} data at 4 Hz (see the online supplementary material), and hence we chose to analyse R_4. It should be noted, however, that similar results were obtained when R_6 and R_8 were considered (table 2). Our results are in close agreement with those of BRUSSEE et al. [11], who prospectively investigated the interrupter airway resistance (R_{int}) in children 4 yrs of age; they employed similarly defined wheezing phenotypes, but included 2.5 times more children in their study than we did. They found that children with persistent wheeze had a higher baseline R_{int} than those who never

wheezed. In contrast, our FOT resistance also differentiated the group of children with early transient wheeze from the group of children who never wheeze, and the group of children with persistent wheeze from the group of children with early transient wheeze. This suggests that resistance measurements with FOT are more sensitive than R_{int} measurements in children of this age. In accordance with this, DELACOURT et al. [20] concluded that FOT is more sensitive than R_{int} measurements for the detection of obstruction and its reversibility in children with asthma or a chronic cough.

TABLE 3	Number of children in each group giving a significant bronchodilator response as determined by the fifth percentile for the children who never wheeze		
	Never	**Early**	**Persistent**
Subjects n	139	121	53
$|\Delta R_4|$ >5.5 hPa·s·L^{-1}	6 (4)	6 (5)	**7 (13)**
$|\Delta AX|$ >31.0 hPa·L^{-1}	6 (4)	**17 (14)**	**12 (23)**
$|\Delta R_4/R_4|$ >43%	7 (5)	6 (5)	5 (9)
$|\Delta AX/AX|$ >81%	6 (4)	9 (7)	**8 (15)**

Data are presented as n (%), unless otherwise indicated. Values are presented as modulus. Numbers in bold indicate a significant difference relative to the group of children who never wheeze ($p<0.05$, Pearson's Chi-squared test). R_4: resistance at 4 Hz; AX: area under the reactance curve.
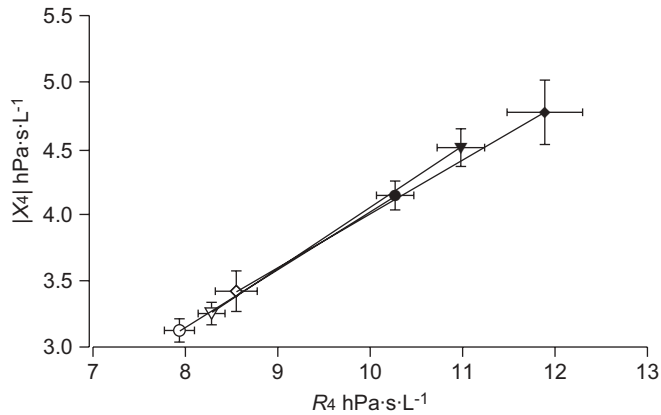
FIGURE 4. Relationship between baseline (closed symbols) and post-bronchodilator values (open symbols) of reactance at 4 Hz (X_4) and resistance at 4 Hz (R_4) in the groups of children who never wheeze (●), or who have early transient wheeze (▼) or persistent wheeze (◆). Average values ± SEM are shown.

LOWE et al. [21] studied the specific airway resistance (sR_{aw}) in 3-yr-old children taking part in a prospective birth cohort. sR_{aw} was found to be significantly higher in the children who had experienced more than two wheezing episodes than in the children who had never wheezed. In our study, the children who had stopped wheezing by 3 yrs of age (the children with early transient wheeze) still had a significantly higher respiratory resistance at 4 yrs of age than the children who had never wheezed at all.

As far as we are aware, the bronchodilator response has not been assessed previously in preschool children with different wheezing phenotypes. We detected significant differences in the responses to a short-acting bronchodilator: the children with persistent wheeze displayed a larger decrease in R_{rs} than those children who never wheeze or who have early transient wheeze (table 2). It is noteworthy that the baseline X_{rs} values and the change after bronchodilator administration also distinguished the different wheezing phenotype groups. In contrast with R_{rs} at low frequency, the post-bronchodilator X_{rs} data were all very similar among the groups with different wheezing phenotypes. How should these data to be interpreted?

A higher baseline R_{rs} was always associated with a lower X_{rs} at low frequency, and thus with higher values of AX and f_{res} (table 2 and table 1 of the online supplementary material). Further, the effect of the short-acting bronchodilator was an upward shift in X_{rs}, which was largest in the groups with the lowest baseline X_{rs} values. There are a number of mechanisms that may explain the concomitant changes in R_{rs} and X_{rs}. Perhaps the most probable explanation for lower X_{rs} values in small children with larger values of airway resistance is the effect of the upper airway shunt [22]. This shunt effect, exerted by the elastic properties of the soft tissues of the cheeks and floor of the mouth, increases as the airway resistance is increased. It results in a phase shift between pressure and flow, especially at low frequency, with the net effect that X_{rs} decreases as the airway resistance increases. A similar effect is obtained when the peripheral airway constriction in these young children is sufficiently severe and inhomogeneous to cause peripheral time constant differences and an altered frequency dependence of the pulmonary impedance [23]. This mechanism was earlier offered

as the most likely explanation for the increase in apparent tissue compliance observed after bronchodilation in adult asthmatics [24]. Both of the previously mentioned mechanisms explain the parallel changes observed in R_{rs} and X_{rs} after bronchodilation. Indeed, all the wheezing phenotype groups exhibited a joint path of bronchodilator-induced changes in R_4 and X_4 (fig. 4). Children with more constricted airways display higher resistances associated with more negative reactances. The bronchodilator-induced changes in both resistance and reactance are larger in these children, which results in a rather uniform post-bronchodilator impedance among the groups.

The bronchodilator responsiveness in our groups of 4-yr-old children was remarkably large. In the children who never wheeze, an average decrease of 22% in R_4 was observed after bronchodilation, indicating a significant bronchomotor tone at baseline. When we used the coefficient of repeatability of R_4 [10] as a cut-off value, as many as 35% of the children who never wheezed demonstrated a significant positive bronchodilator response. To the best of our knowledge, the bronchodilator responsiveness of children who never wheeze has not been assessed previously in a prospective study. In cross-sectional studies, however, the bronchodilator response of healthy young children has been reported to be significant. THAMRIN et al. [25] and MALMBERG et al. [26] reported similar decreases (19–21%) when higher doses of salbutamol were used, whereas HELLINCKX et al. [27], and NIELSEN and BISGAARD [28] observed much smaller changes (10–13%).

The threshold for R_4 to detect a significant bronchodilator response as determined in the children who never wheeze was -43% of the baseline value. Similar cut-off values were determined for R_6 and R_8 (-41% and -43%, respectively; see table 2 of the online supplementary material). These cut-off values are close to previously published threshold values in healthy preschool children, which ranged from -28% to -42% [25–28]. On use of this threshold value, the number of responders in the groups of different wheezing phenotypes were similar (table 3). In accordance with this finding, both THAMRIN et al. [25] and HELLINCKX et al. [27] reported that use of this threshold did not allow the distinction of children with asthma or wheeze from healthy preschool children. We are aware of only one study in which preschool children at risk of persistent asthma were investigated because of repeated wheezing episodes at a young age. MAROTTA et al. [29] reported that children with suspected asthma exhibited a larger relative change in R_5 than children without asthma, but with a comparable baseline lung function.

When we used a cut-off value based on the absolute change to detect a positive bronchodilator response, significant differences were observed between the wheezing phenotype groups, suggesting that limits based on absolute change are more sensitive than limits based on relative change (table 3). A higher baseline airway resistance, caused by an increased bronchomotor tone, will be associated with a larger absolute response to a bronchodilator (fig. 4). Consequently, the expression of the change relative to the initial level will tend to homogenise the different responses to bronchodilation in subjects with different baseline bronchomotor tones.

TURNER et al. [5] demonstrated that a reduced pulmonary function at 1 month of age and airway responsiveness are

independently related to persistent wheeze at 11 yrs of age. Moreover, it was recently concluded that the pattern of wheeze and the lung function level at 6 yrs of age determine the respiratory symptoms and respiratory function in adolescence [30]. The two factors that may explain the relationship between a reduced lung function at an early age and an increased wheeze during childhood are 1) wheeze due to narrow, small airways, and 2) altered airway wall properties that may result in a more pronounced wheeze. Asymptomatic infants with a history of wheeze have been reported to have a lower airway wall compliance than that of healthy age-matched controls [31]. A recent study reported that reticular basement membrane thickening is already detectable in the airways of preschool children who suffer from a severe, recurrent wheeze [32]. A diminished lung function was detected in infants 1 month of age who subsequently exhibited episodes of wheezing or coughing, suggesting that alterations in the airways may precede the onset of wheeze [33]. The findings of BRUSSEE et al. [11] and the results of our own study uniformly indicate that 4-yr-old children with persistent wheeze manifest an increased airway resistance compared with children who never wheeze. Moreover, our results on the bronchodilator response point to narrower airways being associated (at least partially) with an increased bronchomotor tone.

In summary, our study has demonstrated that children at 4 yrs of age with various wheezing phenotypes possess different baseline lung functions. Children with persistent wheeze have an elevated baseline respiratory resistance, and their bronchodilator response is more marked than that of children who never wheeze or who have early transient wheeze.

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