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Asthma phenotypes in childhood: lessons from an epidemiological approach

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Summary Asthma is a heterogenous disease with variable signs and symptoms among patients. It also presents significant individual variability over time. Recently, some important population-based studies that followed children from birth or from early childhood into adulthood have shed new light on how we understand this syndrome. Three phenotypes have been identified in children with asthma: transient wheezing, non-atopic wheezing of the toddler and pre-school-aged child and IgE-mediated wheezing. Transient wheezing is associated with symptoms that are limited to the first 3–5 years of life, decreased lung function, maternal smoking during pregnancy and exposure to other siblings or children at daycare centres. There is no association between transient wheezing and family history of asthma or allergic sensitisation. Children wheezing with respiratory syncytial virus in the first years of life are more likely to be wheezing up to 13 years of age; this is independent of atopy (non-atopic wheezers) and is not related to atopic sensitisation. Wheezing associated with evidence of allergic sensitisation has been identified as the 'classic' asthma phenotype. Early allergic sensitisation is a major risk factor for persistent asthma.

The presence of different conditions that may be associated with lower airway obstruction during childhood complicates our understanding of the pathogenesis of the disease. Asthma is a heterogeneous condition with different phenotypes and clinical expressions that depend on age, gender, genetic background and environmental exposures.[1] Wheezing, its major clinical expression, is a non-specific sign associated with airflow restriction through narrowed airways. A turbulent flow causing oscillation of the bronchial walls is the most likely cause of the characteristic high pitch, polyphonic 'whistling' sound.[2,3] Since air flow in peripheral small airways is rather slow, it does not generate enough energy to cause this oscillation at an audible range. Hence, the common wheezing sound heard in children with obstructive airway diseases is an expression of the narrowing of larger, central airways. Small airways obstruction is silent but it can cause dynamic compression of the central airways thereby generating wheeze.

Patterns of asthma expressed during childhood will be present up to adulthood.[4,5] Children who present with mild disease during the first years of life and those without a significant family history of asthma and/or allergies are most likely to remit after the first decade of life. Children with significant symptoms in the first years of life, especially those with a family history of asthma, are likely to develop persistent respiratory symptoms later in life.[6] Defining which children are at risk for persistent asthma could allow for better management and, potentially, for reduced morbidity and mortality.

The understanding of the scope of asthma during childhood is a task that requires an understanding of the natural history of the disease. Even though many aspects of this natural history, especially during childhood, are still unclear, longitudinal data from studies in different locations have indicated how asthma progresses during the first decades of life and have shed some light on

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possible mechanisms associated with different phenotypes.

COHORT STUDIES AND ASTHMA FOLLOW-UP FROM CHILDHOOD TO ADULTHOOD

The recent publication of adequately powered, well-designed longitudinal studies with follow-up starting during the first years of life has produced a remarkable change in our understanding of asthma, its beginnings, its clinical expression and its evolution.

A recent study by Sears *et al.*[7] evaluated a cohort from Dunedin, New Zealand, followed from 9 to 26 years of age with questionnaires, pulmonary function tests, bronchial challenge testing and allergy testing. The authors defined wheezing as persistent when it was present at every assessment after it was first mentioned. Remission was defined as the absence of wheezing after it had been reported at two or more successive previous assessments. Relapse was recorded if wheezing was reported at two or more successive assessments, was then absent at one or more successive assessments and was then reported at all subsequent assessments. Intermittent wheezing was defined by the presence of symptoms at some assessments but not at others, not at two consecutive assessments and not fitting the patterns described above. Wheezing reported at one assessment alone was classified as transient wheezing.

Of the 613 subjects who had complete data from every assessment in the New Zealand study, 72.6% had reported wheezing during at least one assessment by the age of 26 years and 51.4% had reported wheezing at more than one evaluation. At 26 years of age, 26.9% of the study participants were still wheezing; in 14.5%, wheezing had persisted from onset, whereas 12.4% presented a remission followed by a relapse by the age of 26 years. These data are consistent with data from Australian studies in Tasmania[8] and Melbourne[9] which found that approximately two-thirds of subjects with asthma in the first years of life did not persist with their symptoms during adulthood.

Table 1 shows the distribution of wheezing on these longitudinal wheezing categories. Wheezing was considered to be transient in 21.2% of the participants (this number includes 4.6% who only reported wheezing at 26 years of age). At this age, study members with persistent or relapsing wheezing had a higher prevalence of sensitivity to house dustmites and cat allergen and of airway hyperresponsiveness and lower lung function measurements than those whose wheezing did not persist or relapse. The highest risk for either persistent or relapsing wheezing was for airway responsiveness between 9 and 21 years of age and for positive skin test for house dust mites at 13 years of age. Female sex and smoking were also predictors of persistent wheezing, whereas an early age of onset predicted relapse (Table 2). The symptoms of asthma appeared much earlier in cases that seemed to remit during adolescence only to relapse during early adulthood than in remitting cases in which a relapse did not occur. These findings by Sears *et al.*[7] provide strong support for the contention that environmental factors, acting during early life and interacting with specific 'asthma genes', are crucial for a primary prevention strategy, which will necessarily be focused on events that occur in infancy and early childhood.

From childhood to adulthood, study participants who were persistent wheezers had consistently lower lung function measurements, expressed as the ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC), when compared with other study participants who never reported any wheezing (Fig. 1). This was confirmed by a generalised estimation equation, showing lower mean FEV_1/FVC ratios for males with persistent or relapsing wheezing compared with those who never wheezed. No significant differences in mean FEV_1/FVC ratio were observed among children with remission, intermittent wheezing or transient wheezing. Moreover, the slopes of change in FEV_1/FVC were similar in each group, indicating that impairment of lung function occurred in early childhood. These deficits are strongly associated with the severity of disease and are believed to represent alterations in lung function and structure that contribute to the

Table 1 Outcomes at 26 years of age among 613 study members who provided respiratory data at every assessment, according to sex.

Outcome	% (no. of study members)		Total ($n = 613$)
	Male study members ($n = 317$)	Female study members ($n = 296$)	
Persistent wheeze (from onset to 26 years of age)	12.6 (40)	16.6 (49)	14.5 (89)
Relapse (wheezing stopped then recurred)	12.9 (41)	11.8 (35)	12.4 (76)
In remission (free of wheezing at 26 years of age)	15.5 (49)	14.5 (43)	15.0 (92)
Intermittent wheezing	9.5 (30)	9.5 (28)	9.5 (58)
Transient wheezing	19.9 (63)	22.6 (67)	21.2 (130)
Wheezing never reported	29.7 (94)	25.0 (74)	27.4 (168)

Adapted from Sears M *et al. N Engl J Med* 2003; **349**: 1414–1422.

Table 2 Odds ratio for factors predicting persistence of wheezing from onset to 26 years of age or relapse by 26 years of age.*

Model	Persistence		Replace	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Univariate				
PC_{20} or BDR at 9 years of age	4.32 (2.64–7.06)	<0.001	6.82 (3.89–11.95)	<0.001
$PC_{20} \leq 8$ mg/mL at any assessment from 9 to 15 years of age	4.24 (2.64–6.79)	<0.001	6.93 (4.07–11.77)	<0.001
$PC_{20} \leq 8$ mg/mL or BDR at any assessment to 21 years of age	4.13 (2.59–6.59)	<0.001	7.22 (4.29–12.17)	<0.001
Positive skin test for house dustmite allergen at 13 years of age	3.38 (2.12–5.37)	<0.001	4.17 (2.49–7.01)	<0.001
Positive skin test for cat allergen at 13 years of age	2.81 (1.65–4.79)	<0.001	3.27 (1.78–6.03)	<0.001
Smoking at 21 years of age	2.05 (1.30–3.24)	0.002	1.84 (1.11–3.04)	0.02
Father smoked when study member was a child	0.63 (0.40–1.00)	0.05	1.29 (0.79–2.11)	0.31
Mother smoked when study member was a child	0.84 (0.53–1.37)	0.46	0.98 (0.60–1.61)	0.93
Family history of wheezing	1.44 (0.92–2.27)	0.11	1.59 (0.98–2.60)	0.06
Age at onset of wheezing†	0.97 (0.94–1.01)	0.11	0.87 (0.83–0.91)	<0.001
Female sex	1.37 (0.87–2.16)	0.17	0.95 (0.58–1.55)	0.84
Multivariate (significant factors only)				
$PC_{20} \leq 8$ mg/mL or BDR > 10% at any assessment from 9 to 21 years of age	3.00 (1.71–5.26)	<0.001	3.03 (1.65–5.55)	<0.001
Positive skin test for house dustmite allergen at 13 years of age	2.41 (1.42–4.09)	0.001	2.18 (1.18–4.00)	0.01
Female sex	1.71 (1.04–2.82)	0.03		
Smoking at 21 years of age	1.84 (1.13–3.00)	0.01	0.89 (0.85–0.94)	<0.001
Age at onset of wheezing†				

Adapted from Sears M *et al. N Engl J Med* 2003; **349**: 1414–1422.

* The odds ratio (OR) for persistence of wheezing is the comparison with all other study members except those who never reported wheezing. The OR for relapse is for the comparison with all other study members except those with persistent wheezing and those who never reported wheezing. CI, confidence interval; PC_{20}, concentration of methacholine causing a 20% decrease in the forced expiratory volume in one second (FEV_1); BDR, response of the FEV_1 to a bronchodilator (increase from baseline).

† The OR was calculated for persistence or relapse per year of increase in the age of onset (i.e. a later age at onset was protective).

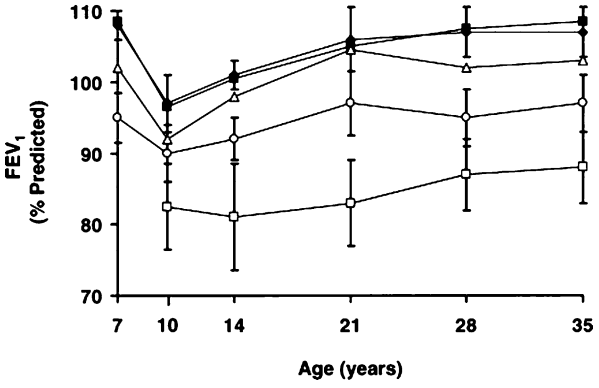

Figure 1 Forced expiratory volume in 1 s (FEV_1) as percentage of predicted values in different groups of subjects enrolled in the Melbourne longitudinal study of asthma. Subjects were classified according to their diagnosis at time of enrollment: ◆, control; ■, mild wheezy bronchitis; △, wheezy bronchitis; ○, asthma; □, severe asthma. Assessment of the participants every 7 years showed that those with asthma and severe asthma at age 7–10 years of age showed diminished lung function as adults than those with asthma having relatively mild abnormalities. These abnormalities tracked with age. Adapted from Oswald *et al. Pediatr Pulmonol* 1997; **23**: 14–20.

persistence of symptoms of asthma. Until recently, the origin of these deficits was not well understood. It now appears that lower levels of lung function are already present by the early school years in patients in whom persistent asthma will ultimately develop, with no further deterioration after that age.

Similar results as those found in New Zealand[7] were observed in an earlier longitudinal study. The Australian study started in 1964, in Melbourne, following children with asthma into adulthood.[10] A total of 401 children drawn from a large population base were enrolled at 7 years of age. The results were based on parental responses to a questionnaire concerning their child's history of asthma, wheezing episodes and bronchitis. The children were classified into four categories: those who never wheezed; those with fewer than five episodes associated with apparent respiratory infection (mild wheezy bronchitis); those with five or more episodes associated with apparent respiratory infections (wheezy bronchitis) and those with wheezing not associated with respiratory infection (asthma). A fifth group of children with severe asthma was added to the same cohort at 10 years of age and evaluations were conducted every 7 years.[4] At follow-up at 35 years of age, participants were categorised as: no recent asthma (not having wheezed for 3 or more years previous to the evaluation), infrequent wheeze (having wheezed in

the previous 3 years but not in the 3 months before evaluation), frequent asthma (having wheezed less than once per week in the 3 previous months) or persistent asthma (having wheezed at least once weekly in the previous 3 months). Of the subjects who had mild wheezy bronchitis at 7 years of age, 77% were free of symptoms at 35 years of age, whereas only 23% had frequent or persistent asthma.[10] Of the participants with asthma at 7 years of age, 50% had no recent asthma or infrequent asthma as adults, whereas 50% had frequent or persistent asthma. Importantly, 75% of those who had severe asthma at 10 years of age had frequent or persistent asthma at 35 years of age. According to these results, many children do not remit from their asthma; the more severe their asthma is, the less likely they are to remit. These data support the tracking concept of the disease; children with mild disease had remission or continued with mild disease into their adult years, whereas children with severe asthma suffered persistent severe asthma when they reached adulthood.

Subjects with asthma and severe asthma at 7 years of age who were followed up to 28 years of age experienced abnormal pulmonary function as adults, although in the participants with mild asthma, the abnormalities were relatively minor (Fig. 2). Children with mild wheezy bronchitis and wheezy bronchitis at 7 years of age had no evidence of airway obstruction at 35 years of age. These patterns presented in Fig. 2 suggest once again that no significant loss of pulmonary function occurs after the age of 7–10 years up to 35 years of age, even in individuals with severe disease. It may be inferred that children are either born with reduced pulmonary function or that there is a loss of pulmonary function in the first few years after which no additional loss occurs.

Data from the Tucson Children's Respiratory Study suggest that this loss of lung function occurs very early in life.[11] At 6 years of age, children were classified into four wheezing categories based on the current and previous history of their wheezing symptoms: non-wheezers (children who never wheezed), transient wheezers (at least one lower respiratory tract illness with wheezing during the first 3 years of life but who had no wheezing at 6 years of age), late-onset wheezers (no lower respiratory tract illness with wheezing during the first 3 years of life and wheezing at 6 years of age) and persistent wheezers (at least one lower respiratory tract illness with wheezing during the first 3 years of life and wheezing at 6 years of age). Based on pulmonary function measurements made before 1 year of age,[12] non-wheezers and persistent wheezers showed no significant difference in pulmonary function parameters. At 6 years of age, however, persistent wheezers had significantly lower pulmonary function compared with non-wheezers. This difference was still detected at 11 years of age.[13] Therefore, significant loss of pulmonary function, for children who will become persistent wheezers, seems to occur after birth but before 6 years of age; consequently, the deficits in lung function in wheezing children are not significantly present shortly after birth but seem to be acquired during the first years of life.

ASTHMA PHENOTYPES

These wheezing syndromes are characterised by the persistence or remittance of wheeze and wheeze-associated symptoms from childhood to adulthood. We have proposed that three can be defined based on specific characteristics: transient early wheezers (wheezing up to 3–5

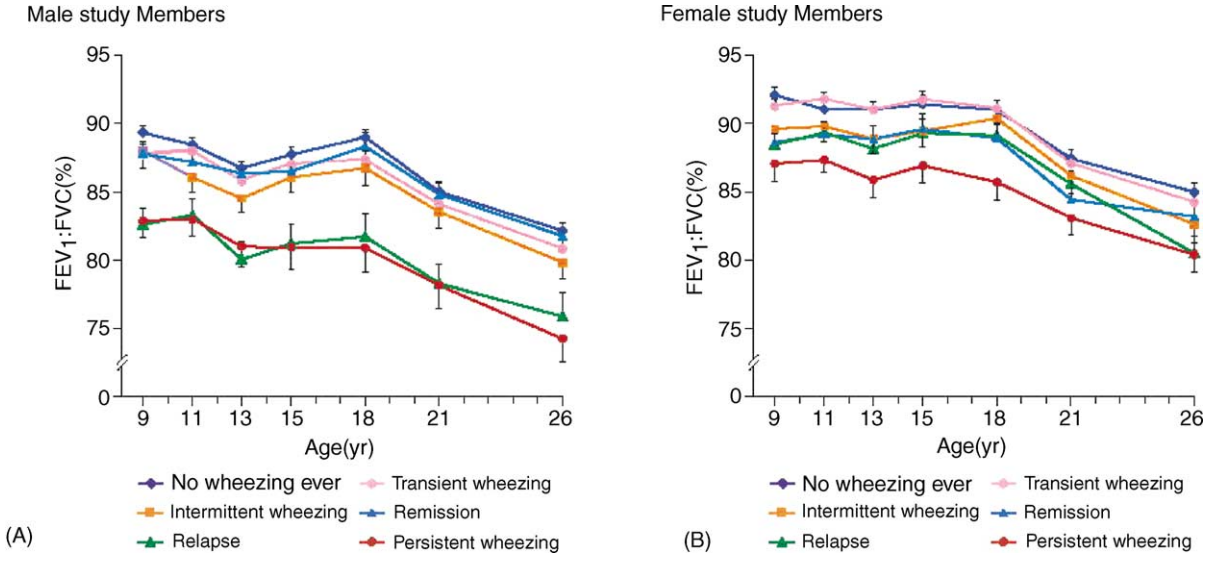

Figure 2 Mean (±SE) forced expiratory volume in 1 s (FEV_1): forced vital capacity (FVC) ratios measured at 9, 11, 13, 15, 18, 21 and 26 years of age in male (A) and female (B) study members according to the pattern of wheezing. Adapted from Sears M *et al. N Engl J Med* 2003; **349**: 1414–1422.

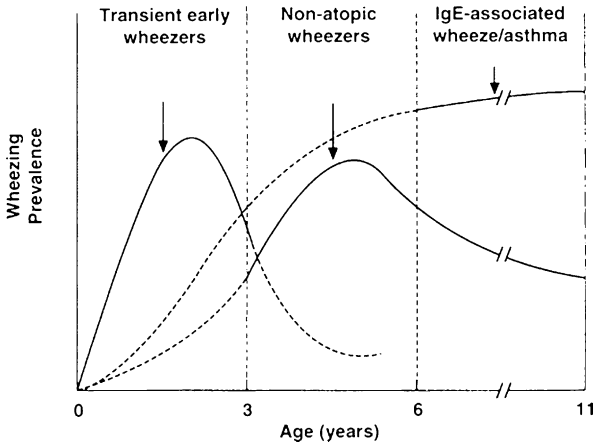

Figure 3 Hypothetical yearly peak prevalence of wheezing according to phenotype in childhood. Asthma phenotypes reflect a heterogeneous group of conditions characterised by recurrent airway obstruction. Three of these phenotypes are shown. This classification of wheezing phenotypes should not imply that the groups are exclusive. Dashed lines suggest that wheezing can be represented by different curve shapes resulting from many different factors, including overlapping of the groups. Adapted from Stein RT *et al*. *Thorax* 1997; **52**: 946–952.

years of age but not thereafter), non-atopic wheezing and IgE-mediated wheezing/asthma (Fig. 3).

Transient early wheezing

For the majority of infant wheezers, most wheezing and wheeze-related symptoms resolve between the ages of 3 and 5 years. The transient wheezing phenotype is not commonly associated with a family history of asthma or with atopy.[14] The primary risk factor seems to be reduced lung function[15] diagnosed before any event of lower respiratory illness had occurred. This lower level of lung function seems to track over the years along individual growth curves. Transient early wheezers had no increased prevalence of methacholine hyper-responsiveness or positive peak flow variability at 11 years of age, suggesting that mechanical pulmonary characteristics, such as reduced airway resistance or increased dynamic compliance,[16] play a significant role in this non-persistent form of wheezing of the first few years of life.

Prematurity[17] or being exposed to siblings or to children at daycare centres[18] are risk factors associated with transient wheezing. Maternal smoking during pregnancy[19] as well as post-natal exposure to tobacco smoke[20] are also risk factors.

Non-atopic wheezing

Lower respiratory illnesses (LRI) in the first 3 years of life are associated with persistent wheezing. As a group, non-atopic wheezers are different from transient wheezers, since these present lower lung function early in life before any respiratory insult. Although their lung function improves with growth, it remains lower than that in infants or children who never wheezed. This is in contrast to non-atopic wheezers, who start out with normal lung function but end up with slightly lower lung function and enhanced airway reactivity later in childhood. Among children who wheeze with LRIs in the first 3 years of life, approximately 60% are atopic at 6 years of age.[11] Stein *et al*.[21] examined the relationship between early LRIs and the subsequent development of wheeze or atopic markers during the first decade of life. Most wheezing episodes were viral respiratory infections, with respiratory syncytial virus (RSV) being detected in almost 50% of all episodes. Analyses demonstrated that RSV infections that occurred before 3 years of age were associated with an increased risk of wheezing during the first 10 years of life, independently of other known risk factors for asthma or asthma-related symptoms, such as family history of asthma or atopy. However, the risk decreased with age and was no longer significant by 13 years of age (Fig. 4). RSV-LRIs were not associated with an increased risk for allergic sensitisation or higher total serum IgE levels.

Children who had RSV-LRIs early in life were more likely to have lower levels of lung function at 11 years of age compared with children who had no apparent infecting agent. This difference remained independent of current wheezing at 11 years of age. Children with a history of RSV infection were also more likely to respond to a bronchodilator than their counterparts with no such history. We can speculate that many schoolchildren with a history of RSV and lower levels of pulmonary function were born with this reduced function but we cannot exclude the possibility that in some children, RSV infection led to a specific immune response that caused this reduced lung function.[21]

In conclusion, a significant number of children who wheeze during the first decade of life do so in association with viral respiratory agents, especially RSV, independently of allergic sensitisation. This phenotype seems to be associated with less severe and less persistent wheeze. Among school-aged children, this phenotype is likely to be less prevalent than the atopic phenotype in developed countries but this may not hold true in other environments. A recent study in Peru[22] showed that current wheeze in 8–10 year olds in a population living in a shanty town was not associated with allergic sensitisation or other atopic markers. These and other findings from less socially developed populations have led to the hypothesis that different risk factors from those found in more developed societies may be associated with increased expression of this milder asthma/wheeze phenotype that is not associated with atopy.

Atopic wheezing/asthma

More than half of the cases of persistent asthma start very early in life, most before 6 years of age. In different

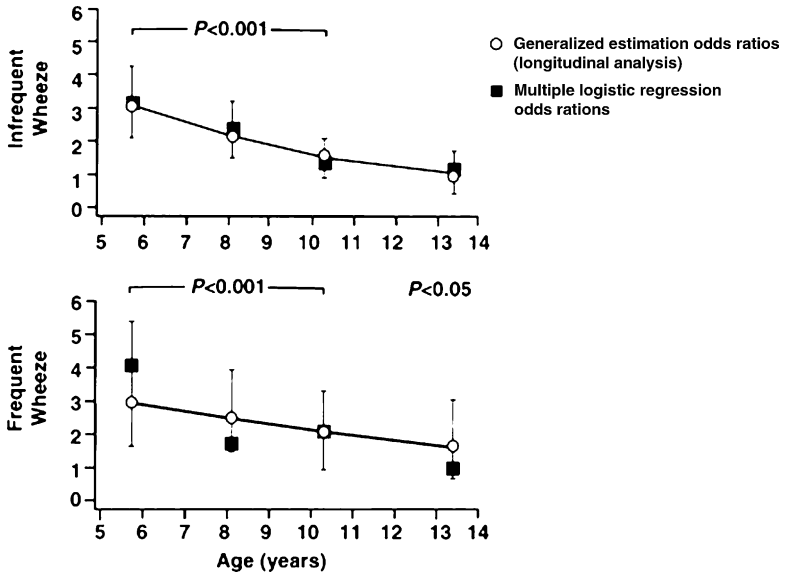

Figure 4 Adjusted odds ratio (95% confidence intervals) for infrequent and frequent wheeze associated with respiratory syncytial virus (RSV) lower respiratory tract infections before 3 years of age. RSV infection significantly increased the risk for wheezing during the first 10 years of life. The risk decreased with age and was no longer significant at 13 years of age. Results were adjusted for confounding variables including family history of asthma, positive skin tests at 6 or 11 years of age, gender, maternal education, birth weight and current maternal smoking. Adapted from Stein RT *et al*. *Lancet* 1999; **354**: 541–545.

population-based studies,[7,11] persistent wheezers present with atopy and increased airway hyper-responsiveness as major associated risk factors. There is a significant association between an early onset of wheezing symptoms and severity of disease and airway hyper-responsiveness among these children. We have already stressed that, as a group, children who will become persistent wheezers present with normal lung function at the beginning of life and will have significant deficits in pulmonary function growth. Children with atopy have been shown to present lower levels of lung function by 3 years of age.[23] It is clear that important changes in airway physiology start very early in life.[11]

For persistent wheezers, early allergic sensitisation increases the prevalence of respiratory symptoms, chronic airway inflammation and the risk of declining pulmonary function. Several studies have shown that asthma and recurrent wheezing during childhood are strongly associated with elevated serum IgE and with allergic sensitisation to local aero-allergens.[24–26] Peat *et al*.[27] reported that early (before 8 years of age) but not late allergic sensitisation to common aero-allergens is associated with increased risk for the development of bronchial hyper-responsiveness and asthma. Similar findings by Sherrill *et al*. showed that elevated serum IgE levels at 9 months of age directly correlated with the risk of persistent wheezing, suggesting a form of IgE-mediated sensitisation during the first year of life.[28] A German multi-centre allergy study followed 1314 children from birth to 7 years of age. Children who had asthma by 7 years of age were sensitised very early in life and had persistent sensitisation when compared with children who did not have asthma at 7 years of age.[29] These data suggest that a genetic pre-disposition for sensitisation to certain local aero-allergens is associated with asthma symptoms that start early in life.

PRACTICE POINTS

- Asthma is a heterogeneous disease with well recognized wheeze phenotypes in childhood.
- Wheezing in the first years of life is not associated with atopy, and is thus called transient wheezing. It is known to be associated with diminished lung function.
- A group of asthmatic children who are still symptomatic with episodes of wheezing up to adolescence do present a milder form of disease, associated with RSV and not with atopy, i.e., non-atopic wheezers.
- Persistent wheezing, the 'classic' asthma is associated with atopy and atopic markers, early allergic sensitization, significant loss of lung function in the first years of life, and airway hyper reactivity.
- The distribution of these wheezing phenotypes is dependent upon the interaction of genetic characteristics and the environment.

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