

# Peak flow variability, methacholine responsiveness and atopy as markers for detecting different wheezing phenotypes in childhood

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## Abstract

**Background** – There is increasing evidence that wheezing during childhood may be a heterogeneous condition, and that different forms of wheezing may be associated with different risk factors and prognosis. The aim of this study was to determine if measures of airway lability and of atopy could identify distinct wheezing phenotypes during childhood.

**Methods** – In a cohort of children followed from birth peak flow variability (n = 600) was evaluated and methacholine challenge responsiveness (n = 397) was measured at age 11 in relation to wheezing before the age of three, and at age six and 11 years total serum IgE and skin test reactivity to allergens were determined.

**Results** – Neither positive peak flow variability nor methacholine hyperresponsiveness measured at age 11 were associated with wheezing occurring only during the first three years of life. Both methacholine hyperresponsiveness and positive peak flow variability were associated with wheezing at both ages six and 11 (OR 5.1 (95% CI 2.4 to 10.6) and 2.3 (1.2 to 4.5), respectively). In addition, positive peak flow variability was associated with wheezing up to the age of six but not at age 11 in non-atopic children (OR 2.9 (95% CI 1.0 to 8.8)). Methacholine hyperresponsiveness measured at age 11 was more frequently observed in boys (OR 2.1 (95% CI 1.2 to 3.5)) and was strongly associated with serum IgE levels measured at ages six and 11 (p < 0.001) and with positive skin test reactivity (OR 4.5 (95% CI 2.0 to 10.1)). Peak flow variability was unrelated to sex or markers of atopy (IgE and skin test reactivity).

**Conclusions** – Methacholine responsiveness and peak flow variability assessed at age 11, together with markers of atopy (IgE and skin test reactivity to allergens) identify three different wheezing phenotypes in childhood: “transient early wheezing” limited to the first three years of life and unrelated to increased airway lability; “non-atopic wheezing” of the toddler and early school years associated with positive peak flow variability but not with methacholine hyperresponsiveness; and “IgE-associated

wheeze/asthma” associated with persistent wheezing at any age and with methacholine hyperresponsiveness, peak flow variability, and markers of atopy.

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There is increasing evidence to suggest that wheezing in childhood may represent a heterogeneous condition, with distinct phenotypic expressions associated with different clinical manifestations and risk factors.<sup>1</sup> We recently reported, for example, that at least two different wheezing syndromes coexist in infants and young children<sup>2</sup>: wheezing which is associated with lower levels of lung function at birth and with a high probability of remission before six years of age and wheezing associated with the classical risk factors for asthma and persistence of symptoms at the age of six. Although a strong correlation between bronchial hyperresponsiveness and frequency and severity of wheezing is known to exist among children aged 8-15 years,<sup>3-7</sup> no such correlation was recently found among children aged 4-5 years<sup>8</sup> which suggests that wheezing during the toddler years may be different phenotypically from wheezing in older children.

Both methacholine responsiveness and peak flow variability have been used to assess airway lability in children of different ages. Although the association between methacholine hyperresponsiveness and markers of atopy has been well established<sup>9-11</sup> there is little information on the alterations in the airway responsible for increased peak flow variability as assessed by the use of peak flow meters.<sup>12-14</sup> Recent reports<sup>13-16</sup> suggest that peak flow variability and measures of bronchial responsiveness to pharmacological agents probably yield information on different but related phenomena.

The aim of our study was to assess the relation of two indices of airway lability – peak flow variability and the methacholine dose-response slope – measured at the age of 11 years to wheeze at different ages (<3, 6, and 11 years) and to markers of atopy in a large population sample followed from birth.

## Methods

Participants in the study were enrolled as newborn infants between May 1980 and October

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1984 as part of the Tucson Children's Respiratory Study (CRS).<sup>17</sup> A total of 1246 children were initially enrolled. Details on data collection and procedures are presented elsewhere.<sup>17,18</sup>

During the first three years of life parents were instructed to see their paediatricians whenever their children presented with signs or symptoms of lower respiratory tract illness. When children reached a mean (SD) age of 6.3 (0.9) years ("age 6", n=1024) and 10.9 (0.6) years ("age 11", n=956) the parents completed questionnaires regarding their children's respiratory symptoms. For both the age 6 and age 11 surveys wheeze was defined as parental reporting of any wheezing episode in the previous 12 months, regardless of a diagnosis of asthma. To assess the association of measurements of airway lability with persistent or remitting wheezing, subjects were classified according to their wheezing status at ages <3 and 6 years and then at ages 6 and 11 years.

The study was approved by the Human Subjects Committee at the University of Arizona. Parents signed separate consent forms for the initial enrolment of the infants and for other studies described in this paper.

#### PEAK EXPIRATORY FLOW AND METHACHOLINE CHALLENGE TESTS

A total of 754 children were still living in Tucson at the time of the age 11 survey. Of these, a total of 676 children took home peak flow meters to measure peak flow (PEF) three times daily for one week. Children and their parents were trained by study nurses on the use of the PEF meter. Subjects were asked to record on a diary the best of three attempts after waking up in the morning, when they came home from school in the afternoon, and before going to bed at night. To assess the "learning effect" on PEF measurements we tested Cochran's Q<sup>19</sup> using all three sessions for the seven day period. Only measures from the first morning of the study were found to be lacking homogeneity with the rest of the week's values and were thus eliminated from the analysis. Only children who recorded PEF measurements at least twice per day (after elimination of measures from the first morning of the study) for at least 4 days were included in the analysis.<sup>16</sup>

The amplitude percent mean (Amp%mean) was chosen as the peak flow variability index<sup>15,19</sup> and defined as:

$$\text{Amp\%mean} = \frac{\Sigma (\text{maximum daily PEF} - \text{minimum daily PEF}) / \text{mean daily PEF}}{\text{number of days in the period}} \times 100$$

Positive peak flow variability was considered to be present in subjects with Amp%mean values above the 90th percentile for a healthy reference subgroup (subjects who were skin test negative, had never wheezed, nor had been diagnosed as having asthma, n=136). To validate the Amp%mean variable and cut off level better we also assessed an index of PEF variability that considers "labile" subjects with at

least one PEF value exceeding 30% of the daily mean.<sup>12,20</sup> Results using this 30% amplitude index were not different from those obtained using the Amp%mean and for this reason only the latter results are presented here.

Because at the time the study was designed there were concerns regarding parental acceptability and safety of the methacholine challenge for symptomatic patients, children who had used asthma medications in the previous three months were excluded from methacholine testing. Children who had had an upper respiratory infection in the previous four weeks or a lower respiratory infection in the previous six weeks, those with cardiac problems, other systemic diseases, or with reactions such as severe headaches were also excluded. Challenges were performed using the protocol described by Yan *et al*<sup>21</sup> with nebulised cumulative doses of methacholine ranging from 0.004 to 2.048 mg.

Results for methacholine challenge were expressed as the methacholine-DRS. The end point was defined as a 20% fall in forced expiratory volume in one second (FEV<sub>1</sub>) from baseline or FEV<sub>1</sub> at the final cumulative dose of 2.048 mg. The response was calculated as the two point slope between baseline and end point FEV<sub>1</sub> per log dose<sup>9</sup>:

$$\text{methacholine-DRS} = \frac{(\text{last FEV}_1 - \text{baseline FEV}_1)}{\log \text{ last dose}}$$

We defined bronchial hyperresponsiveness as methacholine-DRS values below the 10th percentile of the methacholine-DRS distribution for a healthy reference subgroup (as defined for the PEF group, n=100). The methacholine response was also determined by the PD<sub>20</sub>, as described previously.<sup>22</sup> Results using PD<sub>20</sub> were not different from those of the methacholine-DRS index and therefore will not be presented in this paper.

#### MEASURES OF MARKERS OF ATOPY

Skin prick tests were performed using extracts of common allergens in the Tucson area. At six years of age house dust, bermuda grass, olive, careless weed, alternaria, mesquite, and mulberry were used and at age 11 *Dermatophagoides farinae* and cat dander were added (allergens provided by Holister-Stier Laboratories, Everett, Washington, USA). Skin test positive subjects were defined as those who had at least one positive reaction (weal size measuring 3 mm or more after subtraction of the control value) in either of the two surveys in which they were performed.

Blood for serum IgE analysis was obtained at birth from the umbilical cord, at a median age of 9.3 months (the "9 month" sample), and again at ages 6 and 11. Total serum IgE levels were measured with paper radioimmunosorbent test (Pharmacia Diagnostics, Piscataway, New Jersey, USA).<sup>23</sup>

Table 1 Characteristics at the age 11 survey of subjects who performed peak expiratory flow (PEF), of those who performed methacholine challenge, and of subjects with no tests (reference group)

	PEF (n = 600)	Methacholine (n = 397)	No tests (n = 303)
Age (years)	10.8**	10.7***	11.2
Sex (male)	48%	48.2%	48.0%
Maternal asthma	12.8%	8.6%	12.8%
Wheeze with LRIs (age ≤ 3)	39.8%	36.6%	37.2%
Wheeze (age 11)	27.8%	19.9%*	25%
Mean (SE) baseline FEV <sub>1</sub> (l/s)	2.18 (3.4)	2.18 (3.3)	†
Skin test positive	63.0%	65.1%	†

\*\*\* p ≤ 0.001; \*\* p ≤ 0.01; \* p ≤ 0.05.

Groups of children who did PEF and methacholine tests are not exclusive. Statistical differences were calculated between PEF and methacholine groups in relation to the no tests group. Data were missing for certain characteristics in some children.

† A very small number of subjects were tested in this group (27 with FEV<sub>1</sub> and 79 with skin tests), and thus comparisons may not be meaningful.

#### STATISTICAL ANALYSIS

Contingency tables and the  $\chi^2$  distribution were used for bivariate analysis and logistic regression for multivariate evaluation of dichotomous outcome data. The 95% confidence intervals (CI) for odds ratios were calculated with standard algorithms. The continuous distribution of IgE levels at each survey was categorised in quartiles and assessed for relation with Amp%mean and methacholine-DRS using a  $\chi^2$  for trend test. Statistical significance was defined by a two-sided alpha level of 0.05.

### Results

#### STUDY POPULATION

Of the 655 children contacted for methacholine testing, 213 were excluded (78 because of the use of asthma medications in the previous three months, 93 because they refused or missed the appointment, and 42 because of infections of the upper or lower respiratory tracts in the previous weeks, headaches, congenital problems, or other associated diseases) and 45 had poor test performance, leaving 397 subjects with valid tests. Of the 676 children who were sent home with PEF meters, diaries were recovered from 664, of which 64 had inadequate or insufficient data. A total of 350 children had both valid PEF measures and methacholine challenge tests; 303 children had no data either

for peak flow variability or for methacholine-DRS. There were no significant differences in sex distribution, height, maternal level of education, maternal history of asthma or wheezing with lower respiratory tract infections in the first three years of life for children with valid methacholine challenge and peak flow variability tests compared with children who did not perform any of the tests (table 1). The prevalence of wheezing at 11 years of age was significantly lower in the methacholine group than in the group that underwent no tests, probably because of the exclusion of children requiring asthma medication in the previous three months from the methacholine group. Baseline FEV<sub>1</sub> at age 11 was similar for children who performed either PEF or methacholine challenge tests. The children in the group that performed no tests were slightly older. There were 711 children who had allergy skin tests in both surveys, 68% of whom had at least one positive skin test.

#### AMP%MEAN AND METHACHOLINE-DRS CUT OFF VALUES

Subjects were classified as having positive peak flow variability if Amp%mean values were greater than or equal to the cut off value of 16.6% (the 90th percentile for the healthy reference population sample). Among children who performed methacholine challenge, those who had a coefficient less than or equal to -0.403 ml/log dose unit represented the lower 10th percentile and were thus defined as having methacholine hyperresponsiveness.

ASSOCIATION OF METHACHOLINE HYPERRESPONSIVENESS AND POSITIVE PEAK FLOW VARIABILITY AT AGE 11 TO WHEEZING AT DIFFERENT AGES, ALLERGY SKIN TESTS, AND SEX Bivariate analysis (table 2) showed that children who had positive peak flow variability at age 11 were almost twice as likely to have wheezed at age <3 compared with children who did not wheeze at that age (odds ratio (OR) 1.9 (95%

Table 2 Association† of methacholine hyperresponsiveness and peak flow variability at age 11 to wheezing at different times, allergy skin tests, and sex (univariate analysis)

	Methacholine positive			Peak flow variability positive		
	n	%	OR (95% CI)	n	%	OR (95% CI)
Wheeze ≤ 3 yr						
Yes	126	27.8	1.1 (0.6 to 1.7)	192	14.1	1.9 (1.1 to 3.3)*
No	218	26.6		322	8.1	
Wheeze age 6						
Yes	83	32.5	1.6 (0.9 to 2.6)	163	15.3	2.0 (1.1 to 3.4)**
No	312	23.4		427	8.3	
Wheeze age 11						
Yes	78	51.3	4.4 (2.6 to 7.4)***	166	13.9	1.6 (0.9 to 2.8)
No	314	19.4		431	9.0	
Skin test						
(+)	244	34.0	4.3 (2.4 to 7.8)***	372	9.7	0.9 (0.5 to 1.6)
(-)	141	10.6		199	10.6	
Sex						
Male	192	33.9	2.3 (1.4 to 3.7)***	286	11.2	1.2 (0.7 to 2.0)
Female	204	18.1		313	9.6	
URIs††						
Yes	—	—	—	57	17.5	2.1 (1.0 to 4.5)*
No	—	—	—	479	9.0	

\*\*\* p ≤ 0.001; \*\* p ≤ 0.01; \* p ≤ 0.05.

† OR (odds ratio) and 95% CI (95% confidence interval).

†† URIs = upper respiratory infections at age 11; subjects with URIs were excluded from methacholine challenge.

Table 3 Association† of methacholine hyperresponsiveness and peak flow variability at age 11 to wheezing at different times, allergy skin tests, and sex (multivariate logistic regression analysis)

	Methacholine positive (OR 95% CI)†	Peak flow variability (OR 95% CI)†
Wheeze ≤3 yr	1.1 (0.6 to 1.9)	1.6 (0.9 to 2.9)
Wheeze age 6	0.9 (0.5 to 1.7)	2.1 (1.0 to 4.1)*
Wheeze age 11	3.2 (1.7 to 5.9)***	1.1 (0.5 to 2.4)
Positive skin test	3.0 (1.6 to 5.6)***	0.8 (0.4 to 1.5)
Sex (male)	2.1 (1.2 to 3.5)**	1.0 (0.6 to 2.0)
URIs††	-	0.9 (0.8 to 1.0)

\*\*\* p ≤ 0.001; \*\* p ≤ 0.01; \* p ≤ 0.05.

† OR (odds ratio) and 95% CI (95% confidence interval).

†† URIs = upper respiratory infections at age 11; subjects with URIs were excluded from methacholine challenge.

CI 1.1 to 3.3), p < 0.05). There was also a significant association between positive peak flow variability and wheeze at age 6 (OR 2.0 (95% CI 1.1 to 3.4), p < 0.01) but not with wheeze at age 11. Fifty seven children among those who performed PEF tests at age 11 had upper respiratory tract infections in the previous four weeks (there were no children with lower respiratory tract infections among those who performed PEF tests). Children with upper respiratory tract infection at the time of the age 11 survey had a significantly higher prevalence of positive peak flow variability at that age (OR 2.1 (95% CI 1.0 to 4.5), p < 0.05) than those without upper respiratory tract infections. Neither sex nor positive skin tests to allergens were associated with peak flow variability. In contrast, positive methacholine was associated with wheeze at age 11 (OR 4.4 (95% CI 2.6 to 7.4), p < 0.001) but not with wheeze at ages 6 or < 3 years. There was also a fourfold increased risk of being methacholine positive for skin test positive subjects compared with those who were skin test negative (OR 4.3 (95% CI 2.4 to 7.8), p < 0.001). Boys were at a significantly higher risk of having methacholine hyperresponsiveness than girls (OR 2.3 (95% CI 1.4 to 3.7), p < 0.001).

Logistic regression analysis (table 3), with methacholine hyperresponsiveness and positive peak flow variability measured at age 11 as the

dependent variables, showed that only wheezing at age 6 was a significant and independent predictor associated with positive peak flow variability (OR 2.1 (95% CI 1.0 to 4.1), p < 0.05) after adjusting for wheezing at other times, skin test response, sex, and upper respiratory tract infections. At age 11 upper respiratory tract infections were not shown to be independently associated with positive peak flow variability (table 3). In contrast, methacholine hyperresponsiveness at age 11 was associated with wheezing at age 11 (OR 3.2 (95% CI 1.7 to 5.9), p < 0.001), positive skin test results (OR 3.0 (95% CI 1.6 to 5.6), p < 0.001), and with the male sex (OR 2.1 (95% CI 1.2 to 3.5), p < 0.05). Methacholine hyperresponsiveness at age 11 showed no association with wheeze at ages < 3 or 6 years.

ASSOCIATION OF METHACHOLINE HYPERRESPONSIVENESS AND POSITIVE PEAK FLOW VARIABILITY AT AGE 11 TO WHEEZING GROUPS AT AGES 3 AND 6

Children were assigned to four groups according to their wheezing status during the first six years of life (table 4), as described in our previous study.<sup>2</sup> Neither positive peak flow variability nor methacholine hyperresponsiveness at age 11 were associated with “transient early wheezing” – that is, wheezing during the first three years of life but no wheezing at six years of age. Positive peak flow variability at age 11 years was significantly associated with wheezing at age 6 (skin test negative subjects who wheezed at age 6 but not at age 3 (OR 3.3 (95% CI 1.0 to 12.5), p < 0.05), and skin test positive subjects who were wheezing at both surveys (OR 3.3 (95% CI 1.3 to 8.8), p < 0.01)). Methacholine hyperresponsiveness at age 11 was unrelated to any of the groups of wheezers up to age 6, although there was a marginal association for subjects who were wheezing both at ages 3 and 6 among those who were skin test positive.

Table 4 Association† of methacholine hyperresponsiveness (Mch positive) and peak flow variability (PEF var positive) measured at age 11 to wheezing at age 3 and age 6 surveys††††

	Total		Skin test negative		Skin test positive	
	Mch positive	PEFvar positive	Mch positive	PEFvar positive	Mch positive	PEFvar positive
No wheeze by 3/no wheeze at 6						
% positive	26	7	14	8	32	6
N+/N group	49/188	19/262	10/71	8/105	36/113	9/145
OR (95% CI)‡	1.0	1.0	1.0	1.0	1.0	1.0
Yes wheeze by 3/no wheeze at 6						
% positive	22	10	10	9	32	11
N+/N group	18/80	10/100	3/30	3/34	15/47	7/61
OR (95% CI)	0.9 (0.5 to 1.6)	1.4 (0.6 to 3.2)	0.7 (0.2 to 2.7)	1.1 (0.3 to 4.6)	1.0 (0.5 to 2.2)	2.0 (0.7 to 5.8)
No wheeze by 3/yes wheeze at 6						
% positive	28	14	7	22	39	10
N+/N group	13/47	12/85	1/15	5/23	12/31	6/59
OR (95% CI)	0.9 (0.4 to 1.9)	2.1 (1.0 to 4.6)*	0.4 (0.04 to 3.5)	3.3 (1.0 to 12.5)*	1.2 (0.5 to 2.9)	1.1 (0.6 to 5.0)
Yes wheeze by 3/yes wheeze at 6						
% positive	39	19	11	15	52	18
N+/N group	13/33	13/70	1/9	2/13	12/23	10/54
OR (95% CI)	1.7 (0.8 to 3.7)	2.8 (1.3 to 6.2)**	0.7 (0.2 to 7.5)	2.5 (0.4 to 13.7)	2.0 (0.8 to 5.2)	3.3 (1.3 to 8.8)**

\*\* p ≤ 0.01; \* p ≤ 0.05.

† OR (odds ratio) and 95% CI (95% confidence interval) adjusted by sex and for URIs.

†† Groups are the same as described in previous study.<sup>2</sup> No wheeze both by age 3 and age 6 (no wheeze by 3/no wheeze at 6); wheezing by age 3 and no wheezing at age 6 (yes wheeze by 3/no wheeze at 6); no wheezing by age 3, and wheezing at age 6 (no wheeze by 3/yes wheeze at 6); and wheezing both at age 3 and 6 (yes wheeze by 3/yes wheeze at 6).

††† Total number of subjects is greater than subtotals for skin test positive and skin test negative subjects because some subjects did not have skin test results.

‡ Reference odds ratio.

Table 5 Association† of methacholine hyperresponsiveness (Mch positive) and peak flow variability (PEFvar positive) measured at age 11 to wheezing at age 6 and age 11 surveys††††

	Total		Skin test negative		Skin test positive	
	Mch positive	PEFvar positive	Mch positive	PEFvar positive	Mch positive	PEFvar positive
No wheeze by 6/no wheeze at 11						
% positive	21	52	8	8	32	8
N+/N group	56/268	29/356	13/153	12/150	35/108	12/150
OR (95% CI)‡	1.0	1.0	1.0	1.0	1.0	1.0
Yes wheeze at 6/no wheeze at 11						
% positive	11	13	4	19	18	8
N+/N group	5/46	9/70	1/23	6/31	4/22	3/37
OR (95% CI)	0.4 (0.1 to 1.1)	1.6 (0.7 to 3.7)	0.3 (0.04 to 2.5)	2.9 (1.0 to 8.8)*	0.6 (0.2 to 1.9)	1.0 (0.3 to 3.7)
No wheeze at 6/yes wheeze at 11						
% positive	42	10	1	10	48	9
N+/N group	17/40	7/68	1/8	1/10	15/31	5/56
OR (95% CI)	2.8 (1.4 to 5.6)**	1.3 (0.5 to 3.1)	1.0 (0.1 to 9.2)	1.3 (0.1 to 11.3)	2.5 (1.1 to 5.7)*	1.1 (0.4 to 3.1)
Yes wheeze at 6/yes wheeze at 11						
% positive	59	17	—	20	65	15
N+/N group	22/37	16/93	0/2	1/5	22/34	13/85
OR (95% CI)	5.1 (2.4 to 10.6)***	2.3 (1.2 to 4.5)**	—	2.9 (0.3 to 28.1)	4.5 (2.0 to 10.1)***	1.9 (0.9 to 4.4)

\*\*\* p ≤ 0.001; \*\* p ≤ 0.01; \* p ≤ 0.05.

†OR (odds ratio) and 95% CI (95% confidence interval) adjusted by sex and for URIs.

††No wheeze both at age 6 and 11 (no wheeze at 6/no wheeze at 11); wheezing by age 6 and no wheezing at age 11 (yes wheeze at 6/no wheeze at 11); no wheezing at age 6 and wheezing at age 11 (no wheeze at 6/yes wheeze at 11); and wheezing both at age 6 and 11 (yes wheeze at 6/yes wheeze at 11).

†††Total number of subjects is greater than subtotals for skin test positive and skin test negative subjects because some subjects did not have skin test results.

‡Reference odds ratio.

ASSOCIATION OF METHACHOLINE HYPERRESPONSIVENESS AND POSITIVE PEAK FLOW VARIABILITY AT AGE 11 TO WHEEZING GROUPS AT AGES 6 AND 11

Children were also grouped according to their wheezing status at ages 6 and 11 (table 5). Children who had methacholine hyperresponsiveness at age 11 and were skin test positive were more likely to be wheezing at age 11 irrespective of wheezing at age 6 (OR 2.5 (95% CI 1.1 to 5.7), p < 0.05 and 4.5 (95% CI 2.0 to 10.1), p < 0.001 for no wheeze at 6/yes wheeze at 11 and yes wheeze at 6/yes wheeze at 11, respectively). In addition, positive peak flow variability at age 11 was significantly associated with persistent wheezing (OR 2.3 (95% CI 1.2 to 4.5), p ≤ 0.01 for yes wheeze at 6/yes wheeze at 11). Conversely, children

who had positive peak flow variability at age 11 and were skin test negative were also at an increased risk of having wheezed at age 6 but not at 11 (OR 2.9 (95% CI 1.0 to 8.8), p ≤ 0.05 for yes wheeze at 6/no wheeze at 11).

ASSOCIATION OF METHACHOLINE HYPERRESPONSIVENESS AND POSITIVE PEAK FLOW VARIABILITY AT AGE 11 TO TOTAL SERUM IGE MEASURED AT DIFFERENT SURVEYS

Positive peak flow variability at age 11 was not found to be related to high serum IgE levels in any of the surveys at which this variable was assessed (fig 1). In contrast, methacholine hyperresponsiveness at age 11 was marginally correlated with log total serum IgE levels

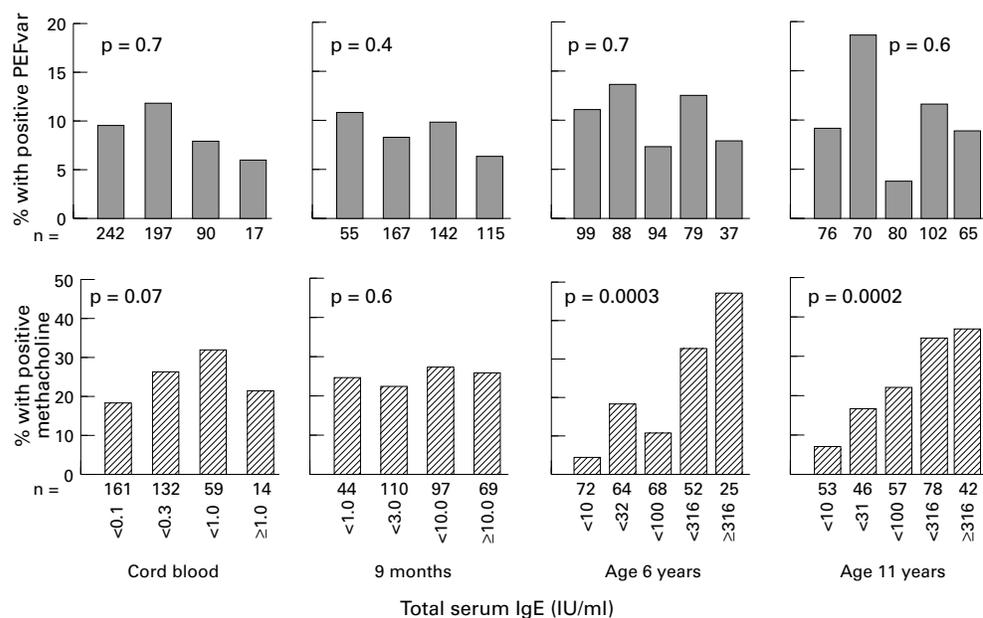


Figure 1 Proportion of subjects with positive peak flow variability (PEFvar) or positive methacholine challenge response in relation to serum IgE levels measured at different ages. The numbers of children (n) tested for each IgE level are displayed under the bars on each of the graphs. p values for trend within groups were determined by the  $\chi^2$  test.

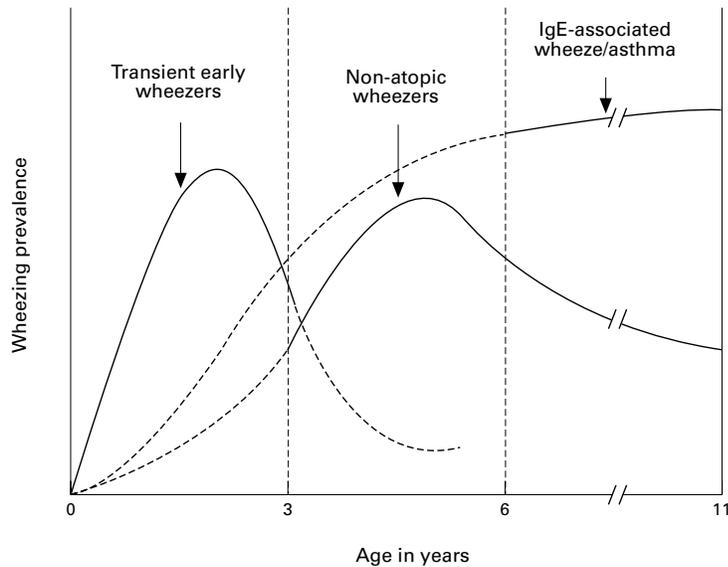


Figure 2 Hypothetical yearly peak prevalence of wheezing for the three different wheezing phenotypes in childhood. Prevalence for each age interval should be the sum of the areas under each curve. This classification of wheezing phenotypes should not imply groups are exclusive. Dashed lines suggest wheezing can present different curve shapes due to many different factors including overlap of groups. Modified from Wilson.<sup>30</sup>

( $p=0.07$ ) at birth and highly correlated with serum IgE levels measured at ages 6 ( $p<0.001$ ) and 11 ( $p<0.0001$ ).

### Discussion

Both methacholine hyperresponsiveness and positive peak flow variability when measured at age 11 were associated with persistent wheezing during the school years (ages 6 and 11). Increased prevalence of positive peak flow variability was also observed in a group of children who wheezed at age 6 but not at age 11 and who were predominantly non-atopic. Methacholine hyperresponsiveness was associated with wheezing at age 11 among atopic subjects, independent of wheezing at age 6. Two previous studies<sup>8,24</sup> that examined bronchial responsiveness in wheezing children of 4–6 years of age reported that these children did not show the expected response to airway challenge tests as reported in older wheezing children or adults. Wilson *et al*<sup>8</sup> speculated that many preschool wheezers do not have the same kind of atopy-related inflammatory airway response which is characteristic of older asthmatic subjects. This notion is supported by our findings of different patterns of response for peak flow variability and methacholine challenge when measured at the age of 11 years. Our data thus confirm the clinical impression that a considerable number of children who wheeze during the toddler and early school years have a condition that may be different from that of the classical, atopy-related asthma seen in older children or adults. Our findings and those of Wilson *et al*<sup>8</sup> have important consequences for our understanding of childhood wheezing which appears to be a heterogeneous group of conditions with a common final pathway represented by recurrent airway obstruction.

Our data do not allow us to define the nature of the alteration in airway dynamics that was present in the non-atopic subjects who had positive peak flow variability at age 11, wheezing around the age of 6, but who were not wheezing at age 11. Peak flow variability was unrelated to skin test reactivity to allergens measured at ages 6 and 11 and to serum IgE levels measured in cord blood and at ages 9 months, 6 years, and 11 years. Conversely, methacholine responsiveness was strongly associated with skin test reactivity to allergens and with total serum IgE levels as measured both concurrently with methacholine measurements and five years earlier at age 6 (fig 1). It thus appears that methacholine responsiveness and peak flow variability identify different types of abnormal airway behaviour.<sup>13</sup> This is in agreement with earlier findings by Siersted *et al*<sup>19,25</sup> who reported that some children with asthma related symptoms but no asthma diagnosis had increased peak flow variability but not methacholine hyperresponsiveness. Thus, it is tempting to speculate that perhaps environmental stimuli such as viruses or tobacco smoke may alter airway dynamics and cause a syndrome of less persistent wheezing through mechanisms which regulate airway tone independently of IgE mediated inflammation.

We have previously reported that the main risk factor for transient early wheezing (wheezing up to age 3 but not after) is a lower level of airway function which can already be detected shortly after birth,<sup>26</sup> tracks along individual “growth curves”, and remains low at age 6.<sup>27</sup> In the present study we observed that this same group of children showed no increased prevalence of methacholine hyperresponsiveness or positive peak flow variability, both measured at age 11. It thus appears that increased airway lability is not the main factor responsible for the lower levels of lung function observed in these children. The decreased lung function is more likely to be the consequence of mechanical characteristics of the lung such as altered airway resistance or increased dynamic compliance.<sup>28</sup> As in our population, Stick *et al*<sup>29</sup> showed that children who wheezed in early life had lower levels of lung function than children who did not wheeze, but that bronchial responsiveness to histamine challenge was not different between these two groups.

There are some limitations in our study that need to be addressed. We did not perform methacholine tests in children with a history of significant asthma symptoms in the previous three months. More recent data suggest that this precaution may have overestimated the possible side effects of methacholine challenge in children with active asthma. The main consequence of this restriction was that a subset of more severely ill wheezers ( $n=78$ ) were underrepresented in the sample of children challenged with methacholine (table 1). A close analysis of the possible consequences of this restriction on our results suggests that our conclusions would not have changed had we included the subjects with more recent wheezing symptoms in our study. Indeed, the associations between methacholine and wheeze at age 11,

atopic markers, sex, and current asthma were all significant among subjects included in this study and would probably have been stronger had we not excluded subjects with more recent asthma symptoms. Methacholine hyperresponsiveness was marginally associated with wheezing both at ages 3 and 6 among skin test positive subjects (table 4). This association would probably have been stronger had the more severe wheezers been tested for methacholine at age 11 since this group has the highest risk of continuing persistent wheeze. However, the exclusion criteria did not affect subjects who were wheezing at age 6 but who were not wheezing at age 11 so the low prevalence of positive methacholine tests in this group cannot be explained by selection bias. Finally, peak flow variability was measured in all cooperative subjects independent of symptoms so no bias with respect to symptoms was present in this group; in addition, the results were similar when the analysis for peak flow variability was restricted to the group who also performed methacholine tests.

In summary, there are at least three different wheezing phenotypes associated with different risk factors which co-exist during the first 11 years of life. We have identified these wheezing phenotypes as "transient early wheezing", "non-atopic wheezing" of the toddler and early school years, and "IgE-associated wheeze/asthma" (fig 2). These phenotypes coincide with the three groups of wheezing children previously described by Wilson.<sup>30</sup> Our data suggest that, whereas the first syndrome is mainly associated with lower levels of lung function which persist throughout childhood,<sup>31</sup> the second group is mainly associated with increased peak flow variability long after wheezing symptoms have ceased – that is, at age 11 in this study. IgE associated wheeze/asthma, on the other hand, may exist at any age during childhood and is related to the known combination of atopy, increased responsiveness to methacholine, and increased peak flow variability.

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