

Early life risk factors for adult asthma: A birth cohort study of subjects at risk

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Background: Prediction of adult asthma is important, and early prevention strategies should be targeted at those most at risk. Identifying high-risk children at an early age, however, is currently difficult.

Objective: We sought to determine those factors present in early life that predict an increased risk of adult asthma.

Methods: A prospective cohort study of subjects at risk of asthma and atopy was undertaken in Poole, England. One hundred babies of atopic parents were recruited at birth. During the first 5 years of life, subjects were recalled annually, all respiratory events were reported, and skin prick tests and total serum IgE measurements were performed. At 11 and 22 years, bronchial hyperresponsiveness was also measured. Seventy-three subjects were followed up at 5 years, 67 at 11 years, and 63 at 22 years.

Results: Twenty-three (37%) adult subjects reported wheezing within the previous 12 months. Fifteen (25%) of these subjects showed signs of bronchial hyperresponsiveness and were regarded as asthmatic. Wheezing before the age of 2 years occurred in 28% and was not significantly related to adult asthma (odds ratio, 0.3; 95% CI, 0.03-1.7; $P = .19$). A positive skin prick test response to hen's egg, cow's milk, or both in the first year was independently predictive of adult asthma (odds ratio, 10.7; 95% CI, 2.1-55.1; $P = .001$; sensitivity, 57%; specificity, 89%).

Conclusion: Prediction of adult asthma remains difficult. In this study of subjects at risk of atopy, skin sensitivity to hen's egg or cow's milk in the first year was predictive of adult asthma. (*J Allergy Clin Immunol* 2001;108:720-5.)

Key words: Asthma, atopy, bronchial hyperresponsiveness, food allergen, aeroallergen, risk factors

The first symptoms of asthma may begin at any age. In childhood there are a number of respiratory syndromes characterized by symptoms of cough and wheeze. Many young children under 2 years of age wheeze with upper respiratory tract infections, and the majority have a good

Abbreviations used

BHR: Bronchial hyperresponsiveness
OR: Odds ratio

prognosis.^{1,2} In older children asthmatic symptoms and bronchial hyperresponsiveness (BHR) are associated with raised serum IgE levels and positive skin prick test responses to common environmental allergens.^{3,4}

There is evidence that the immunopathology of asthma in the airways of young children is present even before symptoms.⁵ Early interventions to prevent asthma with allergen avoidance^{6,7} or drugs⁸ are being advocated in very young children. There is therefore an urgent requirement to predict those most at risk of persistent asthma at a very early age. Atopic family history and cord-blood IgE levels have been used as predictors: recent work has shown that their predictive capacity was not high enough to recommend their use as a screening tool for primary prevention.⁹ Most longitudinal studies have shown that the presence of eczema in infancy is an important risk factor in the development of childhood wheezing.¹⁰ The risk of wheezing illness in childhood is enhanced or mitigated by a range of events and environmental factors. The factors identified include fetal nutrition,¹¹ duration of pregnancy,¹² tobacco smoke exposure,¹³ breast-feeding,¹⁴ nutrition in childhood,¹⁵ maternal age,¹⁶ socioeconomic status,¹⁶ and allergen exposure.¹⁷ The number of respiratory infections in infancy may protect against atopic disorders in childhood.¹⁸ Living on a farm¹⁹ and pet ownership²⁰ may also be protective. It has been suggested that when these factors are allowed for, it becomes possible to identify children who have at least a 50% chance of having asthma in the future.²¹ More sophisticated models with inflammatory or immunologic markers in very young wheezing children have also been devised and used for secondary intervention studies.²¹

In this study a group of subjects at risk of atopic disorders were followed from birth to adult life. This report identifies those factors in early life that predict adult asthma.

METHODS

One hundred subjects were enrolled before birth over a 12-month period from 1976 to 1977. All babies were born in Poole Hospital and were selected on the basis of one or both parents having a history of asthma, hay fever, or both. Informed consent was obtained, and the local ethical committee approved all stages of the study.

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The cohort was studied every 3 months for the first year, annually thereafter until the age of 5 years, and again at 11 years. This study reports on the latest follow-up of subjects at 22 years. There remained 92, 73, 67, and 63 subjects in the cohort at 1, 5, 11, and 22 years, respectively.

Social class was based on the occupation of the head of the household at the time of the child's birth (Registrar General's Classification, 1971).

During the first 5 years, parents reported all respiratory illness to the research team. The presence of wheezing was confirmed whenever possible by means of clinical examination. At the age of 11 years, children completed a questionnaire with the help of their parents. Questions covered asthma and allergic symptoms in the previous 12 months and over the period since the last follow-up. A similar questionnaire was administered at the age of 22 years. Subjects were regarded as having current wheeze if they answered yes to the question, "Have you had wheezing (loud breathing with a whistling sound coming from the chest) at any time in the last 12 months?"

Subjects were examined for eczema at each visit. Eczema was defined as roughening, redness, or intense pruritis that persisted for 4 weeks or more.

BHR to inhaled histamine was assessed at ages 11 and 22 years by using the method of Yan et al.²² The provocation dose of histamine that caused a reduction in FEV₁ by 20% was calculated. Subjects were considered to have BHR if this occurred at or before the maximum cumulative dose of 7.8 μ mol.

Subjects were regarded as having asthma if they had current wheeze and BHR.

The atopic status of subjects was determined at each follow-up by means of skin prick testing with a standard technique to a panel of 6 allergens: *Dermatophagoides pteronyssinus*, mixed grass pollen, cat fur, dog dander, hen's egg, and cow's milk (Bencard UK Ltd, 1976-1989, ALK-Abelló, 1999 [Bencard reagents are no longer available in 1999]) with positive histamine and negative saline controls. The reaction was regarded as positive if the mean diameter of the skin wheal at 15 minutes was 2 mm or greater in subjects less than 2 years of age and 3 mm or greater in subjects older than 2 years. A subject was considered to be atopic if he or she had at least one positive skin prick test response. The atopic status of the parents was also determined by using skin prick tests when the children were 11 years of age.

Venipuncture was performed for immunoglobulin analysis at each follow-up. Total serum IgE levels were expressed in international units per milliliter.

Dust samples were collected by using a standard procedure²³ from the mattress, bedroom floor, and living room carpet in the homes of subjects between October 1979 and March 1980 and again between February and April 1989. Levels of the house dust mite allergen Der p 1 were measured in dust samples and expressed as micrograms of Der p 1 per gram of sieved dust.²⁴ In the analysis the highest recorded level of Der p 1 in the house was used as an index of exposure.

Before embarking on the current follow-up of this cohort, a pilot follow-up study was conducted in the previous year by using a postal questionnaire. There were 52 questionnaires completed and returned, with 40% of respondents experiencing wheeze in the previous 12 months. Before data collection, this information was used to assess the statistical power of the current follow-up. It was anticipated that 74 subjects would be traced. Power analysis suggested that the study would have 80% power to detect as statistically significant (at the 5% level) a factor that occurred with a prevalence of 25% and whose association with adult wheezing could be summarized by a relative risk of 2.3 and a factor that occurred with a prevalence of 50% and whose association with adult wheezing could be summarized by a relative risk of 2.5. The influence of actual sample size on the results was assessed by using CIs.

Throughout, risks within groups are summarized as percentages with 95% CIs. Risks between groups were compared with the Fisher

exact test, and the association was summarized by using odds ratios (ORs) with exact 95% CIs. The distributions of normally distributed interval scaled measures are summarized by means and SDs and compared between groups by using the independent samples *t* test. The distribution of skewed or ordinal measures is summarized by medians, and interquartile ranges are compared with the Mann-Whitney *U* test.

Multivariable analyses were conducted by using LogXact4 for Windows (Cytel Software),²⁵ which produces exact *P* values and CIs by using conditional exact logistic regression, to identify those variables that were independently predictive of adult asthma. This is suitable for small sample sizes because it does not depend on the asymptotic distribution of test statistics. First, the subset of variables that were significant at the 20% level was chosen. This reduced the chance of making a type II error at this stage of analysis and allowed for the possibility that after adjusting for other variables, *P* values might actually be reduced. A careful systematic approach was used to avoid overfitting the regression as a result of the small sample size and large number of factors, looking first at the early wheezing factors, then the skin prick tests, then the environmental and other factors, and then combining factors from the different groups. Each set of analyses was based on the factor with the smallest *P* value, and the other factors were added in one at a time in a series of 2 factor models. Final interpretation focused on those that were significant at the 5% level, although the chance of making a type II error as a result of the small sample size needs to be considered when interpreting the other factors.

RESULTS

One hundred children were recruited at birth. Nineteen children dropped out within the first 2 years, and information on these subjects is limited. Seventy-three subjects remained in the study at 5 years, and 67 remained at 11 years. At 22 years, 60 subjects were recalled for study, and a further 3 subjects returned questionnaires only. The early life characteristics of the 63 subjects who were studied at 22 years were compared with those of the 18 subjects who were lost to follow-up after their second birthday (Table I). The sex distribution, social class, mean maternal age, and occurrence of early wheeze and eczema in those lost to follow-up were not significantly different from those factors in the 63 adult subjects who remained. There was a significant difference in history of maternal asthma between those followed up and those dropping out, but it was in the opposite direction to that expected. (Those dropping out of the study were more likely to have a mother who had asthma.) There is no obvious explanation for this.

Twenty-three (38%) of 60 adults admitted to current smoking (at least one cigarette per day). There was no significant difference in the prevalence of asthma in smokers and nonsmokers.

Prediction of adult asthma and wheeze in early life

Twenty-three of the adult subjects reported having wheezed within the previous 12 months. Fifteen of these subjects also showed symptoms of bronchial hyperreactivity and were therefore defined as asthmatic (OR, 25%; 95% CI, 15%-38%).

Early wheeze

Wheezing before the age of 2 years occurred in 28% and was not predictive of either adult asthma (Table II) or

TABLE I. Comparative data on the study group and those lost to follow-up

	Followed up at 22 y (n = 63)	Lost to follow-up (n = 18)	P value*
Male sex	26 (41%)	9 (50%)	.59
Social class			.35
I	8 (13%)	0	
II	20 (32%)	7 (39%)	
III	17 (27%)	3 (17%)	
IV	3 (5%)	1 (6%)	
V	0	0	
Insufficient information	15 (24%)	7 (39%)	
Mean maternal age (y)	29.4 (SD, 4.4)	29.0 (SD, 3.5)	.83†
History of maternal asthma	9 (14%)	9 (50%)	.003
Wheeze at <2 y	17 (27%)	7 (39%)	.39
Eczema at <2 y	33 (52%)	6 (33%)	.19
Positive skin prick test response to egg, milk, or both at 3 mo, 6 mo, or 1 y	14 (23%)	3 (17%)	.75
Positive skin prick test response to aeroallergens at 3 mo, 6 mo, or 1 y	21 (34%)	8 (44%)	.58

*Fisher exact test.

†Independent samples *t* test.**TABLE II.** Early wheeze, skin sensitization, and eczema as predictors of adult asthma

Predictors of adult asthma	Percentage with adult asthma (95% CI)	OR (95% CI)	P value*
Wheeze before second birthday			
No (n = 43)	30 (17-46)	—	
Yes (n = 17)	12 (1-36)	0.3 (0.03-1.7)	.19
Wheeze between second and fifth birthday			
No (n = 39)	21 (9-36)	—	
Yes (n = 17)	41 (18-67)	2.7 (0.6-11.1)	.19
Wheeze between 10th and 11th birthday			
No (n = 38)	13 (4-28)	—	
Yes (n = 17)	59 (33-82)	9.4 (2.1-45.5)	.001
Positive skin prick test response to egg, milk, or both at 3 mo, 6 mo, or 1 y			
No (n = 46)	13 (5-26)	—	
Yes (n = 13)	62 (32-86)	10.7 (2.1-55.1)	.001
Positive skin prick test response to aeroallergens at 3 mo, 6 mo, 1 y, or 2 y			
No (n = 38)	11 (3-25)	—	
Yes (n = 20)	45 (23-68)	7.0 (1.5-35.9)	.006
Eczema at <2 y			
No (n = 30)	23 (10-42)	—	
Yes (n = 30)	27 (12-46)	1.2 (0.3-4.6)	1.00

*Fisher exact test.

adult wheezing (OR, 0.9; 95% CI, 0.2-3.4). Children who wheezed between 2 and 5 years were more likely to wheeze as adults than children who had not wheezed between these ages (OR, 3.8; 95% CI, 1.0-14.4; *P* = .04). When the stricter definition of asthma (symptomatic BHR) was used, however, this result did not reach statistical significance. Wheezing between the 10th and 11th birthday was highly predictive of both adult wheezing (OR, 20.0; 95% CI, 4.0-125.1) and adult asthma (Table II).

Skin sensitization and eczema

Thirteen subjects had a positive skin prick test response to egg, milk, or both before 1 year of age. The positive reactions to egg and milk were transient, with all but one of the infants with egg allergy losing their sensitivity by the age of 5 years. Aeroallergen sensitization increased throughout childhood. A positive skin prick test response to egg, milk, or both before the age of 1 year was predic-

tive of adult asthma and adult wheezing (OR, 12.3; 95% CI, 2.5-77.1; Table II). Sensitization to aeroallergens before the age of 2 years was also predictive of adult asthma and wheezing (OR, 4.6; 95% CI, 1.3-16.7). Children who had eczema before the age of 2 years were not at a significantly higher risk of having adult asthma.

Total serum IgE

There was no significant relationship between the total serum IgE levels in cord blood and adult asthma. This was also true for IgE levels up to the age of 2 years. By 3 years, however, increased total serum IgE levels were significantly related to adult asthma, and the relationship was stronger still at the age of 11 years (Table III).

Environmental and other genetic factors

Sex, atopic and asthmatic status of parents, number of respiratory infections between birth and second birthday,

TABLE III. Total serum IgE levels as predictors of adult asthma

Predictors of adult asthma	No asthma as adult (n = 45)*	Adult asthma (n = 15)*	Median difference (95% CI)	P value†
Cord-blood IgE	5 (3)	4 (3)	0 (-2 to 2)	.71
IgE at 2 y	19 (34)	34 (110)	9 (-9 to 46)	.44
IgE at 3 y	26 (36)	86 (205)	29 (0 to 152)	.05
IgE at 11 y	79 (373)	278 (1462)	179 (44 to 1118)	.007

*Median (interquartile range).

†Mann-Whitney *U* test.

TABLE IV. Environmental and other factors as predictors of adult asthma

Predictors of adult asthma	Percentage with asthma (95% CI)	OR (95% CI)	P value*
Male sex			
No (n = 36)	25 (12-42)	—	
Yes (n = 24)	25 (10-47)	1.0 (0.2-3.8)	1.00
Maternal asthma			
No (n = 53)	23 (12-36)	—	
Yes (n = 7)	43 (10-82)	2.6 (0.3-17.3)	.35
Paternal asthma			
No (n = 45)	22 (11-37)	—	
Yes (n = 15)	33 (12-62)	1.8 (0.4-7.3)	.49
Mother atopic†			
No (n = 19)	42 (20-67)	—	
Yes (n = 23)	21 (9-39)	0.4 (0.1-1.5)	.13
Father atopic†			
No (n = 15)	13 (2-40)	—	
Yes (n = 37)	35 (20-53)	3.5 (0.6-36.1)	.18
Both parents atopic†			
No (n = 31)	32 (17-51)	—	
Yes (n = 21)	24 (8-47)	0.7 (0.1-2.7)	.55
Environmental smoke exposure in home at <5 y			
No (n = 41)	24 (12-40)	—	
Yes (n = 19)	26 (9-51)	1.1 (0.2-4.4)	1.00
Breast-fed for <12 wk			
No (n = 18)	50 (26-74)	—	
Yes (n = 45)	31 (18-47)	2.2 (0.6-7.8)	.25
Social class 1 or 2			
No (n = 35)	29 (15-46)	—	
Yes (n = 28)	46 (28-66)	2.2 (0.7-7.0)	.19
Exposure to cat in home before fifth birthday			
No (n = 45)	29 (16-44)	—	
Yes (n = 13)	15 (2-45)	0.4 (0.04-2.5)	.48
Exposure to dog in home before fifth birthday			
No (n = 41)	22 (11-38)	—	
Yes (n = 18)	33 (13-59)	1.8 (0.4-7.0)	.52

*Fisher exact test.

†Determined by means of skin testing when child was 11 years of age.

length of breast-feeding, parental smoking in the home before the age of 5 years, and presence of cats and dogs in the home before the age of 5 years were all considered. None of these factors showed consistent statistically significant relationships with adult asthma (Table IV). There was also no relationship with levels of the house dust mite antigen Der p 1 measured in dust samples in the home in 1979 and 1989 and adult asthma (Table V).

Multivariable analysis

The variables (from Tables II-V) with *P* values of less than .2 were selected for multivariable analysis. After

adjusting for sensitivity to ingested allergens, the OR describing the association between adult asthma and sensitivity to aeroallergens dropped from 7.0 (*P* = .006) to 2.0 (*P* = .75). Thus the effect of aeroallergen sensitivity on adult asthma was statistically explained by sensitivity to ingested allergens but not vice versa. Wheezing before the age of 2 years (OR, 0.3; *P* = .37), wheezing between 2 and 5 years (OR, 1.6; *P* = .80), log(IgE at 3 years) (OR dropped from 1.7, *P* = .04, to 1.4, *P* = .27), birth weight (*P* = .07), social class (*P* = .20), paternal atopy (*P* = .34), and maternal atopy (*P* = .21) were still not significant after adjusting for sensitization to ingested allergens.

TABLE V. Continuous environmental and other variables as predictors of adult asthma

Predictors of asthma	No asthma as adult (n = 45)	Adult asthma (n = 15)	Median difference (95% CI)	P value*
Birth weight (kg), mean (SD)	3.3 (0.5)	3.0 (0.7)	-0.3 (-0.6 to 0.0)†	.06‡
No. of respiratory infections before second birthday, median (interquartile range)	6 (5)	6 (6)	0 (-2 to 3)	.66
1979 Der p 1 levels in home (µg/g dust), median (interquartile range)	18 (27)	13 (18)	-4 (-14 to 7)	.49
1988 Der p 1 levels in home (µg/g dust), median (interquartile range)	16 (27)	13 (22)	-4 (-16 to 6)	.36

*Mann-Whitney *U* test.

†Mean difference.

‡Independent samples *t* test.

The only variable that remained statistically significant after adjusting for other factors was sensitivity to ingested allergens (adjusted OR, 11.4; 95% CI, 2.1-84.4; $P = .003$).

The sensitivity and specificity of a positive skin prick test response to egg, milk, or both at 6 or 12 months of age are 57% (95% CI, 29% to 82%) and 89% (95% CI, 76% to 96%), respectively.

DISCUSSION

In this birth cohort study of 63 subjects with atopic parents, 25% of the subjects had asthma in adult life. Wheezing before the age of 2 years did not predict adult asthma, but wheezing between the 10th and 11th birthday was highly predictive. A positive skin prick test response to hen's egg, cow's milk, or both in the first year of life was independently predictive of adult asthma. Total serum IgE levels were significantly related to adult asthma by the age of 11 years. We studied a number of genetic and environmental factors in children before the age of 2 years that may influence the development of asthma; none of these achieved statistical significance as risk factors for adult asthma.

We believe that this study provides unique data on an at-risk population followed from birth to adult life. The sample size of our cohort remaining on follow-up at 22 years is not large (63 subjects). This results in a relatively low power of the statistical tests used and relatively wide CIs. Those results that are not significant should be interpreted cautiously, and the presentation of 95% CIs encourages this. As with most longitudinal studies, there was some loss to follow-up over the 22 years. Because those who remain in the study may not be representative of the original sample, there is a possibility of bias in the results. Those who remained in the study did not differ significantly from those who did not in terms of age, parent's social class, sex, and early wheezing, although the sample size was small. Children of mothers who had asthma were less likely to be followed up, although their own atopic status did not appear to influence follow-up.

The relationship between wheezing illness in the first 2 years of life and adult asthma was not statistically significant and in the direction of a protective effect, but the CI was wide. It is known that wheezing before the age of 2 years tends to remit in early childhood.^{1,2} Abnormalities in respiratory function can precede symptoms in

some wheezy toddlers, and such respiratory function abnormalities persist into childhood.^{1,26} Whether these 2-year-old children with virus-related wheezing remain symptom free throughout adult life remains unknown, but spirometric abnormalities in adult life independent of atopic sensitization have been reported.^{27,28} There now seems little doubt that respiratory viruses are important precipitating causes of wheeze in many of these very young children,^{29,30} and atopy is not necessarily associated with wheeze or BHR in this age group.³¹ Wheezing between the second and fifth birthday and wheezing at 10 to 11 years of age do show a statistically significant association between adult wheezing and adult asthma, respectively. This finding suggests caution before advising 11-year-old children born to atopic parents that they will grow out of their asthma.

Small cohort studies have shown that sensitization to foods in infancy is a risk factor for the later development of aeroallergen sensitization.³² A multicenter German study has shown that hen's egg-specific IgE at the age of 12 months is a valuable marker for aeroallergen sensitization at 3 years³³ and, if combined with atopic parenthood, for allergic airway disease at the age of 5 years.³⁴ We have shown a strong positive association between early sensitization to hen's egg and cow's milk before the age of 2 years and adult asthma. This accords with the findings of the German study³⁴ and extends the relevance into adult life.

In this study we examined some of the environmental factors that have been considered risk factors for the development of asthma. We have been unable to show that any environmental factor present at less than 2 years of age increases or decreases the risk of asthma in adult life. This may be due to the low power of the study. It may also reflect that different risk factors operate for asthma in childhood and adult life. The relationship with parental atopy should be viewed with particular caution given that children of mothers with asthma were less likely to be followed up. The effect of birth weight was of borderline significance and needs further investigation; other studies have shown a relationship between lower birth weight and asthma,³⁵ but some have not.³⁶

Although exposure to high levels of Der p 1 antigen in infancy did influence asthma at 11 years in these subjects,³⁷ this effect was not statistically significant at 22 years, although again this may be a type II error. One explanation

may be that 4 of the adult asthmatic subjects had wheezing after the age of 11 years. Three of these subjects had low Der p 1 levels in the home in infancy (values below the threshold of 10 µg/g dust). A further explanation may be that risk factors for asthma vary with age. In a Swedish study risk factors for incident cases of asthma in childhood differed from risk factors for prevalent cases, indicating a change in the nature of asthma at different ages.³⁸

The possibility of identifying high-risk children at a very early age for asthma-prevention strategies remains an ideal. In this study of a genetically at-risk cohort, wheezing in the first 2 years was not predictive of adult asthma, suggesting that relying on early symptoms to identify at-risk children is unlikely to be reliable. We have shown that sensitization to egg or milk in the first year of life is a risk factor for adult asthma. The specificity of a positive skin prick test response to egg and milk in the first year of life is 89%, and therefore the majority of those without adult asthma did not show sensitivity to ingestants in infancy. The relatively low sensitivity (57%) indicates that many adult asthmatic subjects will not exhibit this early marker, but because of low numbers, the estimation of sensitivity was not very reliable (wide CIs).

Overall, these results suggest that skin prick testing at 1 year of age merits further study as a marker of persistent adult asthma. At present, any therapeutic interventions in young children will need to be carefully balanced between potential benefits and the intrusiveness of the therapeutic program.

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