

Prediction of asthma in children at 6 and 12 years of age: Perth infant asthma follow-up study

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Longitudinal studies, starting in infancy, provide an opportunity to assess risk factors prior to long-term exposure to environmental factors. The status of the infant soon after birth is determined by genetic background and factors related to *in utero* influences. As a result of recent advances in molecular biology, the genetic component can now be evaluated.

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There are several distinct advantages of longitudinal studies over cross-sectional observations (1). The most important of these are that the predictive power of early factors can be assessed and age effects clarified. The few studies that have operated over a sufficient time-period to be able to provide data relevant to children's asthma are now able to examine the association between long-term outcomes through childhood and factors measured both during pregnancy and in early life. These studies have provided unique and important contributions to our understanding of respiratory disease in childhood. For example, the Tucson study has reported that the group of children who wheeze in the first 3 years of life have reduced maximal flow at functional residual capacity ($V_{\max}$ FRC) in the first few months of life compared with the groups who wheeze throughout the first 6 years of life or only between 3 and 6 years of age (2). These data have been interpreted as evidence that viral-induced wheeze in early life is related to pre-existing geometric abnormalities of airway physiology, rather than the factors that contribute to asthma in children of school age, and that the early wheezers have a different disease than the asthma found in older children.

The Perth longitudinal respiratory follow-up study began in 1987 and 253 infants were recruited over 3 years. All subjects were full-term and selected randomly from a normal population

presenting to a metropolitan public hospital. The main parameters measured in the study are presented in Table 1. Lung function and airway responsiveness (AR) to histamine were assessed in infants using the tidal volume forced expiration technique (3) and in older children by using spirometry. This study is, to date, the only longitudinal follow-up study that has assessed AR in early life and outcomes in childhood. The level of AR was taken as the concentration of histamine that produced a 40% fall in $V_{\max}$ FRC (PC₄₀). One of the main aims of the study was to evaluate the initial level of AR in infants and to determine whether this predicted later respiratory outcome. We reasoned that the level of AR is a major determinant of respiratory status at any given time and that the initial level may reflect underlying genetic levels of responsiveness that continue to influence respiratory status throughout life. One of the advantages of measuring AR at such an early age is that the level would be unlikely to be influenced by environmental factors, although possible *in utero* or early life factors could not be entirely eliminated from consideration.

In the initial evaluation at 1 month of age, flow-limitation on tidal expiration was identified in $\approx 8\%$ of the population (4). This finding was unexpected, as flow-limitation on expiration during tidal breathing is only found in marked degrees of airway disease in adults and signifies

Table 1. Parameters measured in the Perth infant longitudinal respiratory follow-up study

	Age at follow-up		
	1 month (n = 253)	6 years (n = 120)	12 years (n = 190)
Lung function	$V_{\max}$ FRC	FEV_1	FEV_1
Airway response to histamine	+	+	+
Skin-prick test	+	+	+
Total and specific IgE	Chord	+	+
Questionnaire	+	+	+
Genotype			+

FEV_1 , forced expiratory volume in 1 s; IgE, immunoglobulin E; $V_{\max}$ FRC, maximal flow at functional residual capacity.

a lack of reserve airway function at any age. The predisposition to airway disease was demonstrated by the observation that 92% of the infants identified received the diagnosis of asthma from their local doctor during the first 2 years of life (4). We examined the flow-limited infants at 12 years of age and our data suggest that they still have an increased risk of having a current diagnosis of asthma and that they have increased airway responsiveness (5) compared with those who were not flow-limited in infancy. The reasons for otherwise normal, healthy infants having flow-limited expiration is not known. In the infant evaluation, we also noted that AR was greater in those with a family history of asthma vs. those without such a history (6), but subsequent analyses on the complete cohort did not support this observation (7).

The 6-year follow-up revealed that, of all the assessments made in infancy, AR to histamine (PC_{40}) was the best predictor of outcome (Table 2) (7). The diagnosis of asthma and symptoms were strongly associated with the level of AR, and forced expiratory volume in 1 s (FEV_1) also correlated with PC_{40} (7). As AR in infancy did not correlate with immunoglobulin E (IgE) levels in early life or with levels at 6 years of age, it appears to be acting as an independent risk factor. The mechanism of this association is not clear, but the increased risk of AR is not apparent in the first 2 years of life, as AR in wheezy infants has been

shown to be the same as in normal infants (8). Thus, the increased risk for asthma and respiratory symptoms at 6 years of age, that can be attributed to AR, can be identified soon after birth, but does not appear to affect respiratory status until children are past the first few years of life. $V_{\max}$ FRC was also found to be correlated with respiratory function at 6 years of age, but the association was with forced expiratory flow between 25% and 75% of vital capacity (7). Both parameters are determined, to a large extent, by flow in the latter part of expiration, suggesting that the intrinsic factors that affect small airway function during childhood can be identified from birth.

The 12-year follow-up of this cohort has been in a greater proportion of the original cohort compared with the 6-year follow-up (Table 1). To date, only preliminary results are available, but in general, these appear to show that the strength of the correlations between factors measured at 1 month of age and outcomes at 12 years of age is less than those described at 6 years (7). A possible reason for this is that environmental factors would have a greater influence on current status with increasing age than underlying or genetic factors.

The importance of genetic processes in asthma is now well established (9). Longitudinal data on cohorts spanning childhood offer the potential to identify age-related genetic factors. The probability that different genetic predispositions are important at different ages is high, as asthmatic symptoms are most common in early life and distinct asthma phenotypes have been noted (2). For example, because atopy has a strong association with asthma after approximately 3 years of age (2), genetic predispositions that relate to IgE production will probably become evident at a corresponding age. If there are strong age-related genetic associations, cross-sectional studies that include individuals with a broad range of ages and aim to show relationships between particular DNA variations and asthma, could fail to detect associations. This would be caused by the lack of numbers of those in the relevant age bracket and the dilution of their results owing to the inclusion of others outside this age range. We have begun the genetic analysis of the Perth cohort, and preliminary results on a sample of the cohort suggest that AR in infancy may be increased in those with the $\beta 2$ -adrenoreceptor Arg16 polymorphism (10). If data from the complete cohort supports these observations, this would be of interest, as it would raise the possibility that the initial level of airway responsiveness is genetically influenced by this $\beta 2$ -adrenoreceptor polymorphism and that this could be the factor responsible

Table 2. Adjusted odds ratios (AR) of the association between airway responsiveness to histamine at 1 month of age and outcomes at 6 years (7)

Outcome at 6 years	Adjusted OR (95% CI)	p-value
Physician diagnosed asthma ever	0.65 (0.48–0.86)	0.003
Physician diagnosed asthma currently	0.52 (0.37–0.75)	<0.001
Wheeze with colds	0.63 (0.46–0.81)	0.003
Wheeze apart from colds	0.40 (0.24–0.65)	<0.001
Usual cough	0.59 (0.35–0.99)	0.05

95% CI, 95% confidence interval; OR, odds ratio.

for the relationship between early AR and respiratory outcome during childhood.

In summary, the Perth Infant Asthma Follow-up study has followed a cohort from birth to 12 years of age and is unique in having assessed AR in infancy. The most striking finding is that, of the risk factors measured, the initial level of AR is the best predictor of respiratory outcome during childhood. The other important predictive factor is early infant lung function. The genetic analysis of this cohort may detect the etiological factors that underpin these relationships.

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